



NATIONAL INSTITUTES OF HEALTH

**REPORT OF THE
ADVISORY COMMITTEE
ON RESEARCH ON
WOMEN'S HEALTH**

FISCAL YEARS 2015–2016

**Office of Research on Women's Health and
NIH Support for Research on Women's Health**



National Institutes of Health
Office of Research on Women's Health

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Letter from the ORWH Director

I am honored to share with you a range of accomplishments from the National Institutes of Health (NIH) in this fiscal year (FY) 15–16 biennial report, a report of the NIH Advisory Committee for Research on Women's Health. This report reflects research investments and scientific advances made in women's health research and related programs. It describes major Office of Research on Women's Health (ORWH) programs, initiatives, and activities, as well as research highlights from NIH Institutes and Centers and program offices.

Chief among these developments is the launch and implementation of the NIH policy accounting for sex as a biological variable (SABV). The SABV policy is one critical element of the NIH initiative to enhance reproducibility through rigor and transparency. The goal of the policy is to help ensure that SABV is factored into the design, analysis, and reporting of NIH-funded research on vertebrate animals and humans. Over time, we hope to build a robust body of evidence about female and male biology that will expand our understanding of the health of women and men.

Starting in June 2015, the policy was incorporated into NIH business processes, and went into effect for grant applications submitted as of January 2016. ORWH has been working with our colleagues to orient a variety of stakeholders within NIH and its Institutes and Centers and beyond to the value of accounting for SABV in the context of multiple scientific disciplines. We have collaborated with NIH colleagues to provide resources related to SABV to support grant reviewers, review and program staff, and other stakeholders and are considering ways to evaluate implementation and application of the policy.

ORWH's work on SABV stands on a foundation created by many scientists, clinicians, health advocates, and others who saw this critical gap in knowledge early and continue to help close it. We are particularly grateful to NIH Director Francis S. Collins, M.D., Ph.D., and other NIH leaders for making SABV a priority at NIH.

The SABV policy complements NIH's longstanding policy of requiring the inclusion of women in NIH-supported clinical studies. To ensure that the inclusion policy was firmly implemented, Congress set it into law through a section in the NIH Revitalization Act of 1993. Today, over half of participants in NIH-funded clinical trials are women.

Taken together, the SABV policy and inclusion of women in clinical studies will help ensure that sex is considered throughout the research process — from basic to preclinical to clinical studies — so that both women and men, as well as girls and boys, can receive the full benefit of biomedical investigations. Accounting for SABV enhances transparency and rigor and can lead to discoveries that pave the way to delivering truly personalized care to each individual.

Janine A. Clayton, M.D.

Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health
September 2017



Preface

This **Report of the Advisory Committee on Research on Women’s Health for Fiscal Years 2015 and 2016** describes the programs and initiatives undertaken across the National Institutes of Health (NIH) in service of the core mission of the Office of Research on Women’s Health (ORWH). That mission—as outlined in the NIH Revitalization Act of 1993 (Public Law 103-43, Section 486B)—is to strengthen and enhance NIH basic, translational, and clinical research with the following goals:

- To increase the understanding of the diseases and conditions that affect women, including investigation and elucidation of the role of sex and gender factors in health and disease
- To build NIH programs to develop a cadre of researchers, both women and men, who are trained to conduct interdisciplinary research in these areas
- To ensure the appropriate representation of women in NIH research
- To support the advancement of women in biomedical careers

The members of the Advisory Committee on Research on Women’s Health (ACRWH) are pleased to submit this report to the NIH Director, through the Associate Director of Research on Women’s Health.

Over the past year, ORWH has been actively involved in implementing the NIH policy requiring research funded by NIH to incorporate sex as a biological variable (SABV), a policy that will improve the health of both women and men. The adoption of this policy and the establishment of the trans-NIH SABV Working Group have contributed substantively to NIH’s efforts to improve rigor and transparency in biomedical research. The Working Group has played a key role in the development

and coordination of the SABV policy among the NIH Institutes and Centers (ICs). The rationale behind the new policy was recently published in “Studying both sexes: a guiding principle for biomedicine”¹ and addresses the entire research community, both inside and outside the NIH.

The members of the ACRWH have reviewed this biennial report and find that it provides essential information about the research, programs, and related activities of ORWH. The report describes the breadth and depth of the work ORWH undertook to achieve its mission in fiscal year (FY) 15 and FY 16, including:

- NIH-supported research on women’s health and on the influence of sex and gender on health and disease. This research was supported by ICs across the NIH, as well as by program offices within the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) in the NIH Office of the Director
- NIH budget allocations for women’s health research during FY 15 and FY 16, as supplied by the U.S. Department of Health and Human Services’ Office of the Assistant Secretary for Financial Resources
- The inclusion of women and minorities in NIH-funded clinical research during these years and the implementation of the new SABV policy, which became effective January 25, 2016

Established in 1990, ORWH is committed to promoting women’s health by supporting research on diseases and conditions that affect women and by ensuring that women are appropriately represented in all NIH-supported research studies. The ORWH Director had a significant role in establishing and disseminating NIH’s SABV policy, and continues to foster and facilitate activities in support of the ORWH mission. The ACRWH also

¹ Clayton, JA. *FASEB J.* 2016 Feb;30(2)519–24



acknowledges the accomplishments of the NIH Coordinating Committee on Research on Women's Health (see **Appendix A**), the trans-NIH SABV Working Group, the Working Group on Raising the Bar, and the NIH Working Group on Women in Biomedical Careers. These dedicated professionals are furthering the cause of women's health in significant and meaningful ways.

At the heart of ORWH's success is its diverse staff, consummate professionals from a range of backgrounds and scientific disciplines. The ACRWH recognizes that none of ORWH's accomplishments, either at NIH or in the broader research community, would be possible without their exemplary work and leadership.

Advisory Committee on Research on Women's Health, FY 15–16

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Director, Office of Research on Women's Health
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Organization of the FY 15–16 Report of the Advisory Committee on Research on Women’s Health

The FY 15–16 report of the ACRWH illustrates how the NIH has put science to work for the health of women. Highlighted in the following sections are examples of implementation of the SABV policy, ORWH research programs, initiatives, activities, and research on women’s health undertaken at ICs across the NIH. It highlights NIH research on women’s health, but it is not an exhaustive listing. Rather, the projects described herein illustrate the breadth and depth of work to further women’s health that the NIH is undertaking.

This report is divided into two major parts. Part 1 describes ORWH activities and programs. In Part 2, the individual NIH ICs and program offices in the NIH Office of the Director report on their own successful efforts and ongoing work to promote women’s health research.

Part 1

- I. ORWH Background
- II. ORWH Research
- III. ORWH Biomedical Career Development Activities
- IV. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research
- V. NIH Budget for Women’s Health Research

Section I: ORWH Background describes ORWH’s development and mission. It provides historical perspective for the Office, describes the significant research gap addressed by the SABV policy, and places that policy in the context of the NIH Strategic Plan for Women’s Health Research.

Section II: ORWH Research provides an overview of the Office’s ability to leverage research investments and co-funding dollars to encourage novel approaches to answering key questions that will drive the research of all fields toward a

better understanding of the biology of male and female subjects. It also highlights specific ORWH programs to advance women’s health research and outlines activities for disseminating such research to broader, more diverse audiences.

Section III: ORWH Biomedical Career

Development Activities highlights programs designed to increase the number of women in biomedical careers as well as the number of researchers focused on women’s health concerns. It describes training and mentoring programs and programs that facilitate reentry of women into the biomedical workforce after an extended absence.

Section IV: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

describes efforts to monitor and foster the inclusion of women and minorities in NIH-funded clinical research. It includes aggregate data on the numbers of women and minorities who participated in this research.

Section V: NIH Budget for Women’s Health

Research outlines NIH’s funding of research that focuses on diseases and conditions relevant to women. It includes expenditures for specific diseases, conditions, and initiatives, showing the amounts allocated specifically for research on women’s health, men’s health, and both women’s and men’s health. It also provides the total dollar amounts and percentages of the NIH research allocations for women only and men only.

Part 2

Part 2 contains reports from the individual NIH Institutes, Centers, and Offices summarizing each one’s research, publications, and other efforts related to furthering women’s health. The biennial report appendices also are available online at www.nih.gov/women.





REPORT OF THE
OFFICE OF RESEARCH
ON WOMEN'S HEALTH



I. ORWH Background

The History of the Office of Research on Women's Health

ORWH has a long history of highlighting and promoting efforts to improve knowledge about women's health at the NIH through research on women's health, inclusion of women in research, and support for women in biomedical careers. ORWH's path began in 1983, when the U.S. Public Health Service Task Force on Women's Health Issues was established by Assistant Secretary for Health, Dr. Edward N. Brandt, Jr., in response to the lack of research on diseases, conditions, and disorders that affect women. Two years later, the Task Force published a report, "Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume I," recommending an expansion of women's health research (U.S. Public Health Service, 1985), and the next year the NIH incorporated a policy in line with these recommendations, urging greater inclusion of women in its clinical research (NIH, 1986a; NIH, 1986b). The following year, an additional policy recommended similar efforts to increase inclusion of minority populations in clinical research (NIH, 1987). In response to a request from the Congressional Caucus for Women's Issues, the General Accounting Office, now known as the Government Accountability Office, investigated the implementation of these policies in 1990 and found a number of issues hindering their uptake, including poor communication of the new standards, delays in implementation, and a continued lack of routine gender analysis in studies (NIH, 1990). The study also found that implementation of these policies had caused little effect overall.

These findings prompted the establishment of ORWH that year within the Office of the Director, and in 1993, the NIH Revitalization Act established the ORWH in statute. The ORWH Director is mandated by this act to advise the NIH Director and

staff on issues related to women's health research, strengthen research on health issues that affect women, ensure NIH research addresses women's health and includes appropriate representation of women, and develop opportunities for women in biomedical careers. The ORWH Director also must support research on women's health broadly.

Additionally, the Act created two committees that advise the ORWH Director on issues related to women's health research. The Advisory Committee on Research on Women's Health is comprised of leading non-federal experts in many fields and provides the ORWH Director with recommendations from an external perspective. The Coordinating Committee on Research on Women's Health is a trans-NIH group of IC directors or their designees who can offer suggestions utilizing internal knowledge of the NIH and its processes.

In 2006 the NIH Reform Act required a reorganization of the NIH Office of the Director. ORWH was placed in the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), which focuses on trans-NIH concerns. ORWH's statutory responsibilities were unchanged, but its new placement under DPCPSI emphasized its role as the focal point for NIH's research on women's health across the ICs. This interconnection allows ORWH to fully engage with ICs and ensure that all science at the NIH properly incorporates women's health. ORWH's current mission statement emphasizes the importance of biomedical research that appropriately includes women and considers sex and gender, and it also highlights ORWH's role in facilitating this research to improve women's health. Additional efforts shepherded by ORWH include understanding and assuaging disparities among populations of women defined by demographic factors, including age, socioeconomic status, and racial and ethnic group membership, and supporting research and training in interdisciplinary areas.

NIH Strategic Plan for Women's Health Research and Emerging Strategic Priorities

Guiding Tomorrow's Research on Women's Health

In September 2010, ORWH released the Trans-NIH strategic plan for research on women's health entitled, "Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research" (ORWH, NIH, HHS, 2010a; ORWH, NIH, HHS, 2010b; ORWH, NIH, HHS, 2010c). This research agenda was informed by input from the scientific community and public partnerships including patient and advocacy groups. Three volumes—an executive summary, reports from regional scientific workshops, and public testimony—summarize the NIH Strategic Plan for Research on Women's Health for 2010–2020. These documents serve as a framework for research investigations galvanized by cutting-edge technologies and emerging scientific concepts to advance women's health research through collaborations among the disciplines and across the research spectrum, from basic to clinical and translational (Pinn, Clayton, Begg, & Sass, 2010). In addition to providing a framework for research on the health of women across NIH ICs, it guides all

ORWH activity, ensuring that the Office allocates resources to capitalize on key opportunities for advancing scientific research and aids in the advancement of scientific career objectives.

The research agenda comprises the following six crosscutting goals, each containing several objectives:

- Increase the study of sex differences in basic biomedical and behavioral research.
- Incorporate findings of sex differences in the design of new technologies, medical devices, and therapeutic drugs.
- Actualize personalized prevention, diagnostics, and therapeutics for women and girls.
- Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research.
- Achieve a clearer and wider understanding of women's health issues through strategic communications of research findings to diverse audiences.
- Employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce.

Read the entire strategic plan at www.orwh.od.nih.gov/research/strategicplan/index.asp.

The mission statement of ORWH continues to emphasize its historic role in improving women's health through research.



Increasing Consideration of Sex in Preclinical Research

The NIH Strategic Plan of 2010, “Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women’s Health Research” (ORWH, NIH, HHS, 2010), outlined areas in which ORWH can move forward with its efforts to improve the foundation of knowledge about women’s health. This strategic plan evaluated and highlighted areas in which women’s health knowledge was particularly lacking; the most critical gap was the dearth of preclinical research data related to female biology, physiology, and pathology. This gap was caused by the historical tendency of research studies to include primarily male animals, ignore the sex of cell study donors, and overlook any potential differences in study effects between males and females.

Assuaging this gap in animal and cell model research knowledge is critical, because these models provide foundational knowledge about basic biological processes and pathways to treatment of both male and female humans. ORWH’s current mission includes significant participation in the NIH-wide efforts to ensure that all studies appropriately address sex as a biological variable (SABV) by including males and females in research studies and considering potential effects of sex on study results. These efforts are a component of the NIH’s broad efforts to increase rigor, reproducibility, and transparency² in all NIH-funded research.

ORWH now is collaborating in this project with the Office of Extramural Research (OER), prompted by a 2014 paper published in *Nature* by ORWH Director Janine Clayton and NIH Director Francis Collins urging greater consideration of SABV in animal and cell studies. The collaboration between ORWH and OER focuses on ensuring that NIH-

² NOT-OD-15-103: Enhancing Reproducibility through Rigor and Transparency - grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html

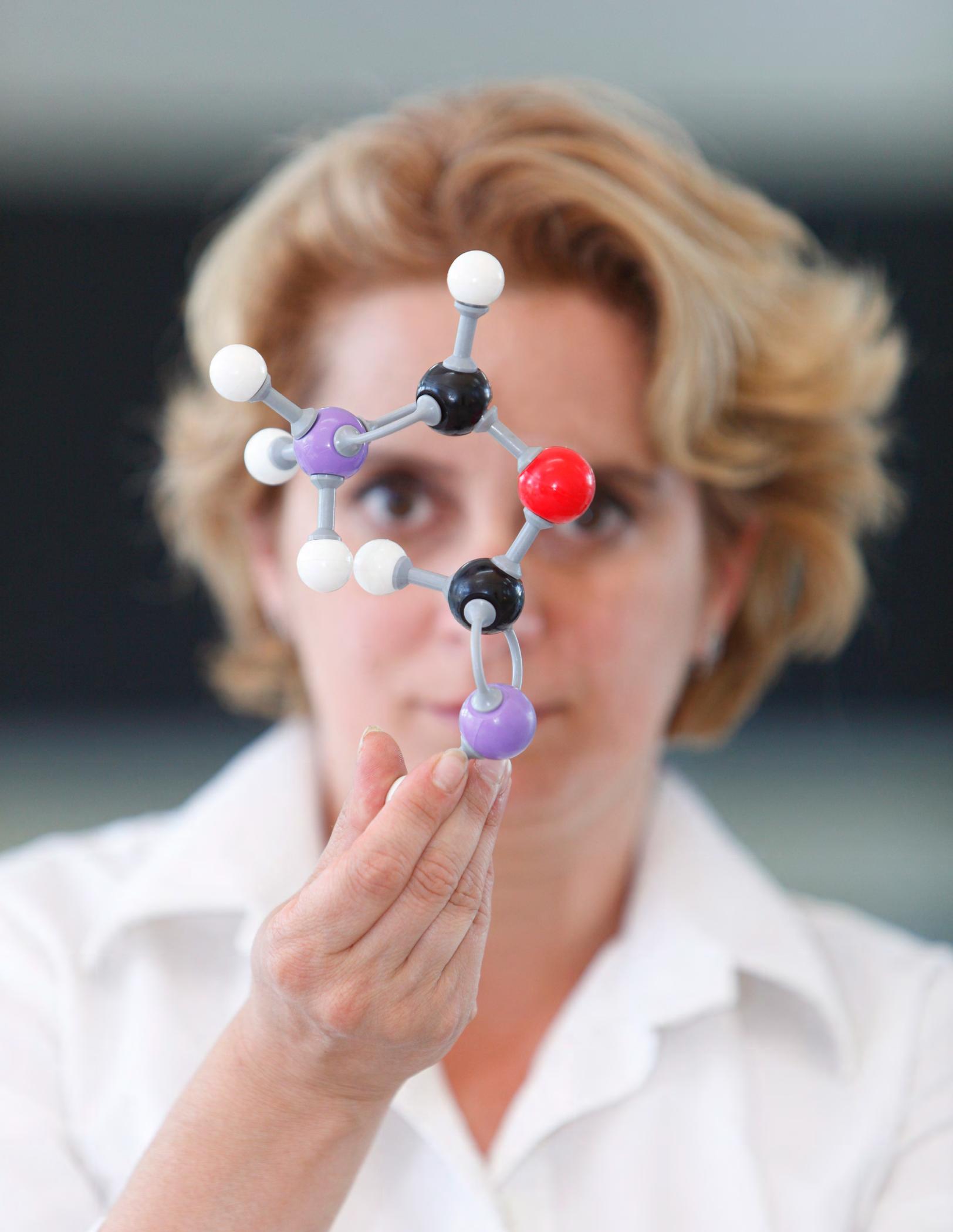
funded research purposefully addresses the biology of females and males. As of January 2016, scientists are required to account for SABV in studies of vertebrate animals and humans.³ The appropriate strategy to do so will depend on the research question and the current understanding of sex influences on that question, but applicants must define how they plan to account for SABV, and study sections must assess these plans.

ORWH is actively helping to implement these programs across NIH and with its external stakeholders by providing supplemental funding to existing NIH grants to add the subjects, tissues, or cells necessary to study both sexes equally and providing funding to increase the power of a study to ensure that it can address differences in sex or gender.

³ NIH Guide Notice NOT-OD-15-002: Consideration of Sex as a Biological Variable in NIH-funded Research: grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html

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II. ORWH Research

Introduction

Research Mission

Housed within the NIH Office of the Director, ORWH's mission is to help put science to work for the health of women. This includes stewardship of research on the diseases, disorders, and conditions that affect women's health. ORWH works across the NIH to ensure that women are appropriately represented in biomedical and behavioral research studies funded by the NIH and promotes exploration of SABV to ensure that key sex influences in biomedical research and clinical trials are not overlooked. ORWH promotes effective interdisciplinary and collaborative partnerships and invests in programs that strengthen the diversity of the biomedical workforce. At the core of ORWH's research efforts is collaboration with the NIH ICs to co-fund research in these areas and to implement the 2010–2020 NIH Strategic Plan for Women's Health Research.

ORWH: Driving the NIH Women's Health Research Agenda

Consideration of SABV is necessary to illuminate potential differences in females and males, both in terms of the way diseases or conditions present and the effects of treatments. ORWH's commitment to women's health depends on supporting research that can lead to safe, effective clinical care for women, which is only possible when clinicians fully understand how treatments will affect women. ORWH fulfills this commitment by partnering with ICs to fund research that will address gaps or topics specific to women's health. When a topic or area in need of further study is identified, typically by a strategic plan or conference of experts, ORWH may issue a Funding Opportunity Announcement (FOA) to prompt research that would address this gap. Successful programs that have been developed through such FOAs include the Specialized

Centers of Research on Sex Differences program, the Building Interdisciplinary Research Careers in Women's Health program, and administrative supplements.

In addition to FOAs produced by or with the support of ORWH, funding of women's health research also may be initiated via an internal request for co-funding from an IC. These requests are submitted to ORWH on a regular basis and carefully reviewed to determine whether such research would support ORWH's research mission and the goals of the 2010 Strategic Plan. Links to the abstracts for all supported projects are listed in Appendix B.

ORWH Programs to Advance Women's Health Research and Understanding of the Influence of Sex and Gender on Health and Disease

SCOR on Sex Differences

The Specialized Centers of Research (SCOR) program was established in 2002 to foster interdisciplinary and collaborative approaches to bridge basic and clinical research on sex differences. These SCOR programs were funded as Specialized Center (P50) awards in major health areas, including musculoskeletal diseases; vascular dysfunction; health of the urinary tract; pain; depression; cognitive decline; substance use; tobacco dependence; and reproductive health, such as polycystic ovary syndrome, hormonal transitions, and the pelvic floor consequences of the reproductive process. ORWH works in partnership with NIH ICs and the U.S. Food and Drug Administration's (FDA) Office of Women's Health to implement and fund this program. Currently, ORWH is supporting 11 SCORs with co-funding from six NIH institutes (NIA, NIDA, NIMH, NICHD, NIAMS, and NIDDK).



- In FY 15, ORWH funding for the SCORs was \$9.39 million
- In FY 16, ORWH funding for the SCORs was \$9.45 million

Since FY 13, ORWH has sponsored an annual SCOR Directors' meeting at the NIH campus. These meetings highlighted the benefits of interdisciplinary and translational research and team science, providing a forum for presentations on scientific advances from the SCOR.

Research from the SCOR program has provided numerous insights into the sex differences observed in addiction and stress response, like gender-sensitive treatment for tobacco dependence, and sex differences and progesterone effects on impulsivity, smoking, and cocaine stress; musculoskeletal diseases; mental disorders, including depression, stress response, and the brain's response to drug cues and to treatment; pelvic floor dysfunction, fracture risk, and long-term outcomes; and understanding the mechanisms that are necessary for developing new therapeutic targets for recurring

urinary tract infections. Over the years, the SCOR program has led to successful cross-organization collaborations, team science approach, and high impact peer-reviewed publications and new therapies improving human health.

Administrative Supplements for Research on Sex/Gender Differences

In 2001, the Institute of Medicine (now the National Academy of Medicine) published a report titled "Exploring the Biological Contributions to Human Health: Does Sex Matter?"⁴ and highlighted that women and men are characterized by both sex and gender. In this context, sex was referred to as being male or female, according to the reproductive organs and biologic function assigned by chromosomal complement. Gender was referred to socially defined and derived expectations and roles rooted in biology and shaped by the environment and experience. Sex and gender are important considerations in many areas of research,

⁴ www.nap.edu/read/10028/chapter/1

including basic biological, psychological, social, and behavioral studies. Consideration of these variables is critical to the accurate interpretation and validation of research findings that affect the various aspects of women's health.

In 2013, ORWH initiated a trans-NIH program to catalyze exploratory research on sex and gender differences by providing administrative supplements to ongoing peer-reviewed NIH-funded grants. The administrative supplement initiative provided 1-year supplements of approximately \$100,000 total cost to funded research; new work and approaches were required to fall within the scope of the original funded "parent" grants. For preclinical work,⁵ applicants could propose the addition of subjects (human or animal models) or tissues or cells of the sex opposite to that used in the parent grant to allow sex-based comparisons. For both preclinical and clinical work, applicants could also propose the addition of more subjects (human or animal) of one sex to a sample that already included both males and females to increase the study's ability to analyze for sex/gender differences. For clinical, methodological, computational, and modeling research, applicants could also propose new analyses of existing samples containing data from male and female subjects.

Funding for FY 15 and FY 16:

- In FY 15, ORWH supported 74 awards with 18 ICs for a total of \$7.0 million
- In FY 16, ORWH awarded 61 supplements with 19 ICs for a total of \$6.0 million

Since the inception of this program in 2013, ORWH has invested almost \$24 million in supplemental funding by supporting 250 investigators across Institutes, Centers, and Offices at NIH to explore research on sex/gender differences in preclinical and clinical studies. To further advance this important area of research, ORWH anticipates continued funding for this program in FY 17. This effort directly addressed the policy proposal aimed at accounting for SABV in all biomedical research.

ORWH R56 Program

The ORWH R56 Program is a trans-NIH initiative by which ORWH partners with NIH Institutes, Centers, and Offices (ICOs) to fund or co-fund meritorious research on women's health that, without ORWH funding and support, would not otherwise be funded. The R56 activity code is a recognized NIH grant mechanism designed to provide short-term funding for high-priority projects. The objective of the R56 program is to allow the investigators to significantly improve their research proposal so that the submission/resubmission application can succeed in the highly competitive peer review and fiscal environment. In addition, the use of the R56 activity code can potentially enhance research in targeted areas, such as the influence of sex and gender on health and disease, by allowing the PI to incorporate new content into the revised application to address content relevant to the ORWH research mission. Only ICs can apply for R56 funding; investigators cannot directly submit R56 applications. Some of these projects involve novel and unique approaches to understanding women's health research problems and issues that may not be fully realized by the review score. Thus, ORWH funding helps promote novel, meritorious research projects on women's health.

The ORWH R56 Program was initially conceptualized in 1997, when ORWH created the Research Enhancement Awards Program (REAP). REAP developed into a larger collaborative program with the NIH Office of Behavioral and Social Science Research (OBSSR), similar in structure to the current R56 configuration, which was offered annually until 2014. In 2014, REAP was absorbed into the ORWH R56 Program with the structure as it is currently configured today. The R56 program is a collaborative effort sponsored by the following three program offices within DPCPSI: ORWH, the Office of AIDS Research, and the Office of Dietary Supplements. This collaboration greatly enhances the breadth, depth, and range of research topics of mutual interest available to NIH ICs.

⁵ Preclinical work is research using animals to find out if a drug, procedure, or treatment is likely to be useful. Preclinical studies take place before any testing in humans is done.

In FY 15, ten R56 projects were funded from eight ICs and NIH Offices for a total of \$2.98 million. Projects were funded in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) (2); National Institute on Aging (NIA) (1); National Institute on Alcohol Abuse and Alcoholism (NIAAA) (1); National Institute of Dental and Craniofacial Research (NIDCR) (1); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (2); National Institute of Mental Health (NIMH) (1); National Institute of Neurological Disorders and Stroke (NINDS) (1); and the Office of the Director (OD) (1). The research topics were:

1. Improving heart transplant allocation to reduce high waitlist mortality in women
2. Immune modulation of hypertension
3. Stress and decision-making in older persons: Toward a neurobehavioral phenotype
4. The interaction of varenicline, ethanol, and central nervous system development
5. Circulating microRNAs and TLR8 activation in chronic pain
6. Mitochondrial function and insulin sensitivity in African-American women
7. The female urinary microbiome and urinary incontinence
8. Neurodevelopmental features of sexual dimorphism in pediatric psychopathology
9. Estradiol and hippocampal development
10. Altering the physical microenvironment and enhancing lipid availability for *in vitro* follicle and oocyte development.

In FY 16, ORWH funded fourteen R56 applications from ten ICs: the National Cancer Institute (NCI) (1), NHLBI (1), NIA (1), NIAAA (1), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (2), National

Institute on Drug Abuse (NIDA) (3), NIDCR (1), National Institute of Environmental Sciences (NIEHS) (2), NIMH (1), and the National Institute of Nursing Research (NINR) (1). Selected abstracts for FY 15–16 are included at the end of this section. ORWH awarded \$4.13 million for applications addressing research on:

1. Tunable polymer-graphene oxide composite for single-cell analysis of breast cancer circulating tumor cells and cancer stem cells
2. Sex differences in angiotensin-induced vascular disease
3. Helping behavior in older adults
4. Impact of supportive policies on minority stress, drinking, and health among women
5. Follicle-stimulating hormone and IGF1R signaling crosstalk in ovarian granulosa cells
6. Ovarian-specific transcription networks regulated by the Transcription factor IID Subunit TAF4b
7. Strategies for reducing drug abuse in rhesus monkeys
8. Regulation of craving under stress: Novel model and neural mechanisms
9. Marijuana use and pregnancy
10. Proteins, microRNAs, and genes associated with temporomandibular disorders
11. Bisphenol A and phthalates: Effects on inflammatory markers in the breast and breast density in young women
12. Phthalates and ovarian toxicity
13. Interactions of 17-beta estradiol and ketamine on depression-like behavior, hippocampal synaptic function, and cognition in ovariectomized rats
14. Pain management for older adults in nursing homes.

Examples of R56 Grants Awarded

(A complete listing of R56 awardees and links to their abstracts can be found in Appendix B.)

Grant #: 2 R56 DK091462-04A1

Title: Mitochondrial function and insulin sensitivity in African-American women

The goal of the study is to better understand diabetes and obesity in African-American women (AAW). Objectives are (1) to evaluate insulin sensitivity (IS) and resistance (IR) in certain subpopulations, and (2) to investigate the contributions of mitochondria to sex differences and racial differences. Objective #1 will be studied by characterization of hepatic and peripheral IS, mitochondrial content and respiration, fiber type, and skeletal muscle lipid accumulation in obese AAW versus Caucasian women (CW). Objective #2 will examine potential mechanisms for racial differences in mitochondrial capacity by assessments of reactive oxygen species production and protein levels involved in fission/fusion/mitophagy and glucose transport in obese AAW and CW. The study will also examine the relationship between genetic admixture, mitochondrial haplotype, mitochondrial function, and insulin sensitivity. Potential impacts include possibilities to learn essential information that expands our knowledge of racial differences in diabetes, racial differences in mitochondrial function and IS, and expand our understanding of the relationship between mitochondrial function and IR in skeletal muscle.

Grant #: 1 R56 HL125420-01A1

Title: Improving heart transplant allocation to reduce high waitlist mortality in women

The goals of the study are to understand why women awaiting heart transplantation have a higher mortality rate than men, and to optimize timing and candidacy for advanced heart failure therapy to reduce heart transplant waitlist mortality. Objectives are (1) to evaluate sex differences in heart transplant waitlist mortality, and (2) to create a survival model that better predicts need for advanced heart failure therapy. Objective #1 will correlate sex-specific risk factors versus survival in heart failure patients awaiting transplantation. Objective #2 will develop the survival model using the Scientific Registry of Transplant Recipients, and validate the model for prediction of mortality for the overall target population. The proposed research is significant because the approach uses innovative machine-learning statistical methods, the results may suggest improvements to the transplantation allocation system, and few studies have explored sex differences in prognostic risk factors despite known sex differences in heart failure survival.

ORWH Co-funding with ICs in Targeted Research Areas

Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative

The BRAIN Initiative (www.braininitiative.nih.gov and www.braininitiative.org) catalyzes the development and application of innovative technologies to revolutionize our understanding of the human brain. Despite the many advances in neuroscience in recent years, the underlying causes of most neurological and psychiatric

conditions remain largely unknown due to the vast complexity of the human brain. To develop effective ways of helping people suffering from these devastating conditions, researchers will first need a more complete arsenal of tools and methods for understanding how the brain functions both in health and disease. ORWH continues to support this initiative with other participating NIH ICs, focusing on opportunities to explore new and emerging methods for large scale recording of neural circuits across multiple brain regions, computational modeling of brain function, and for overcoming barriers to more invasive types of brain recording. ORWH's investment will deepen our

understanding of fundamental brain processes and will lay the foundation to address major gaps in our current knowledge.

Pain Research at NIH

The NIH Pain Consortium⁶ was established to enhance pain research and promote collaboration among researchers across the many NIH ICs that have programs and activities addressing pain. The consortium supports initiatives, develops research resources and tools, and hosts events to promote collaboration and highlight advances in pain research. ORWH recognizes the significant difference between women and men in pain perception and reporting as well as the number and severity of pain conditions that overwhelmingly affect women more than men. In this capacity, ORWH plays a major role in integrating SABV in all pain research conducted with NIH support. Created in 2015, ORWH supports the Centers of Excellence in Pain Education⁷ that will act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing, and pharmacy schools. ORWH also co-funds research projects under the Chronic Overlapping Pain Conditions FOA⁸ initiatives addressing pain management and prescription pain drug use by women⁹ and research on the neurobiology of migraine.¹⁰ ORWH also contributed staff expertise to help develop the National Pain Strategy¹¹ which includes population research, health disparities, prevention and care, professional education and training, and public education and communication.

⁶ www.painconsortium.nih.gov/index.html

⁷ www.painconsortium.nih.gov/Funding_Research/CoEPEs

⁸ www.grants.nih.gov/grants/guide/pa-files/pa-14-244.html; grants.nih.gov/grants/guide/pa-files/pa-14-243.html

⁹ www.prevention.nih.gov/programs-events/pathways-to-prevention/workshops/opioids-chronic-pain

¹⁰ www.grants.nih.gov/grants/guide/pa-files/pa-14-069.html; grants.nih.gov/grants/guide/pa-files/pa-14-068.html

¹¹ www.iprcc.nih.gov

¹² Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Scientific and Data Coordinating Centers (U01) (www.grants.nih.gov/grants/guide/rfa-files/rfa-dk-14-018.html) and Lower Urinary Tract Symptoms in Women: Bladder Health Clinical Centers (PLUS-CCs) (U01) (www.grants.nih.gov/grants/guide/rfa-files/rfa-dk-14-004.html)

¹³ www.grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-507.html

Bladder Health, Lower Urinary Tract Symptoms, and Chronic Pelvic Pain Disorders Research

Urologic diseases affect women and men of all ages and result in significant health impairment and quality of life issues. Programs from NIDDK support basic and clinical research on the normal and abnormal development, structure, function, and injury repair of the genitourinary tract. Lower urinary tract symptoms are associated with a broad range of diagnoses including bladder infections, urinary incontinence, voiding dysfunction, overactive bladder and interstitial cystitis/bladder pain syndrome. These symptoms are common, costly, and consequential for females from childhood to old age.

ORWH cosponsors and supports a range of unique research, including research on the identification and characterization of modifiable risk factors for lower urinary tract symptoms and urinary incontinence in women through center grants.¹² ORWH also supports research on the identification of biomarkers for diagnosis or treatment of multiple painful bladder conditions through the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network and the Limited Competition of the MAPP Research Network.¹³ With co-funding from ORWH, projects for the bladder health initiative began in FY 15, and are progressing well. For more information, please see www.niddk.nih.gov/about-niddk/strategic-plans-reports/Pages/NIDDK-recent-advances-emerging-opportunities-2015.aspx.



Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study

Originally funded in the mid-1990s, the Diabetes Prevention Program (DPP) was a randomized, controlled clinical trial that determined whether certain interventions could prevent or delay type 2 diabetes (T2D) in adults at high-risk for developing the disease. The multicenter study enrolled 3,234 overweight participants with blood glucose levels that were higher than normal but not yet in the diabetic range. Forty-five percent of participants were from minority groups that are disproportionately affected by T2D: African Americans, Hispanic, Asian, Pacific Islanders, and American Indians. The trial also recruited other groups at higher risk for T2D, including individuals age 60 and older, women with a history of gestational diabetes, and people who have a first-degree relative with T2D. The DPP intervention group demonstrated the beneficial effects of

lifestyle interventions and metformin, as compared to a placebo group, in preventing or delaying the onset of T2D over a 3-year period. Based on these results, the DPP lifestyle program was widely implemented. Subsequently, the DPP Outcomes Study (DPPOS) was then established to explore the longer-term effects of T2D prevention, bridging the period between pre-diabetes and T2D, based on the treatment regimen in the DPP and the risk for micro-cardiovascular disease and stroke incidence and severity.

The DPPOS has continued to evaluate the participants, especially the longer-term effects of metformin and lifestyle changes on the rates of cardiovascular disease and cancer. Sixty-seven percent of the DPPOS cohort is women, and sex differences in the rates of these outcomes will be evaluated. ORWH support facilitated recruitment and retention of these women.

For more information, please see www.niddk.nih.gov/news/for-reporters/diabetes-prevention-program-outcomes-study/pages/default.aspx.

Osteoarthritis Initiative

Osteoarthritis (OA) affects more than 27 million individuals in the United States. Knee OA is associated with significant pain and the development of disability over time. People who are severely compromised have few effective treatment options other than joint replacement. Differences exist in the prevalence, incidence, and severity of OA between men and women and among races. Currently, no disease-modifying agents are available for treating OA.

The discovery of OA biomarkers, including structural characteristics that can be observed with magnetic resonance imaging, could lead to the identification of new treatment targets and mechanisms for shorter, more efficient trials of disease-modifying agents. The Osteoarthritis Initiative (OAI) is a multicenter, longitudinal, prospective observational study of knee OA. OAI is a public-private partnership between NIH and private industry that seeks to improve the diagnosis and monitoring of OA and foster the development of new treatments. The OAI cohort of 4,796 participants is 58 percent female and, at the time of recruitment, ranged in age from 45 to 79 years. As of fiscal year 2016, the entire OAI cohort had completed baseline, 12-month, 24-month, 36-month, 48-month, and 72-month, visits in a clinic with questionnaires, a functional exam, biospecimen collection, and imaging.

Data and images have been publicly released from all visits and are available on the OAI website. To date, clinical data, images, and biospecimens are available for visits through 96 months. Nearly 400 manuscripts have been produced and published to date based on use of the OAI data and images (see www.oai.ucsf.edu/datarelease/Publications.asp). For more information, please see www.niams.nih.gov/grants-funding/funded-research/osteoarthritis-initiative.

With support from ORWH and other NIH components, NIAMS provides a robust information dissemination and outreach program to distribute research-based information to patients, health care providers, and other members of the public. For example, NIAMS oversees the NIH Osteoporosis and Related Bone Diseases National Resource Center (ORBD~NRC), which is co-funded by NIA, NICHD, NIDCR, NIDDK, ORWH, and the U.S. Department of Health and Human Services' Office on Women's Health.

ORWH Research Dissemination Activities

In FY 15 and FY 16, ORWH continued to leverage new and innovative strategies and technologies to engage with its internal and external stakeholders and partners. These tools and strategies allow ORWH to effectively and efficiently strategize, plan, and execute communications activities, initiatives, and events. ORWH continues to develop and implement new communication and social networking technologies to increase understanding and appreciation of women's health research as well as research on SABV's impact on health. ORWH has continued to accomplish these goals by working closely with partners across the Federal Government and with elected representatives, the media, health and advocacy organizations, and the public. Major FY 15 and FY 16 research dissemination activities are described below.

ORWH Website: Putting Science to Work for the Health of Women

ORWH launched its newly designed website in September 2016. Important women's health content and new research reports and spotlights, such as the Improving the Health of Women in the United States report, the Women of Color Health Data Book, the A to Z guide on sex and gender influences on health, and the free online courses on sex and gender in health and disease are now available across all platforms, including desktops, tablets, and mobile devices. ORWH's

digital resources and materials are widely accessible to audiences and comply with plain language standards.

Research Meetings, Conferences, and Workshops

ORWH keeps abreast of the current status of specific scientific areas and considers where further stimulus may be needed. This is accomplished through NIH sponsored meetings, conferences, and workshops where scientific experts and other stakeholders in women's health discuss current clinical and research advances. These activities often inspire the development of new funding opportunities. In some cases, ORWH holds meetings, conferences, and workshops to provide a forum for educating researchers on techniques or methods to enhance their understanding of the complexities associated with a particular research field. A list of meetings, conferences, and workshops that ORWH sponsored or cosponsored, along with short descriptions of the purpose of these events, is provided below.

Meetings, Conferences, and Workshops Held in FY 15–16

39th NIH Advisory Committee Meeting on Research on Women's Health

Sponsored by ORWH, April 10, 2015

This advisory committee meeting featured presentations and discussion topics including sex-focused experimental design, methods and statistics, gender gaps in cardiovascular care, and the health of women in the United States.

Raising the Bar: Improving the Health of Women in America

Co-sponsored by ORWH, September 25, 2015

ORWH and the National Academies of Sciences, Engineering, and Medicine held a workshop on why women in the United States are less healthy than women in other high-income countries. The workshop, "Raising the Bar: Improving the Health

of Women in the United States," sought to identify ways to reverse this growing disparity. The goal of the Raising the Bar workshop was to drill down on the causes of the differences in health outcomes, including higher mortality, between U.S. women compared with women in peer countries and to develop a research agenda to systematically reverse this trend.

40th NIH Advisory Committee Meeting on Research on Women's Health

Sponsored by ORWH, October 20, 2015

This advisory committee meeting included a celebration of science in honor of ORWH's 25th anniversary and featured presentations and discussion topics including ORWH's Building Interdisciplinary Research Careers in Women's Health and Specialized Centers for Research on Sex Differences Programs, SABV, and the NIH-ORWH Outreach Toolkit, created to engage, recruit, and retain women in clinical research.

41st NIH Advisory Committee Meeting on Research on Women's Health

Sponsored by ORWH, April 19, 2016

This advisory committee meeting included information on the relationship of the SABV Policy to scientific rigor, reproducibility, and transparency. The Mid-Course Progress Report on the NIH Strategic Plan for Women's Health Research was also presented. Additionally, the meeting featured a special presentation by NICHD Acting Director Catherine Spong, M.D., on the Zika virus. Michael S. Lauer, M.D., Deputy Director for Extramural Research, OER, NIH, discussed evidence-based funding, and George Koob, Ph.D., NIAAA Director, spoke about sex differences in addiction.

Inaugural Vivian W. Pinn, M.D. Symposium

Sponsored by ORWH, May 10, 2016

The NIH Vivian W. Pinn Symposium recognizes Vivian Pinn, M.D., the first full-time director of ORWH (1991 to 2011), acknowledging her longstanding leadership in women's health research. Throughout her 20-year career as director

of ORWH, Dr. Pinn was dedicated to enhancing women's health research at NIH and led efforts to implement and monitor the inclusion of women and minorities in clinical research. The annual symposium highlights key topics that are relevant to scientific audiences or the general public. The inaugural event was held during the 17th Annual National Women's Health Week, featuring a keynote address from Lauren Wood, M.D., on the value of translational research to women and a new NCI vaccine study.

Bridging Knowledge Gaps to Understand How Zika Virus Exposure and Infection Affect Child Development

Cosponsored by ORWH, September 22–23, 2016

ORWH and NICHD cosponsored this workshop to (1) develop research strategies on how to appropriately assess, evaluate, and monitor the neonate/infant/child affected by the Zika virus based on available clinical guidelines; (2) identify research strategies to improve evaluation for new/emerging complications of *in utero* Zika virus exposure and infection and understand the prospective impact of these complications on the developing child; (3) use available information from other vertically transmitted pathogens to provide

recommendations for assessment, evaluation, and management; (4) outline the research needs for treatment and rehabilitation approaches that optimize cognitive and physical function for Zika-affected children; and (5) evaluate and expand on treatment options currently offered.

42nd NIH Advisory Committee Meeting on Research on Women's Health

Sponsored by ORWH, September, 27, 2016

This advisory committee meeting featured a timely presentation from the National Institute of Allergy and Infectious Diseases (NIAID) Director Anthony Fauci, M.D., on the Zika virus. At the meeting, Dr. Fauci reported that NIAID is accelerating research in areas such as the natural history of the disease, basic research on the Zika virus, how it causes disease (called pathogenesis), and diagnostics to rapidly determine if someone is or has been infected with Zika and to distinguish from other flaviviruses, as well as treatments and vaccines. Other presentation topics included sexual and gender minority research activities at NIH, the role of sociodemographic characteristics on pain care, the Raising the Bar report, and the inclusion policy in NIH clinical research.

ORWH holds meetings, conferences, and workshops to educate researchers on techniques to enhance understanding of complexities associated with a particular research field.





III. ORWH Biomedical Career Development Activities

This section summarizes FY 15–16 ORWH support in two major areas: (1) interdisciplinary research and career development programs and (2) career development opportunities for women in biomedical research.

ORWH research and career development programs are based on the view that interdisciplinary approaches are essential to moving forward the science associated with women’s health and to increase understanding of the influence of sex and gender on human health and disease. Furthermore, they are designed to advance research in women’s health and sex differences that can be translated into clinical practice. These programs use the institutional career development (K12) mechanism.

A major component of the ORWH mandate is to develop opportunities and support for the recruitment, retention, reentry, and sustained advancement of women in biomedical careers. Accordingly, ORWH has initiated programs to nurture the participation and advancement of women in biomedical careers and to address career issues and barriers to participation.

Building Interdisciplinary Research Careers in Women’s Health (BIRCWH)

ORWH designed, developed, and implemented the BIRCWH K12 program in 1999 to increase the number and skills of investigators that conduct research on sex/gender influences on health. BIRCWH provides for mentored research training and career development that prepares investigators for independent scientific careers. BIRCWH funding provides opportunities for training and development that would otherwise not be available to facilitate the transition to research independence for junior faculty researchers who are conducting interdisciplinary research in women’s health.

The BIRCWH Program is built around three pillars: interdisciplinary research, mentoring, and career development. Interdisciplinary research, as defined by the National Academy of Sciences, is a mode of research that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines or bodies of specialized knowledge to advance fundamental understanding, or to solve problems whose solutions are beyond the scope of a single discipline or area of research practice. As such, interdisciplinary science teams work to advance fundamental understanding and solve problems that those from a single discipline could not.

ORWH and its NIH IC partners consider interdisciplinary mentoring teams an essential component of the BIRCWH Program. These teams usually include mentors from diverse disciplines to carry out interdisciplinary research projects. Team members and mentors may include individuals from medical, dentistry, pharmacy, nursing, biotechnology, social sciences, bioengineering, anthropology, genetics, and other disciplines representing different perspectives and areas of expertise. These mentoring teams come together to collaborate as a unit, with the common goal of supporting a BIRCWH Scholar in the transition from trainee to independent researcher. The interdisciplinary team approach is applied to the study of women’s health across the lifespan, bridging basic and clinical science and incorporating new models of collaboration and institutional support. In most of the BIRCWH programs, the program directors and principal investigators, sponsoring and collaborating departments, centers, or institutes, form an inter-professional, team-based approach for mentoring BIRCWH Scholars. Mentors from collaborating departments provide needed expertise and resources to the BIRCWH Scholars’ projects on research relevant to women’s health, including



research on sex and gender influences, as well as research on factors that contribute to disparities in health status or health outcomes for different populations of women.

To understand whether the BIRCWH program has been meeting its intermediate and long-term goals, and to determine whether changes in program management and policies are warranted prior to the reissuance of an RFA in the next calendar year, an evaluation of the BIRCWH program using a mixed-methods approach was conducted in FY 15. Surveys and interviews were administered to gather both qualitative and quantitative data from current and former principal investigators, mentors, scholars, and NIH staff involved with the BIRCWH program.

Since the BIRCWH program's inception in FY 2000, ORWH has made 81 K12 institutional career development grant awards to 45 academic institutions that have sponsored 630 Scholars, based in more than 28 U.S. states. The program continues to expand the network of scientists and clinicians who have the interdisciplinary research skills to further the study of women's health and sex differences. As of the end of FY 16, 24 BIRCWH

programs were actively funded across the country. Approximately 70 percent of BIRCWH scholars had submitted at least one research project grant application after completing their BIRCWH scholar appointment. Among those who applied, 49 percent of the Scholars ultimately received an award from NIH and other Federal funding agencies.

ORWH is responsible for the programmatic aspects of the BIRCWH program, and the grants management is provided by NICHD. The first BIRCWH grants were awarded in FY 2000. From FY 2000 through FY 16, ORWH has issued eight requests for applications (RFAs) through the *NIH Guide to Grants and Contracts*. Over the 16 years, ORWH has been joined in its funding support by the Agency for Healthcare Research and Quality and many NIH ICs, including NCI, NIA, NIAID, NIAAA, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NICHD, NIDCR, NIDA, NIEHS, NIMH, NINDS, and the NIH Office of Dietary Supplements.

Between FY 2000 and FY 16, ORWH has provided nearly \$146,905,011 million in funding for the BIRCWH program. Another round of BIRCWH

awards was funded via an RFA in FY 15. Seven NIH Institutes – NIA, NIAID, NIAMS, NICHD, NIDCR, NIDA and NIEHS – joined ORWH in this reissued RFA, RFA-OD-15-001 (www.grants.nih.gov/grants/guide/rfa-files/rfa-od-15-001.html). For more information on the 24 current BIRCWH awardees, please see **Table 1**. The most recent BIRCWH RFA, www.grants.nih.gov/grants/guide/rfa-files/RFA-OD-16-013.html, was re-issued and published in the *NIH Guide to Grants and Contracts* in July 2016 for funding in FY 17.

Program Outcomes to Date

A primary goal of the BIRCWH program is to support scholars by providing them with protected time to receive career development, to conduct their research and achieve research independence. While the BIRCWH program is open to both women and men, 81 percent of the BIRCWH scholars were women between FY 2000 and FY 13, the most recent period of reporting. Of these, 137 (24 percent) were active BIRCWH scholars, and 443 (76 percent) had completed their BIRCWH program. The information that follows focuses on the BIRCWH scholars who submitted and obtained NIH research project grants. The information is based on data maintained by ORWH and the NICHD Office of Science Policy, Analysis, and Communication.

BIRCWH Scholar Funding Success Since FY 2000

About 40 percent (N=231) of BIRCWH scholars submitted at least one *NIH Mentored Career (K) grant application* after their BIRCWH start date. Of those, 45 percent received an award.

- About 70 percent of scholars (N=408) submitted at least one *NIH research grant application*, and 49 percent of the applicants eventually received at least one NIH research grant.

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81 awards to 45
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- In addition to large independent research grants (R01), substantial numbers of BIRCWH scholars applied for other NIH grant programs; R03 (N=167, or 29 percent) and R21 (N=266, or 46 percent). Of scholars who submitted at least one application to these mechanisms, approximately 37 percent and 30 percent, respectively, eventually received at least one R03 or R21 award.
- Female scholars had significantly higher K-mentored research grant application rates compared to their male counterparts, but nevertheless, there is no significant sex difference in terms of the grant award outcomes.
- Based on the research grants included in the analysis, neither the application rate nor the award rate shows a statistical difference between male and female scholars.

There was a key BIRCWH meeting held in June 2016 that brought together the Scholars, Principal Investigators and their research staff, plus NIH staff, and others interested in the BIRCWH program. Approximately 200 people attended the full day of scientific activities, including a keynote address on the importance of mentoring and how she completed an important

Table 1. Active BIRCWH Programs, FY 15–16

Grant Number	Title of Grant	Principal Investigator	Institution
K12HD051959	Hormones & Genes in Women's Health: Bench to Bedside	Jill M. Goldstein, Ph.D.	Brigham and Women's Hospital/Harvard Medical School
K12HD043446	Building Interdisciplinary Research Careers in Women's Health	Nancy Catherine Andrews, M.D., Ph.D.	Duke University
K12HD085850	Emory University BIRCWH Program	Claire E. Sterk, Ph.D.	Emory University
K12HD085845	The Johns Hopkins Clinical Research Scholars in Women's Health	Daniel Ernest Ford, M.D., M.P.H.	Johns Hopkins University
K12HD043441	Building Interdisciplinary Research Careers in Women's Health in Pittsburgh	Yoel Sadovsky, M.D.	Magee-Womens Research Institute and Foundation/University of Pittsburgh
K12HD065987	Mayo Clinic Interdisciplinary Women's Health Research Program	Virginia M. Miller, Ph.D.	Mayo Clinic
K12HD055885	Building Interdisciplinary Women's Health at MUSC	Kathleen T. Brady, M.D., Ph.D.	Medical University of South Carolina
K12HD055884	Career Development in Women's Health	Andrea Dunaif, M.D.	Northwestern University
K12HD043488	Scholars in Women's Health Research Across the Lifespan	Jeanne-Marie Guise, M.D., Ph.D., and Daniel Michael Dorsa, M.D., M.P.H.	Oregon Health & Science University
K12HD055882	Career Development Program in Women's Health Research at Penn State	Carol S. Weisman, Ph.D.	Pennsylvania State University
K12HD043451	Tulane Building Interdisciplinary Research Careers in Women's Health	Marie A. Krousel-Wood, M.D.	Tulane University
K12HD052163	UCSF/Kaiser Program for Developing Independent Women's Health Researchers	Claire D. Brindis, Ph.D., and Nancy E. Adler, Ph.D.	University of California, San Francisco
K12HD051958	Building Interdisciplinary Careers in Women's Health at UC Davis	Ellen B. Gold, Ph.D.	University of California, Davis
K12HD057022	The Colorado Building Interdisciplinary Research Careers in Women's Health Program	Judith G. Regensteiner, Ph.D., and Nanette F. Santoro, M.D.	University of Colorado, Denver
K12HD055892	UIC Program for Interdisciplinary Careers in Women's Health Research	Stacie E. Geller, Ph.D.	University of Illinois at Chicago
K12DA036150	Kentucky BIRCWH Program: Training the Next Generation of Women's Health Scholars	Thomas Curry, Ph.D.	University of Kentucky
K12HD043489	Maryland's Organized Research Effort in Women's Health	Kathleen J. Tracy, Ph.D.	University of Maryland, Baltimore
K12HD055887	University of Minnesota Building Interdisciplinary Research Careers in Women's Health	Nancy Cox Raymond, M.D.	University of Minnesota
K12HD001441	UNC BIRCWH Career Development Program	Kim A. Boggess, M.D.	University of North Carolina at Chapel Hill
K12HD085848	Training In Sex and Gender Differences Research to Improve Women's Health	C. Neill Epperson, M.D.	University of Pennsylvania
K12HD052023	UTMB Women's Health Research Scholars Program	Abbey B. Berenson, M.D., Ph.D.	University of Texas Medical Branch, Galveston
K12HD085852	Utah Building Interdisciplinary Research Careers in Women's Health Career Development Program	Michael W. Varner, M.D.	University of Utah
K12HD055894	Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Scholars	Elizabeth S. Burnside, M.D., M.P.H.	University of Wisconsin, Madison
K12HD043483	Building Interdisciplinary Research Careers in Women's Health	Katherine E. Hartmann, Ph.D.	Vanderbilt University

clinical research project as part of her research career trajectory. There was a plenary panel that focused on ways to leverage the BIRCWH program with other prominent institutional research funding mechanisms. In the afternoon, there was a mentoring session for the Scholars who met with the staffs from ten NIH ICs to discuss future funding opportunities, as well as a poster session for the accepted Scholar abstracts. These abstracts were published in the *Journal of Women's Health*.

Highlights of BIRCWH Research

BIRCWH research represents an extensive depth and breadth of basic, translational, and clinical science across the NIH-supported research fields. For example, researchers investigated hormonal control of diet-induced type 2 diabetes and lipid and carbohydrate metabolism. Gynecology research includes studies of anti-Müllerian hormone in primate folliculogenesis and fertility preservation and of three dimensional spatial relationships involved in pelvic organ prolapse. In neurology, investigators study clinical and biomarker characterization of inherited frontotemporal dementia and traumatic brain injury among the elderly. Researchers investigate sex and gender-based influences: sex differences in the association of blood pressure response to the cold pressor test and hypertension incidence, sex differences in vascular remodeling diseases, and sex-specific chromosomal and neural markers of aging. The true hallmark of BIRCWH research is not only the breadth, depth, and impact on science and medicine but the interdisciplinary aspects of each research project. A listing of current BIRCWH Scholar research investigations (K12 awards) is included in Appendix B.

Women's Reproductive Health Research (WRHR) Career Development Program

Program Overview

Initiated by NICHD in 1998, the WRHR program was developed to provide the opportunity for obstetrician/gynecologists (OB/GYNs) who recently completed postgraduate clinical training to further their education and experience in basic, translational, and clinical research. ORWH has provided support for this program since its inception. The primary objectives of the program are to (1) bridge clinical training with advanced research career development, (2) provide obstetrics-gynecology junior faculty with state-of-the-art training in women's reproductive health research in an academic department, (3) stimulate women's reproductive health research in a variety of disciplines, and (4) deliver a mentored research experience to help obstetrics-gynecology junior faculty attain careers as independent investigators. Program eligibility is limited to obstetrician-gynecologists (M.D. or D.O. degree) who have completed residency training in obstetrics and gynecology and are beginning basic, translational, or clinical research relevant to obstetrics and gynecology. Subspecialty training is not required of candidates practicing general obstetrics and gynecology. WRHR scholars' scientific projects focus on subspecialty areas and related fields, including maternal-fetal medicine, gynecologic oncology, reproductive endocrinology and infertility, and female pelvic medicine and reconstructive surgery. There are 15 current WRHR sites in departments of OB/GYN throughout the nation. WRHR scholars represent a diverse group of physician-scientists from several subspecialties and emerging areas in OB/GYN; they pursue a broad range of basic science, translational, and/or clinical research topics. More than 215 OB/GYN junior faculty have been appointed to the WRHR Program since its inception.

FY 15–16 Program Sites

- **Augusta University Women’s Reproductive Health Research Career Development Plan¹⁴**
Institution: Augusta University (formerly Georgia Regents University), Augusta, Georgia
Principal Investigator (PI): Michael P. Diamond, M.D.
- **Brown University/Women & Infants Hospital (WIH) Women’s WRHR Career Development¹⁵**
Program: Improving Women’s Health through Career Development in Clinical Research
Institution: WIH Rhode Island/Brown University, Providence, Rhode Island
PI: Maureen G. Phipps, M.D., M.P.H.
- **Colorado Women’s Reproductive Health Research Career Development Center¹⁶**
Institution: University of Colorado, Denver, Denver, Colorado
PI: Nanette Santoro, M.D.
- **Continuation of Wayne State University’s Successful Development of Physician-Scientists as Independent Researchers in the Area of Women’s Reproductive Health¹⁷**
Institution: Wayne State University, Detroit, Michigan
PI: Chaur-Dong Hsu, M.D., M.P.H.
- **Fast Forwarding Women’s Reproductive Health Research: University of Michigan WRHR Career Development Program¹⁸**
Institution: University of Michigan, Ann Arbor, Michigan
PI: Timothy R.B. Johnson, M.D.
- **Magee-Womens Basic and Translational Reproductive Health Training Program¹⁹**
Institution: Magee-Womens Research Institute & Foundation, Pittsburgh, Pennsylvania
PI: Robert P. Edwards, M.D.
- **OB/GYN Faculty Research Career Development Program²⁰**
Institution: University of Alabama at Birmingham, Birmingham, Alabama
PI: William W. Andrews, Ph.D., M.D.
- **Penn Center for Career Development in Women’s Health Research²¹**
Institution: University of Pennsylvania, Philadelphia, Pennsylvania
PI: Deborah A. Driscoll, M.D.
- **Research Career Development in Obstetrics and Gynecology²²**
Institution: Northwestern University, Chicago, Illinois
PI: Serdar E. Bulun, M.D.
- **Utah Women’s Reproductive Health Research Career Development Program²³**
Institution: University of Utah, Salt Lake City, Utah
PI: Robert M. Silver, M.D.
- **Women’s Reproductive Health Research Program²⁴**
Institution: University of California San Diego, San Diego, California
PI: Charles W. Nager, M.D.
- **Women’s Reproductive Health Research²⁵**
Institution: University of California, San Francisco, San Francisco, California
PI: Mary E. Norton, M.D.

¹⁴ www.augusta.edu/mcg/obgyn/wrhr/about.php

¹⁵ www.womenandinfants.org/research/womens-reproductive-health-research.cfm

¹⁶ www.ucdenver.edu/academics/colleges/medicalschoo/departments/obgyn/Divisions/reprosciences/Pages/Womens-Reproductive-Health-Research-WRHR.aspx

¹⁷ www.obgyn.med.wayne.edu/wrhr

¹⁸ medicine.umich.edu/dept/obstetrics-gynecology

¹⁹ mageewomens.org/education/womens-reproductive-health-research-career-development-program

²⁰ www.uab.edu/medicine/obgyn/education/wrhr-career-development-prog

²¹ www.uphs.upenn.edu/obgyn/career/rhr.htm

²² www.feinberg.northwestern.edu/sites/obgyn/research/wrhr

²³ medicine.utah.edu/obgyn/research/wrhr

²⁴ repomed.ucsd.edu/education-training/womans-repro

²⁵ obgyn.ucsf.edu/education-training/wrhr

- **Women's Reproductive Health Research K12 Program**

Institution: Oregon Health & Science University, Portland, Oregon

PI: Aaron B. Caughey, M.D., Ph.D.

- **Women's Reproductive Health Research at the University of Washington²⁶**

Institution: University of Washington, Seattle, Washington

PI: David Eschenbach, M.D.

- **Yale Development Center²⁷**

Institution: Yale University, New Haven, Connecticut

PI: Hugh S. Taylor

Research Supplements to Promote Reentry into Biomedical and Behavioral Research Careers

The ORWH/NIH Reentry into Biomedical Research Careers program assists individuals with high potential, including postdoctoral investigators, to reenter an active research career after a qualifying interruption for family or other responsibilities. The program began as a pilot in 1992 using administrative supplements to existing NIH research grants to support full- or part-time research. It includes three components that help reestablish awardees as independent competitive research scientists: full participation in an ongoing NIH-funded research project, an opportunity to update and enhance research capabilities, and a carefully planned mentoring program developed by the mentor and the awardee.

As of FY 16, more than 164 investigators had received awards under this program with support from ORWH, 25 NIH ICs and Offices in the NIH Office of the Director. An ORWH evaluation of the program in December 2006 showed that, at an average time of 5 years post-award, more than 80 percent of reentry awardees remained in academia

The NIH Working Group on Women in Biomedical Careers leads trans-NIH efforts to address career barriers for women in science... to promote entry, recruitment, retention, and sustained advancement of women in biomedical and research careers.

and in scientific research. More than 80 percent remained active in publishing and grant activities and indicated that the program had helped them advance their scientific careers. In FY 16, NIH reissued the funding opportunity announcement www.grants.nih.gov/grants/guide/pa-files/PA-16-289.html, enhancing the mentoring component.

NIH Working Group on Women in Biomedical Careers

The NIH Working Group on Women in Biomedical Careers was established in 2007 and is co-chaired by the Director of NIH and the Director of ORWH. Members of the Working Group lead trans-NIH efforts to address career barriers for women in science including the development of innovative strategies to promote entry, recruitment, retention, and sustained advancement of women in biomedical and research careers. The group comprises NIH Deputy Directors, Office of the

²⁶ www.depts.washington.edu/obgyn/education/career-development/wrhr-career-development.html

²⁷ www.medicine.yale.edu/obgyn/drs/education/wrhcdc



Director senior staff, IC Directors, and other representatives of NIH intramural and extramural staff (members of the Working Group in FY 15 and FY 16 are listed in Appendix C).

Responding to suggestions from the National Academy of Sciences report “Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering,”²⁸ the Working Group hosts several committees focused on areas related to its mission, including the Women of Color in Biomedical Careers Committee, the Committee on Advancing Women in Independent Positions, and the Intramural Research Program Committee. The Working Group and its committees have sponsored national workshops, seminars, and research symposia on career development research and interventions; issued reports on best practices; created public outreach websites; and developed a funding grant program to study barriers impeding women’s career development. Other notable activities in FY 15 and FY 16 are described below.

²⁸ www.nap.edu/catalog/11741/beyond-bias-and-barriers-fulfilling-the-potential-of-women-in

NIH Women in Science Website

With ORWH staff support and funding, the Working Group maintains a website (womeninscience.nih.gov) that provides a compilation of resources to support women scientists and includes links to news articles, reports, and events. In FY 16 ORWH initiated a project to spotlight prominent women in science, www.womeninscience.nih.gov/women_scientists/index.asp. In FY 16, profiles of 20 women were published. The Working Group also publishes a bimonthly newsletter ADVANCES & INSIGHTS: The NIH Women in Science Newsletter, www.womeninscience.nih.gov/nih_programs/listserv/index.asp. This newsletter contains articles and items pertaining to women in science; profiles of outstanding women scientists; examples of best practices for the recruitment, retention, and advancement of women that are being implemented in institutions and universities across the United States; featured job opportunities at the NIH; and an overview of NIH policies and programs relevant to women in science.

Activities of the Committee on Women of Color in Biomedical Careers

The Working Group Committee on Women of Color in Biomedical Careers (WOC) is charged with addressing the unique career challenges facing women scientists of color. One aim of the committee is to increase visibility and recognition of women of color. To that end, the committee regularly identifies and nominates exceptional female researchers for society awards and lectureships, and it did so in several venues in FY 15 and FY 16. Specifically, in FY 15 the committee nominated 3 women of color from the NIH Intramural Research Program for society awards. Additionally, in FY 15 the committee nominated 14 women for the prestigious NIH Wednesday Afternoon Lecture Series (WALS), and 5 of the nominations were successful. In FY 16, the committee nominated 20 women for WALS, of which 4 were successful.

To promote networking among women scientists of color, the committee developed the Women of Color Research Network (WoCRn), a social media site that provides information, mentoring, and career development opportunities for women of color in biomedical careers and for all who support diversity in the scientific workforce (www.womeninscience.nih.gov/women-of-color/). This effort is supported by both ORWH and NIA. In FY 15, the committee was awarded an NIH Office of the Director Honor Award for establishing the Women of Color Research Network as a national online resource to support the NIH mission and minority women in biomedical sciences. In FY 16, the committee transferred WoCRn from its former platform to LinkedIn to leverage the existing LinkedIn infrastructure and maximize the potential of the site (www.linkedin.com/groups/8501207). In FY 15 and FY 16, the committee continued the support and establish regional networks of WoCRn users to facilitate local interactions and mentoring opportunities. The first two networks, connecting the campuses of Indiana University and those of Research Triangle Park (RTP) in North Carolina,

continue to thrive. An additional chapter is underway in the Washington, DC, metro area.

Activities of the Committee on Advancing Women in Independent Positions

In 2008, the Working Group issued a trans-NIH funding opportunity announcement (RFA-GM-09-012), “Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering.” Through this effort, NIH funded 14 research grants that explored obstacles facing women scientists at all stages of their scientific careers. Some projects evaluated interventions to address these obstacles. The grants totaled \$16.8 million across 4 years with support from 11 NIH ICs and 4 Offices within the NIH Office of the Director. Since receiving the awards, the principal investigators (PIs) have written more than 65 articles on causal factors and interventions, given more than 160 presentations, and received 24 related follow-up grants to continue their research. The PIs also published a collection of articles in the journal *Academic Medicine*. They have also formed an independent group, the Research Partnership on Women in Biomedical Careers, to stimulate research collaborations.

Conference on Evidence-Based Innovations to Support Women in Biomedical Research Careers

In FY 16, ORWH hosted the Conference on Evidence-Based Innovations to Support Women in Biomedical Research Careers featuring the work of awardees of the Causal Factors initiative (RFA-GM-09-012). The conference honored ORWH’s 25th Anniversary and featured the inaugural Ruth L. Kirschstein Lecture given by Dr. Shirley Malcom, head of the Education and Human Resources Programs at the American Association for the Advancement of Science. The conference included presentations and panel discussions with members of the Research Partnership on Women in Biomedical Careers. Agenda topics included retention and predictors of academic success, institutional culture and climate, evidence-based

change to support women in biomedical careers, and the intersection of gender and race/ethnicity. The conference provided an opportunity for ORWH to engage the scientific community on the recruitment, retention, and advancement of women in biomedical research careers. A videocast of the conference is available at videocast.nih.gov/summary.asp?Live=19198&bhcp=1.

Workshop on Advancing Women in Independent Positions

In FY 15, the Committee on Research and Evidence to Promote Women in Scientific Careers was renamed the Committee on Advancing Women in Independent Careers. This committee hosted a Workshop on Advancing Women in Independent Positions in FY 16 to convene scientific societies and other organizations that have a proven record or supporting women in science. The goal of the workshop was to raise awareness of each organization's activities, share best practices, and identify areas of collaboration. A workshop report is available at www.womeninscience.nih.gov/pdfs/Workshop_on_Advancing_Women_in_Independent_Positions_Final_Summary.pdf.

Working Group Initiatives for NIH Employees

In FY 15 and FY 16, the Working Group collaborated with the Office of Intramural Research (OIR), the Office of Equity Diversity and Inclusion (EDI), and the Office of Research Services (ORS) to initiate or continue several programs aimed at improving and enhancing the NIH employee work environment. These initiatives are described below.

Keep the Thread Program

The Working Group's Committee on the NIH Intramural Research Program (IRP) has continued its support for programs aimed at increasing flexibility for IRP fellows. A program that is open to all NIH postdoctoral fellows who are supported by Intramural Research Training Awards or Cancer

Research Training Awards aims to recognize and proactively address common roadblocks to balancing work and personal life. Information and support are provided on topics such as flexible work schedules and teleworking, temporary reductions of effort, fee-for-service contracting, and special volunteer status. More information about the program can be found at www.oir.nih.gov/sourcebook/personnel/recruitment-processes-policies-checklists/keep-thread-policy.

Northwest Child Care Center

The Northwest Child Care Center on the NIH campus began construction in Fall 2015 and is scheduled to open in Summer 2017. Once complete, it will provide an additional 170 child care slots on campus. Support for this center comes from the Office of Research Services, the Office of Research Facilities Development and Operations, the Child Care Board, and the Office of the Director. Members of the Working Group in both OIR and ORWH continue to play an active role in moving these efforts forward.

Back-Up Care Program

Through the efforts of the Working Group and the NIH Child Care Board, the NIH Office of Research Services (ORS) launched a back-up care program in January 2012 that offers short-term child care, elder care, and self-care to NIH employees. The program continued in FY 15 and FY 16. More details about the Back-up Care Program can be found on the ORS website: www.ors.od.nih.gov/pes/dats/childcare/pages/nihback-upcareprogram.aspx.

NIH Resource Matrix

To increase awareness and encourage participation in the many supportive programs and resources at NIH, the Women's Employment Committee, in collaboration with OIR and ORWH, has created the NIH Workforce Resource Eligibility Matrix. The Matrix is a tool designed to assist the NIH Workforce in identifying available resources and determining their eligibility based on employee type.



ORWH Support for Other NIH Career Development Programs and Activities

Office of Intramural Training and Education

The NIH Office of Intramural Training & Education’s (OITE) mission is to enhance the training experience of students and fellows on all of the NIH campuses. The Office works closely with the NIH ICs to support the development of scientific and professional skills to enable junior investigators to become leaders in the biomedical research community. Many of the workshops, seminars, and career development resources also are available to individuals outside of NIH.

High School Scientific Training and Enrichment Program 2.0 (NIH HiSTEP 2.0)

The High School Scientific Training and Enrichment Program (HiSTEP) and HiSTEP 2.0 programs are

for high school students who attend schools in the Washington, DC, area, where 30 percent or more of the students are on the Federal Free/Reduced Lunch Program. Students from these lower-resourced schools traditionally struggle to obtain internships in research groups even though they show great potential and promise to contribute. In FY 16, ORWH provided funds to support students in the HiSTEP2.0 program. These are high school seniors and HiSTEP alumni who have little or no research experience and this program provides them with the opportunity to spend 8 weeks performing biomedical research at the NIH. Students are paired and worked side-by-side with scientists at the main NIH campus in Bethesda, Maryland. With this full-time research experience, HiSTEP 2.0 students further develop their research and scientific skills; gain in-depth knowledge of and explore the breadth of biomedical, translational and/or basic science; and sharpen their critical thinking skills. In addition to research experience, the students participate in a unique curriculum designed to enhance their leadership and communication skills,



experience mentorship throughout and beyond the summer, and have access to resources that help in the transition from high school to college. As a required part of the program, students presented their research at Summer Poster Day alongside other NIH summer interns.

In 2016, 63 percent of HiSTEP 2015 alumni joined the first cohort of HiSTEP 2.0. Of a group of 28 students, 17 (59%) were female and 12 (41%) were male. Students were highly successful and excited about the program. One hundred percent of the first cohort completed the program and would recommend the program to a friend who was interested in conducting biomedical research. Ninety-three percent of the students indicated that they felt more prepared for college after completing the program.

By the end of the program, students indicated an increase in confidence, improvement in the ability to communicate with peers and mentors, expansion of their professional network, further development of their research and scientific skills, and better time management strategies.

Some feedback from students—

- “It provides a supportive environment to gain research experience and college preparation.”
- “This experience really opens one up to the experiences in science and it is a definite confidence booster.”
- “I would recommend this program to a friend because this was a program that I enjoyed and felt as if I grew mentally, emotionally, and academically in a small amount of time.”
- “It gives students a chance to learn and experience things that you won’t get a chance to do in school.”
- “You get to work in a lab and still have a community of support.”

Training in Mentorship, Leadership, Management and Related Topics

For many years, ORWH has partnered with the OITE to support the development and dissemination of materials to enhance mentoring and interpersonal skills in the intramural and

extramural communities. The OITE has developed programming to improve leadership and management skills of our trainees. All trainees are encouraged to participate in the Workplace Dynamics Series to improve the workplace in research environments. This four-part series aims to train fellows to build interpersonal and communication skills using experiential learning with examples relevant to research groups. The series begins by enhancing self-awareness and an understanding of others; transitions to examine differing communication and learning styles; builds to understand and manage workplace conflicts, provides strategies to communicate feedback, and encourages team skills by understanding team dynamics and team behaviors, and finishes with a session to capitalize on diversity.

Postdocs, clinical fellows, and advanced graduate students who complete the Workplace Dynamics Series are eligible for a 2-day management course. This intensive course provides an overview of common management concepts. Topics include managing yourself with emotional intelligence, understanding management theories, strategies to hire the appropriate staff, managing conflict as a supervisor, building staff expectations and motivations, and harnessing diversity. This capstone course has provided valuable knowledge and skills as these advanced trainees transition to their first positions as direct supervisors.

The OITE has developed resources for all trainees in regards to stress-management, mindfulness, holistic self-care, resilience, self-compassion and wellness. OITE facilitates in-person quarterly workshops to provide information on the impact of stress on both physical and mental health and to present strategies designed to enhance wellbeing. A weekly guided meditation group creates an informal atmosphere to explore topics such as body-mind relaxation, breath awareness, practicing stillness and more. Understanding that individuals will embrace wellness initiatives with differing

approaches we have also filmed a YouTube video on resiliency during job hunts and have created many blog posts on the topic such as “[Life’s Got You Down? Staying Strong and Resilient in the Midst of Disappointment.](#)”²⁹ Additionally, two wellness counselors on staff at the OITE meet individually with trainees to help them navigate life and workplace environments.

In the summer of 2016, the OITE hosted a 2 1/2 day workshop on “How to Teach and Advise on Career Development Topics for the Next Generation of Biomedical Scientists: A Train-The-Trainers Event.” This event was created to disseminate ideas and resources to advisors, staff and faculty from across the country who provide career and professional development programming and guidance to graduate students and postdoctoral researchers in the biomedical sciences. This unique conference provided not only content, but instruction on how to deliver the material and access to downloadable resources (such as slide-decks and handouts) so participants would gain skills, knowledge, and confidence to present workshop or meet individually with trainees. One track prepared participants for standard career development needs such as individual career meetings or career workshops (career exploration and decision making, job search skills, CV to resume, etc.). A second track helped participants develop skills talking individually with trainees or presenting workshops in assertiveness, talking with mentors about careers, wellness, resiliency and emotional intelligence. More than 130 people attended from over 70 institutions. Feedback from the event highlighted that participants gained increased confidence in talking to trainees and a great appreciation for the sharing of slide-decks and other materials that attendees could immediately implement in their own institutions.

²⁹ www.oitecareersblog.wordpress.com/2016/11/21/lifes-got-you-down-staying-strong-and-resilient-in-the-midst-of-disappointment

NIH Fogarty International Center Global Health Program for Fellows and Scholars

In FY 15 and FY 16, ORWH continued its support of the Fogarty International Center Global Health Program for Fellows and Scholars that provides mentorship, research opportunities, and a collaborative research environment for early-stage investigators from the United States and low- and middle-income countries. This program aims to enhance scientists' global health research expertise and their careers and includes a summer orientation and training initiative. This program strives to enhance the careers of women in biomedical science and many projects focus on women's health and maternal and child health. In FY 15, 48 of the 85 scholars (56 percent) were women, and in FY 2016, 55 of the 86 scholars (64 percent) were women.

National Institute of Diabetes and Digestive and Kidney Diseases Travel Awards

ORWH continued its support of National Medical Association (NMA) workshops in FY 15 and FY 16 for residents and fellows interested in academic

medicine. The event, held in conjunction with the NMA Annual Convention and Scientific Assembly, covers topics ranging from grantsmanship to time management skills. NIH anticipates that this opportunity will allow more physicians from medically underserved communities to receive training that they can take back to their communities.

Anita B. Roberts Lecture Series: Distinguished Women Scientists and NIH

ORWH cosponsored with the NIH Women Scientist Advisors Committee of the NIH intramural program the Anita B. Roberts Lecture in FY 15–16. This program provides a venue for highlighting the work of distinguished women in Science. In FY 15, the lecture was titled “Precision Medicine in Action: Applying Genomics Tools to Improve Patient Outcomes after Organ Transplantation” presented by Dr. Hannah Valentine, NIH Chief Officer of Scientific Workforce Diversity. In FY 16, Dr. Leslie G. Ungerleider, Chief, Laboratory of Brain and Cognition at NIMH gave a presentation on “Functional Architecture of Face Processing in the Primate Brain.” This lecture series was dedicated

With a focus on providing a wide variety of opportunities for professional growth, ORWH supported programs that meet the needs of a diverse group of scientists at all levels.

to the memory of Dr. Anita B. Roberts, former Chief of the NCI Laboratory of Cell Regulation and Carcinogenesis from 1995 to 2006. NIH postdoctoral fellows also presented at this series.

Online Courses

The Science of Sex & Gender in Human Health³⁰ program is an online, free, self-paced accredited continuing education program for physicians, pharmacists, and nurses. The program was developed and sponsored by ORWH and the Office of Women's Health (OWH) at the Food and Drug Administration (FDA), and builds upon the 2001 Institute of Medicine report [Exploring the Biological Contributions to Human Health: Does Sex Matter?](#),³¹ which was funded by NIH and FDA. ORWH continues to support and update three courses (each with 5-6 lessons) on sex- and gender-related

differences from the perspective of: (1) basic science or biological bases; (2) health and behavior; and (3) and disease expression and treatment. The courses are free and available to the public.

Since the first course was launched in 2006, there has been an exponential expansion of basic science evidence to support the concept of sex as a basic biological variable and that every cell has a sex. It is more important now than ever for clinicians to be familiar with the rapidly expanding findings in basic science and able to translate these findings into epidemiological and clinical context. To meet this demand, ORWH will develop a fourth course that delves deeper into the basic science underlying sex and gender differences and prepares clinicians for translational approaches.

³⁰ www.sexandgendercourse.od.nih.gov

³¹ www.nap.edu/read/10028/chapter/1





IV. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

Historical Perspective

The establishment of policies for the inclusion of women and minorities in NIH-funded clinical research originates from the women's health movement. After the U.S. Public Health Service Task Force on Women's Health issued its report in 1985, NIH established a policy urging the inclusion of women in clinical research. This policy was first published in the NIH Guide for Grants and Contracts in 1987. Later that year, NIH published a policy encouraging the inclusion of minorities in clinical studies.

To ensure that NIH implements the inclusion policies, Congress made previous policy into public law through a section in the NIH Revitalization Act of 1993 (PL 103) titled *Women and Minorities as Subjects in Clinical Research*. In 1994, NIH revised its inclusion policy³² to comply with the statutory language. The Revitalization Act essentially reinforced the existing NIH policies as follows:

- That NIH ensure that women and minorities and their subpopulations be included in all clinical research
- That women and minorities and their subpopulations be included in Phase III clinical trials designed such that valid analysis can be performed
- That cost not be allowed as an acceptable reason for excluding these groups
- That NIH initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as participants in clinical studies.

In October 2015, the United States General Accounting Office (GAO) produced a report examining women's participation in NIH Research titled *Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research* (GAO 16-13).³³ The GAO examined (1) women's enrollment and NIH's efforts to monitor this enrollment in NIH-funded clinical research and (2) NIH's efforts to ensure that NIH-funded clinical trials are designed and conducted to analyze potential sex differences, when applicable. The GAO made recommendations that the NIH examine and report more detailed data on women's enrollment in NIH-funded studies and collect, examine, and report data on the extent to which these studies include analyses of potential differences between men and women. NIH agreed with the report and has begun plans for implementing its Statement of Action addressing the recommendations.

Since the NIH Revitalization Act was passed, the overall number of women, minorities, and children included in NIH-funded studies has increased; however, as the GAO report pointed out, attention is still needed to ensure scientifically appropriate inclusion as well as specific analyses and reporting of population-specific information. In addition, the inclusion of groups in particular diseases and conditions should be monitored and reported. To address these issues, grant applications and solicitations to NIH are required to address inclusion of women, minorities, and children in clinical research and justify the proposed sample in the context of the scientific goals of the study.

³² www.grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

³³ www.gao.gov/products/GAO-16-13



The description and justification of the inclusion plans are evaluated during the peer review process and reviewers are directed to consider inclusion plans as part of the overall priority score. Any concerns about the inclusion plan must be resolved prior to funding. NIH program staff monitor inclusion as participants are enrolled; NIH-supported investigators are required to report at least annually on inclusion of women and minorities in the funded study. In addition, when conducting NIH-defined Phase III trials, applicants are required to address plans for valid design and analysis of potential differences on the basis of sex/gender, race, and ethnicity. Annually, investigators must provide an update on their progress in meeting the NIH-funded objectives including providing the number of individuals enrolled to date, broken out by sex/gender, race, and ethnicity. NIH can also identify the number of awards involving children, adults, or children and adults and can utilize that information to better understand what types of research that involve pediatric populations.

Inclusion Monitoring Activities

Communication and Outreach Efforts to the Scientific Community

NIH regularly updates application, contract proposal, and intramural project instructions and guidance to ensure that investigators address inclusion as part of the proposed projects and report inclusion enrollment at least annually. Numerous policy documents, podcasts, answers to frequently asked questions, and other resources are available for investigators and NIH staff on the [ORWH](#) and [Office of Extramural Research \(OER\)](#) websites. These resources discuss the elements of recruitment and retention; the NIH inclusion policy; current OMB requirements for reporting race and ethnicity data; and application submission, peer review, funding, and reporting requirements.

ORWH staff presented NIH Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research at the 144th Meeting of the American Public Health Association. The NIH Outreach

Toolkit³⁴ is a resource intended to help principal investigators and their research teams fulfill their responsibilities to women in clinical research by providing information on Federal laws, regulations, and NIH policies on the inclusion of women in clinical research. The Outreach Toolkit features case studies with researchers' experiences with including women in their studies and the topic include oral health in pregnancy, caries prevention, HPV, and menopause.

Peer Review Expectations

Scientific Review Groups (SRGs) are instructed to focus on scientific considerations when assessing the planned enrollment for a proposed study described in a NIH grant application. The SRG evaluates the inclusion plans and finds them unacceptable if the applicant (1) fails to provide sufficient information about the planned sample, (2) does not adequately justify limited or lack of inclusion of women or minorities, or (3) does not realistically address recruitment. For NIH-defined Phase III clinical trials, the SRG also evaluates the description of plans for valid analyses and whether investigators need to examine differences in the intervention effect by sex/gender, racial, and/or ethnic groups, as appropriate. For example, previous data suggesting that differences may exist could indicate a need to consider specific analyses. Applications with unacceptable inclusion plans cannot be funded until NIH staff members are assured that revised plans meet the inclusion policy requirements.

Communication and Outreach Efforts Within NIH

The Center for Scientific Review (CSR) and OER provide training for reviewers and applicants. OER has online training tools aimed at applicants.³⁵ These training and outreach efforts improve understanding of the inclusion policy and help extramural and NIH intramural investigators appropriately address these issues throughout the research funding process.

Specifically, these tools help applicants understand how NIH monitors inclusion, reviews the importance of reporting the race and ethnicity of clinical research participants, and describes how grantees and applicants should report race and ethnicity. CSR, which handles approximately 70 percent of the grant applications NIH receives, offers a robust applicant resources page that includes training, resources, and updates for Scientific Review Officers and Program Officers.³⁶

The Extramural Activities Working Group (EAWG), established by the NIH Director as a working group of the NIH Steering Committee, facilitates the governance for the policies, procedures, and utilization of resources for extramural research and research training. The Inclusion Governance Committee (IGC) was formed in 2011 as a subcommittee of the EAWG to discuss policy issues related to inclusion. The IGC³ is currently co-chaired by the Director of ORWH and the Deputy Director of the National Institute on Aging. Members of the IGC are primarily senior-level staff from the NIH Office of the Director and different ICs; other participants include individuals from different business areas involved in the implementation of inclusion policy. In 2015, the IGC provided consultation on the development of the new Inclusion Management System (IMS) that streamlines inclusion data reporting and monitoring.

Monitoring Compliance and Inclusion Enrollment Outcomes

NIH staff continue to monitor and document compliance with the inclusion policy and to work with grantees and contractors to ensure compliance. Program officers and staff provide technical assistance to investigators as they develop their applications and proposals throughout the application process. In preparation for peer review meetings, Scientific Review Officers remind reviewers of the guidelines for evaluating investigators' plans for the inclusion of women and

³⁴ www.orwh.od.nih.gov/toolkit

³⁵ www.grants.nih.gov/grants/funding/women_min/inclusion_training.htm

³⁶ www.public.csr.nih.gov/ApplicantResources/Pages/default.aspx

minorities in clinical research. Also discussed during these preparatory meetings are the instructions and requirements for reviewing NIH-defined Phase III clinical trials, particularly how the proposed work takes into account plans for valid analyses of sex differences. When new and competing continuation applications selected for payment are deficient in meeting inclusion policy requirements, NIH staff members are required to withhold funding until the PI has satisfactorily addressed the policy requirements. At the time of award and submission of progress reports, program officials monitor and verify that progress with inclusion is appropriate for the scientific goals under study.

Inclusion enrollment data aggregated across NIH ICs are presented in this report in summary figures and aggregate data tables (Appendix D), providing documentation of inclusion monitoring with some analysis. Caution should be used in interpreting these figures. Conclusions that can be reasonably drawn from the data are provided.

When assessing inclusion data, avoid directly comparing enrollment figures to the national census figures. The goal of the NIH policy is to ensure that the scientific knowledge acquired through NIH-defined clinical research will ultimately be generalizable to the appropriate population(s), not to satisfy any proportional target based upon census data. The numbers of women, men, and representatives of racial and ethnic groups included in a particular study depend on the scientific question addressed in the study and may take into account a number of factors, such as the prevalence among women, men, or racial and ethnic groups of the disease, disorder, or condition under investigation; gaps in scientific knowledge; and disparities in health risks or outcomes. A key principle of the inclusion policy is that inclusion is integral to conducting good science. Inclusion should not be considered on the basis of absolute numbers of individuals of particular groups; rather, the focus should be on whether a given study has the right people for the scientific goals and how sex/gender, race, and ethnicity may affect outcomes in those groups.

NIH Inclusion Management System

NIH has monitored aggregate inclusion data for study populations since FY 94. All ICs have well-established practices for monitoring compliance with the NIH inclusion policy. One of the goals of NIH's Inclusion Re-Engineering Project was to enhance the NIH's ability to more readily analyze inclusion information at the disease/condition level across ICs. The Project resulted in the NIH's Inclusion Management System (IMS), which facilitates data collection. IMS provides an electronic means to enter, store, approve, monitor, and report the planned and actual enrollment of research participants based on sex/gender, race, and ethnicity. IMS allows grantees to enter and update inclusion information and grantor agency staff to monitor and manage and report the inclusion data. IMS has been deployed and the NIH is exploring ways to understand inclusion information within specific disease and condition reporting categories.

Summary Report of NIH Inclusion Data for FY 15 and FY 16

Introduction

Reporting of sex/gender, racial, and ethnic categories is typically based on self-identification by the participants; participants always have the option not to identify. Although inclusion is mandated for all clinical research projects conducted or supported by NIH, for the purpose of the summary report, the primary focus of the racial and ethnic analyses is on studies involving populations in the United States. Appendix D contains data tables describing inclusion data from FY 15 and FY 16, clinical research data from FY 06 to FY 16 and Phase III Clinical Trial data from FY 11 to FY 16.

Important Considerations When Interpreting NIH Inclusion Data

Analysis of aggregate NIH inclusion data demonstrates that substantial numbers of women

and men and individuals of different races and ethnicities have been included as research subjects in NIH clinical research studies and NIH-Defined Phase III clinical trials. In addition, multi-year data are provided to show inclusion data over time. As explained in the section titled *Monitoring Compliance and Inclusion Enrollment Outcomes*, use caution to avoid over-interpreting the figures and data tables provided in this chapter.

- **Portfolio Composition:** The NIH portfolio is broad and diverse in terms of the types of clinical research studies it supports, the size of the studies, and the expectations for inclusion within them. The size of clinical research and clinical trial portfolios and the studies within those portfolios vary substantially across the ICs, depending on such factors as IC budget, mission, and the scientific goals of any given study. Some ICs do not conduct NIH-defined Phase III clinical trials or support very few of these types of studies.
- **Funding Life Cycle:** It is important to consider the nature of the funding life cycle at NIH and how that can affect inclusion enrollment information. The average length of an NIH grant award is 4 years. This means that every year, approximately 25 percent of the NIH funding portfolio turns over to newly funded awards or competing continuation awards. However, funding can be as short as 1 year or can last up to 10 years. The total amount of funding can vary from year to year, and at times, spikes or dips in appropriations may affect inclusion enrollment. Changes due to the funding life cycle may create noticeable shifts in the inclusion enrollment data, particularly for ICs with small clinical research or clinical trial portfolios. This life cycle also affects the reported enrollment numbers. In any given year, some projects have just begun, so enrollment is low. Other projects are in later years, and their enrollment numbers are higher. Still other projects have ended, so their data are no longer reported. These fluctuations

across studies also can lead to notable shifts in enrollment numbers from year to year.

- **Coding Categories:** The NIH-defined clinical research category includes not only NIH-defined Phase III trials but also many other types of clinical studies, such as observational and epidemiological studies, exploratory studies, and other phases of clinical trials, all of which are monitored for compliance with inclusion policy. The NIH-defined Phase III clinical trial category is a subset of all NIH-defined clinical research.

Summary of Key Trends

The following sections summarize data on the inclusion of women and minorities in NIH-Funded Clinical Research and in NIH-Defined Phase III Clinical Trials. Appendix D has been provided that summarizes all available inclusion data from FY 06 to FY 16. The key trends from the inclusion data summary are as follow:

- In FY 15, investigators reported enrollment of 21,453,866 participants and in FY 16 investigators reported enrollment of 40,327,265 participants.
- Enrollment of women in all NIH-funded clinical research in FY 15 and FY 16 was 50 percent or greater. Enrollment of women in clinical research was highest in the intramural research program at 68 percent for both FY 15 and FY 16.
- Enrollment of research participants from racial and ethnic minority groups across all NIH research was 40 percent in FY 15 and 37 percent in FY 16. Enrollment rates have fluctuated since 2006, but have not shown substantial increases.
- NIH-defined Phase III Clinical Trials are a subset of NIH Clinical Research studies. The proportion of female participants enrolled in NIH-defined Phase III Clinical Trial was 67 percent in in FY 15 and 66 percent in FY 2016.
- Inclusion of participants from racial and ethnic minority groups in NIH-Defined Phase III

Clinical Trials is similar to levels for NIH funded clinical research overall, with 41–43 percent in clinical trial conducted at sites across the United States.

Source of Inclusion Data

The following summary is based on inclusion data tabulated from human subjects involved in NIH-defined clinical research and NIH-defined Phase III clinical trials. NIH defines human clinical research as patient-oriented, epidemiologic, behavioral, outcomes, or health services research that includes human subjects. Patient-oriented research is research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) in which an investigator directly interacts with human subjects. Excluded from this definition are *in vitro* studies that use human tissues that cannot be linked to a living individual. Patient-oriented research includes (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical studies, and (d) development of new technologies. Studies falling under Exemption 4 for human subject research are not considered clinical research by this definition. Under 45 CFR 46, Exemption 4 is defined as “research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”

Clinical Trials are a subset of Clinical Research studies. They are research studies in which one or more human subjects are prospectively assigned to one or more interventions to evaluate their effects on health-related biomedical or behavioral outcomes. Clinical trials test treatment, prevention, and diagnostic strategies and include studies of drugs, devices, surgical techniques, health care delivery systems, and strategies to change health-related behavior such as diet or therapy.

Phase III Clinical Trials are a subset of Clinical Trials. Phase III Clinical Trials usually compare

interventions to other standard or experimental interventions (biomedical or behavioral) in large groups of people, from several hundred to several thousand. Typically, these trials monitor adverse effects, and collect information that will allow the interventions to be used safely.

In FY 15, NIH expanded inclusion monitoring to require submission of planned and actual enrollment data for additional funding mechanisms, such as career development (K) awards and individual fellowship (F) awards. In addition, NIH eliminated most previously allowable exceptions to inclusion monitoring for clinical research studies such as secondary analyses, tissue repositories, early feasibility studies, and studies with small sample sizes.

The following summary of inclusion of women and minorities in NIH research was derived from Inclusion Management System (IMS) data to facilitate the Congressional report required biennially by statute (Public Health Service Act sec. 492B, 42 U.S.C. sec. 289a-2). The data are aggregated across all NIH Institutes and Centers. Each Institute and Center has reviewed and approved their inclusion data to be used in this report. In FY 15, investigators submitted 11,082 Inclusion Data Records (IDR) with 9,925 IDRs reporting enrollment of 21,453,866 participants. The remaining 1,157 IDRs showed that participants had not yet been enrolled. In FY 16, investigators submitted 13,070 IDRs with 11,805 IDRs reporting enrollment of 40,327,265 participants. The remaining 1,265 IDRs showed that participants had not yet been enrolled. The variation in enrollees from FY 15 to FY 16 is due, in part, to the reported enrollment of one large study in 2016 with more than 12 million participants.

Inclusion Summaries

The percentage of women participants in NIH-funded research is the proportion of enrolled participants that selected female as their sex. Sex was unknown or not reported for 1.6 percent of participants in FY 15 and for 3.7 percent of participants in FY 16.

Race and ethnicity are two separate variables. Across all NIH-Funded clinical research studies, race of participants was unknown or not reported for 19.9 percent of participants in FY 15 and for 24.1 percent of participants in FY 16. Across all NIH-Funded clinical research studies, ethnicity of participants (Hispanic or Non-Hispanic) was unknown or not reported for 17.8 percent of participants in FY 15 and for 21.5 percent of participants in FY 16. For clinical research conducted at U.S. sites, race was unknown for 24.2 percent and ethnicity was unknown for 21.5 percent in FY 15; 15.5 percent and 12 percent respectively for FY 16. **Figures 1 and 2** provide a summary of self-reported race and ethnicity for participants enrolled in all NIH clinical research at U.S. sites for FY 15 and FY 16.

Minority status combines information from both race and ethnicity variables to determine the percentage of participants that are members of minority groups. For the purposes of this report, minority enrollment is the proportion of the enrolled participants that self-reported their race as either American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, those reporting more than one race, as well as those who reported their race as White or Unknown/Not Reported and their ethnicity as Hispanic.

Women and minority enrollment data for NIH Clinical Research funded in FY 15 and FY 16 are presented in **Figures 3 through 6** in the following pages. In each figure, the data are summarized for (a) all NIH-funded clinical research (All NIH CR), (b) clinical research conducted at sites within the United States (All CR at U.S. Sites), (c) clinical research supported by the NIH Extramural Research Program (ERP) that is conducted at U.S. sites (ERP at U.S. Sites), and (d) clinical research conducted through the NIH Intramural Research Program (IRP). All NIH CR includes groups (b) through (d) as well as international studies. All CR at U.S. Sites includes studies conducted through the IRP and ERP at U.S. Sites.

The data provided in this report are for studies defined by their investigators as prospective—new data to be collected prospectively. Studies labeled by investigators as involving retrospective data—from the study of existing datasets—were excluded from this report. The exclusion of retrospective data prevents possible inflation of inclusion numbers that could result from re-analysis of inclusion data previously collected and reported. It is possible that retrospective data may have been included in prior ORWH biennial reports. As can be seen in Appendix D, the current strategy to exclude retrospective data has not resulted in substantially different inclusion rates for women and minorities over the time these data have been collected and reported.

Inclusion Trends in NIH-Defined Clinical Research

Figure 3 summarizes the proportion of women enrolled in NIH funded research for FY 15 and FY 16. For all categories presented in **Figure 3**, women account for more than 50 percent of research participants. When studies recruiting only female participants are excluded from the tallies, enrollment of women was still an average of 50 percent for FY 15–16. When all single-sex (i.e., men only, women only) studies are excluded from tallies, inclusion of women was 53 percent in FY 15 and 48 percent in FY 16, an average of 51 percent.

For comparison with previous years, **Tables 1A through 1D** in Appendix D (Aggregate Enrollment Data Tables) present enrollment data for FY 06 through FY 16. These tables show that enrollment of women in all NIH-funded clinical research from FY 06 to FY 16 has been consistently 50 percent or greater.

Figure 4 summarizes the percentage of participants in NIH-funded clinical research that are members of minority groups. Overall, the proportion of enrolled participants from minority groups is lower for studies conducted at U.S. research sites as compared to the aggregate of all NIH clinical research studies, which includes

Figure 1: Enrollment for All NIH Clinical Research at U.S. Sites Racial Categories for FY 15 and FY 16

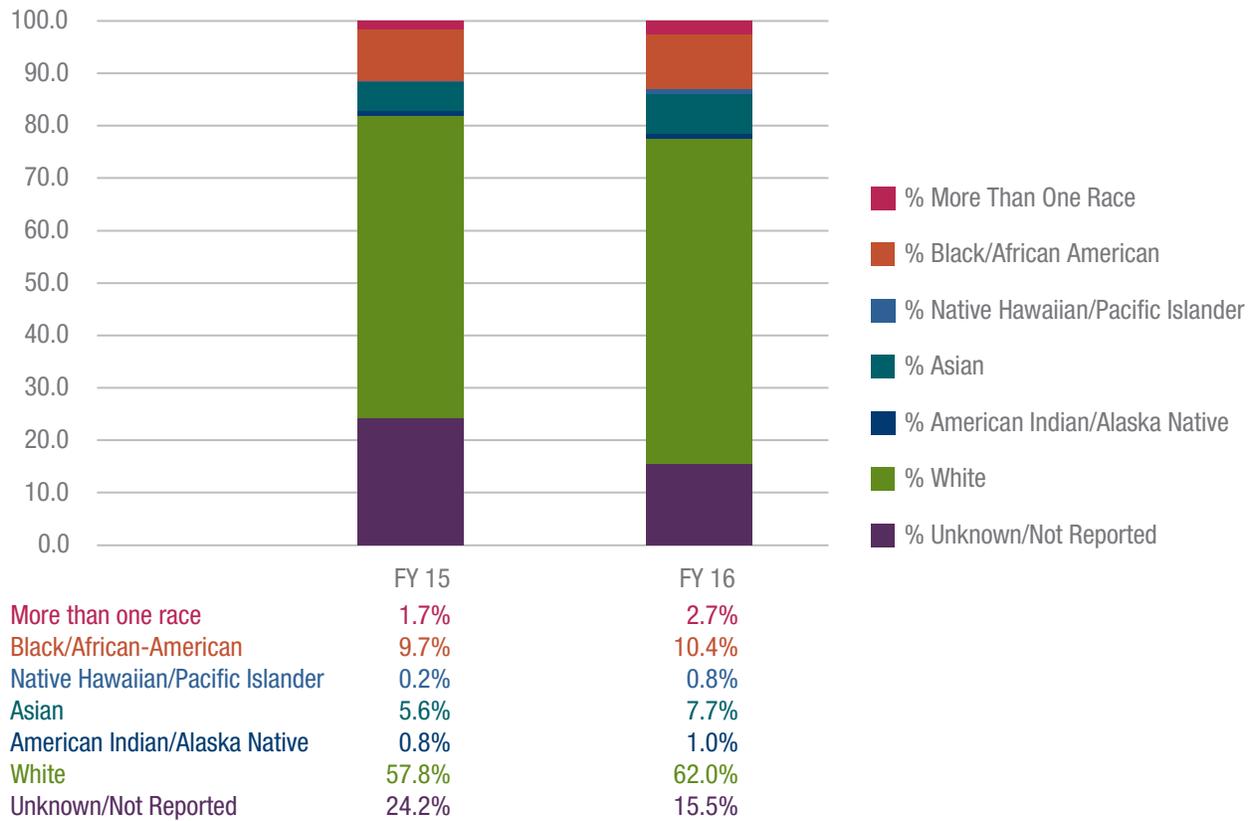


Figure 2: Enrollment for all NIH Clinical Research at U.S. Sites Ethnic Categories for FY 15 and FY 16

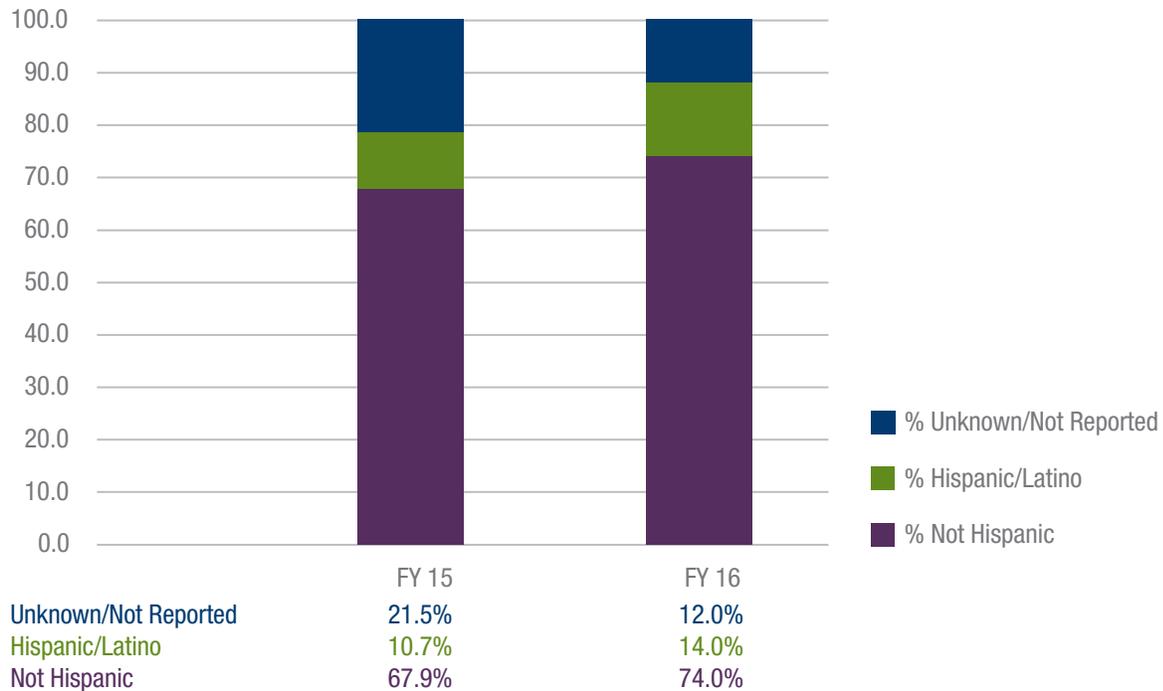


Figure 3: Percentage of Participants in NIH-Funded Clinical Research that are Female FY 15 and FY 16

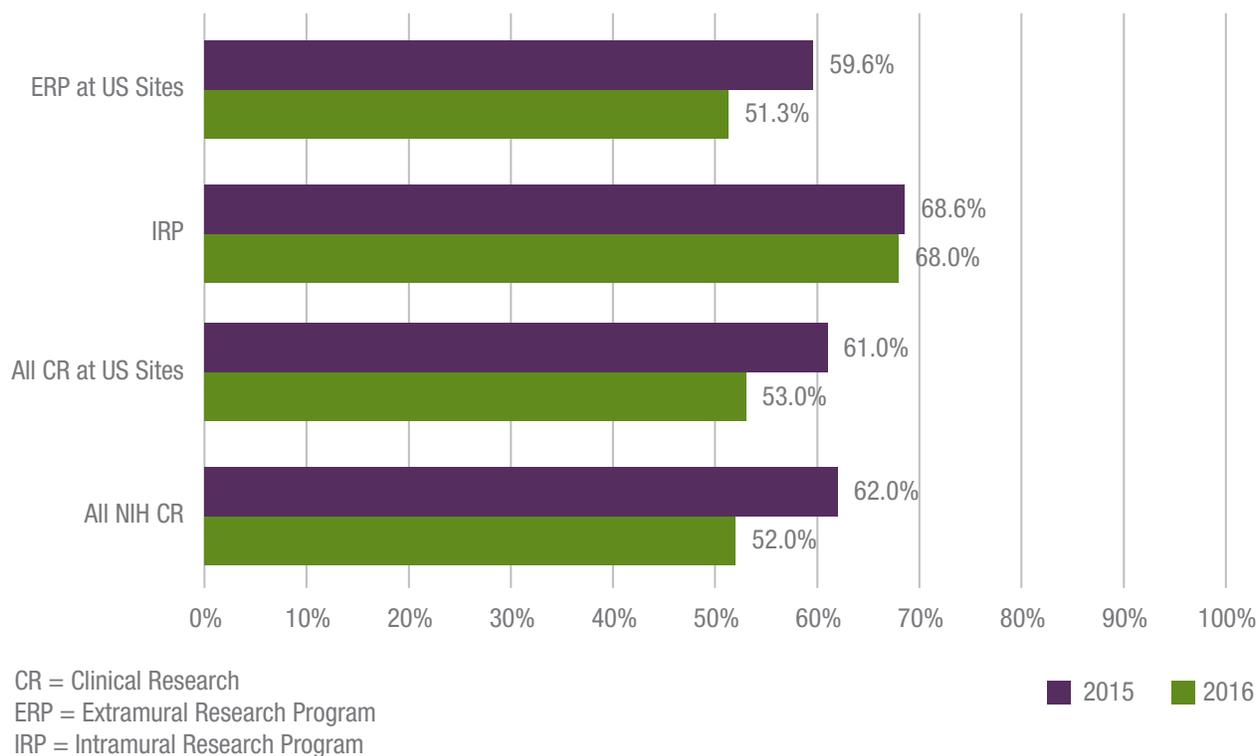
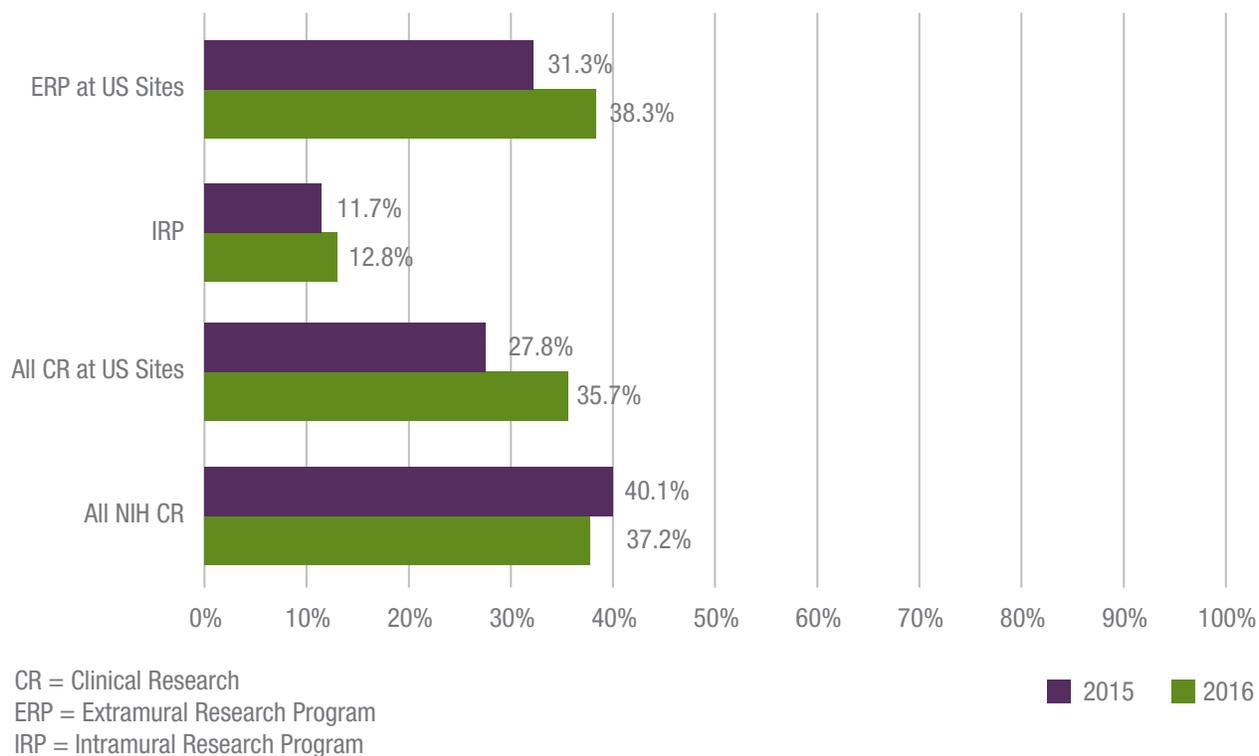


Figure 4: Percentage of Participants in NIH-Funded Clinical Research that are Members of Minority Groups FY 15 and FY 16



studies conducted outside of the United States that may contribute to the minority enrollment numbers. Participants in clinical research conducted through the ERP include a larger portion of enrollees from minority groups than in IRP supported clinical research. Although the proportion of IRP enrollees from minority groups remains lower than that of the ERP, the IRP has seen an increase in the proportion of participants from minority groups in the last three years and continues to address this deficit through targeted outreach efforts and other services provided by the Clinical Center’s Office of Patient Recruitment.

To provide a more complete picture of minority enrollment in clinical research, **Figures 5 and 6** provide a summary of enrollment by sex/gender of minority participants. The percent enrollment of women who are members of minority groups,

39 percent (**Figure 5**), is at a level similar to the proportion of minority participants in clinical research overall (**Figure 4**). One difference is a slightly lower rate of enrollment of women from minority groups in IRP supported clinical research as compared to all minority group participants in IRP clinical research for FY 15 and FY 16. Enrollment of male participants from minority groups (**Figure 6**) is notably higher for IRP clinical research than for female participants from minority groups enrolled in IRP clinical research. **Tables 4A through 4D** in Appendix D provide details of inclusion from FY 11 to FY 16 of male and female participants in clinical research who are members of minority groups. **Tables 4H through 4K** provide a detailed breakdown of enrolled participants by race and ethnicity of male and female enrollees for FY 15 and FY 16.

Figure 5: Percentage of Female Participants in NIH-Funded Clinical Research that are Members of Minority Groups FY 15 and FY 16

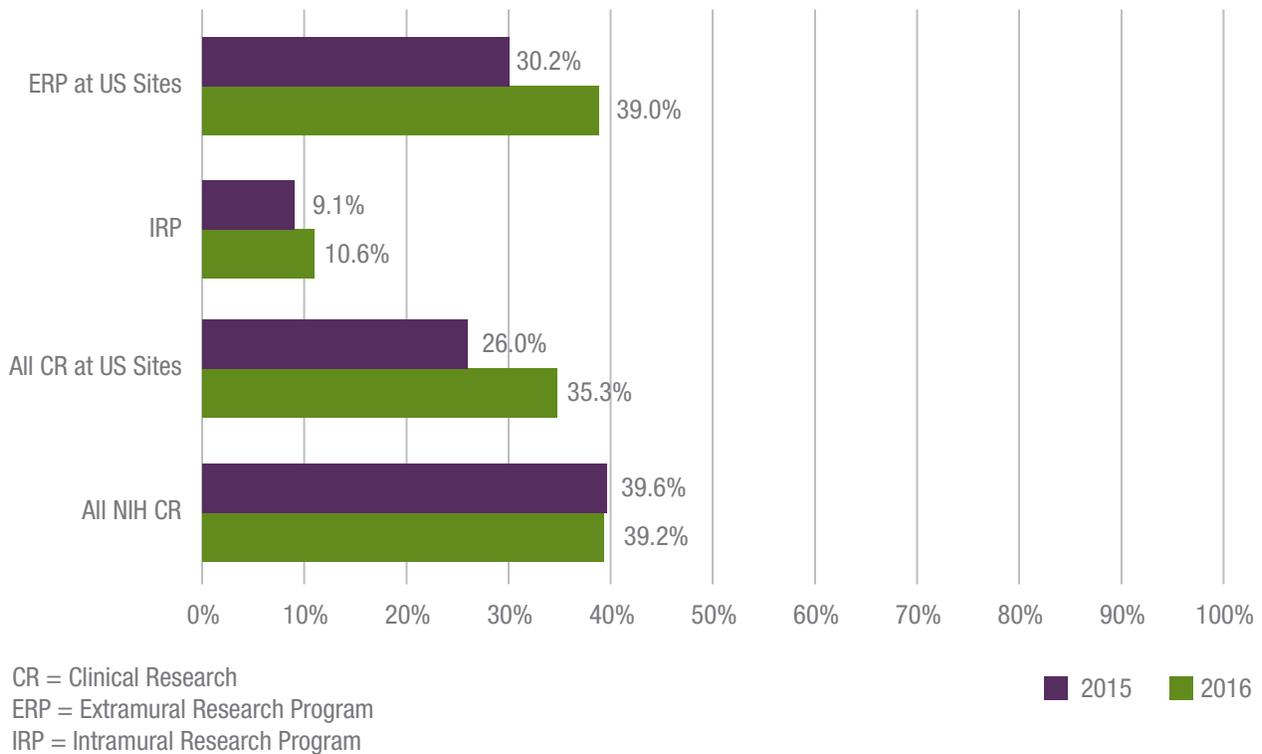
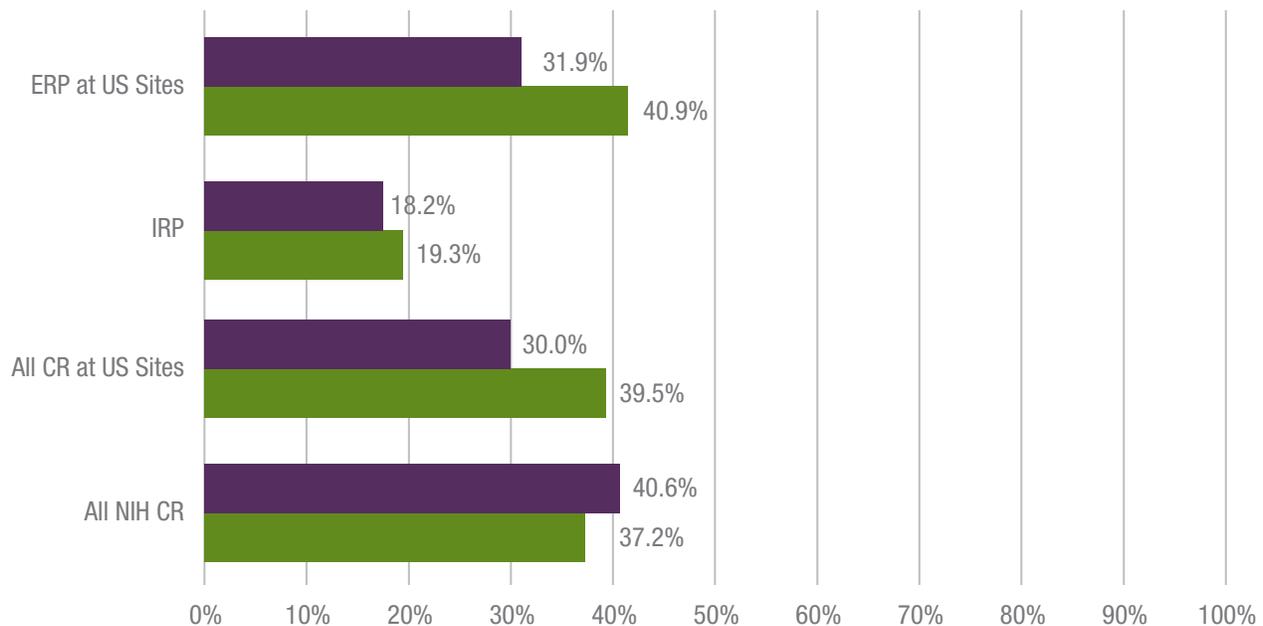


Figure 6: Percentage of Male Participants in NIH-Funded Clinical Research that are Members of Minority Groups FY 15 and FY 16



CR = Clinical Research
 ERP = Extramural Research Program
 IRP = Intramural Research Program

■ 2015 ■ 2016

Inclusion Trends in NIH-Defined Phase III Clinical Trials

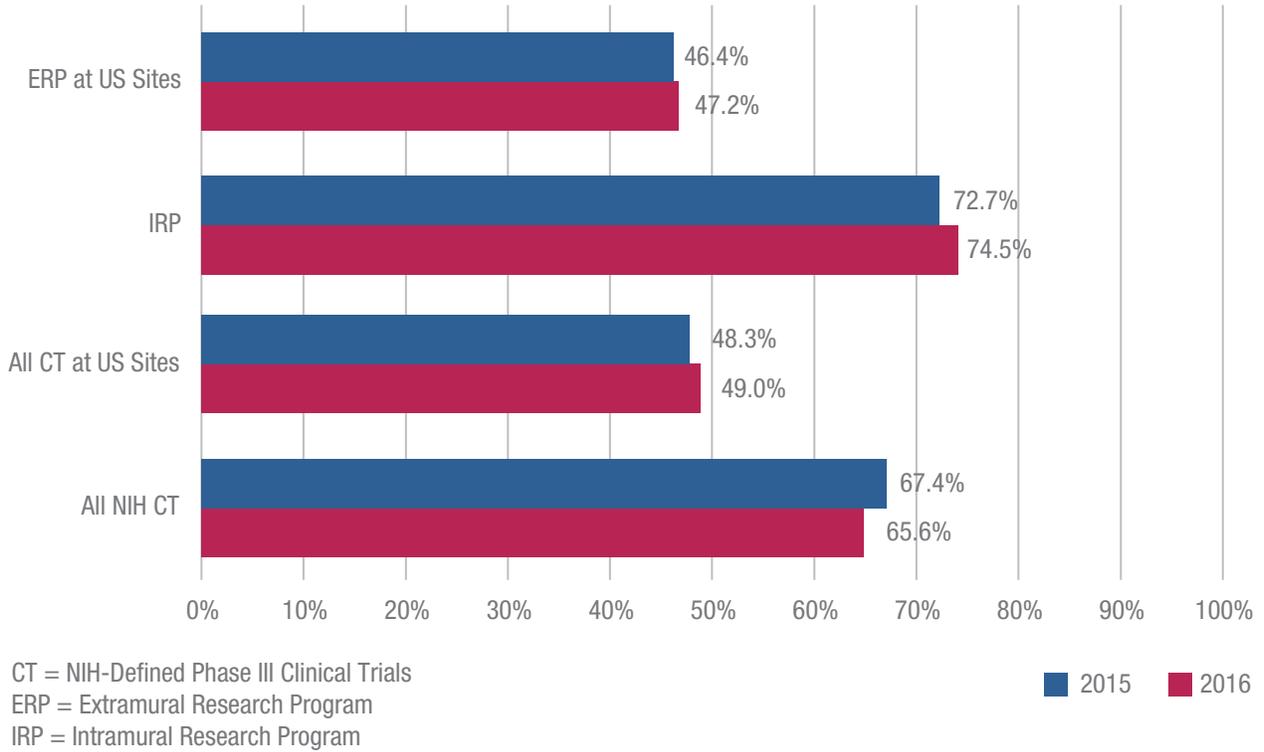
NIH-defined Phase III Clinical Trials are a subset of NIH Clinical Research studies. Enrollment for Phase III clinical trials are presented in **Figures 7** through **10**. As mentioned above, NIH defines Phase III Clinical Trials as those designed to determine the efficacy monitor adverse effects of biomedical or behavioral interventions in large groups of people (from several hundred to several thousand).

Figure 7 summarizes the proportion of women enrolled in NIH-Defined Phase III Clinical Trial in FY 15 and FY 16. For all categories presented in the Figure, women account for 46 percent–75 percent of research participants. **Tables 1E through 1H** in Appendix D (Aggregate Enrollment Data Tables) present enrollment data for FY 11 through FY 16. Enrollment of women in all NIH-defined Phase III clinical trials across this time period has been consistently greater than 50 percent. When studies

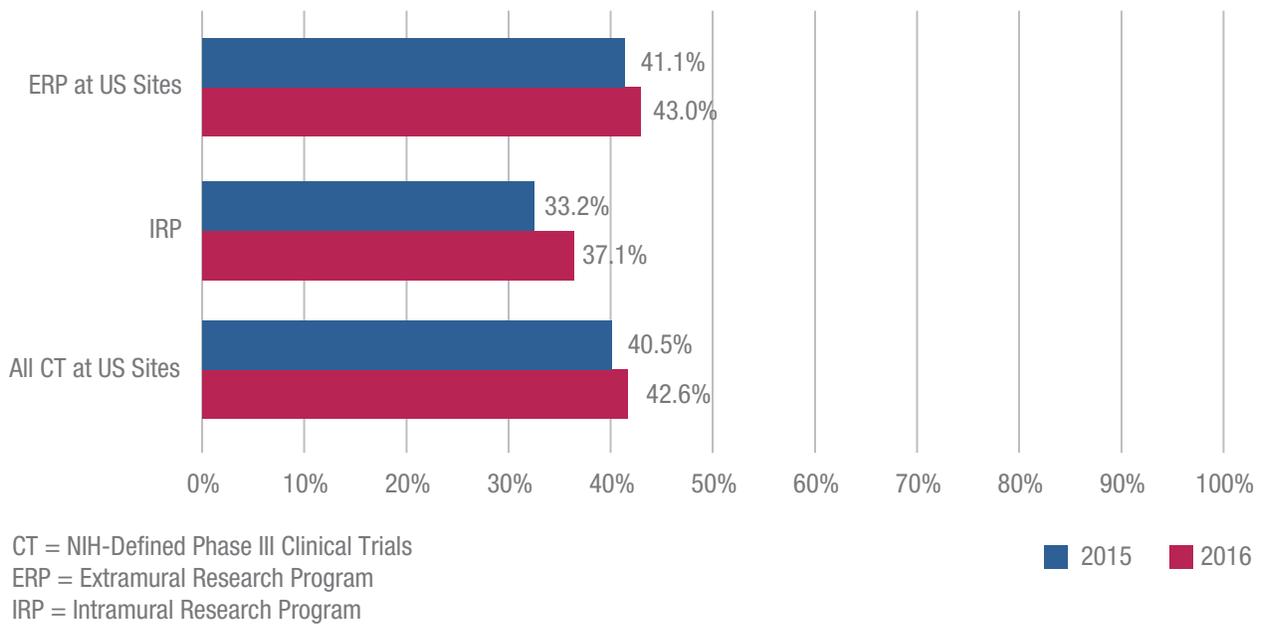
recruiting only female participants are excluded from the tallies, enrollment of women was 67 percent in FY 15 and 65 percent in FY 16. After exclusion of single-sex studies (i.e., men only, women only), the enrollment of women in Phase III clinical trials remains the same (67 percent in FY 15; 65 percent in FY 16).

Figure 8 summarizes the percentage of participants in NIH-Defined Phase III clinical trials at United States research sites and within the IRP that are members of minority groups. A summary of data for minority enrollment across all NIH Defined Phase III clinical trials, including those conducted outside of the U.S., is not provided in **Figures 8** through **10**, but is included in Appendix D (see **Table 3A**). Several large international Phase III clinical trials have included participants who self-report as members of minority groups and incorporation of those data in the overall summary inflates the minority proportion.

**Figure 7: Percentage of Participants in NIH-Defined Phase III Clinical Trials that are Female
FY 15 and 2016**



**Figure 8: Percentage of Participants in NIH-Defined Phase III Clinical Trials that are Members of Minority
Groups FY 15 and FY 16**





Participants in Phase III clinical trials conducted through the ERP include a larger portion of enrollees from minority groups than in IRP conducted clinical trials, although the difference is not as large as seen across all NIH clinical research (see **Figures 4-6**). **Tables 3A through 3D** in Appendix D provide a summary of minority enrollment in Phase III clinical trials from FY 11 to FY 16. **Tables 3E through 3L** provide a detailed breakdown of enrolled participants by race and ethnicity for FY 11 through FY 16.

To provide a more complete picture of minority enrollment in NIH-Defined Phase III clinical trials, **Figures 9 and 10** provide a summary of enrollment by sex/gender of minority participants. The percent of participant enrollment in clinical trials for women who are members of minority groups, 36–43 percent (**Figure 9**), is similar to the proportion of minority participants overall (**Figure 8**). Enrollment of male participants from minority groups, 25 to 44 percent (**Figure 10**), is lower for Phase III clinical trials

conducted through the IRP than for women from minority groups enrolled in IRP clinical trials. For clinical trials supported by the ERP, enrollment of male participants from minority groups is similar to enrollment levels for women from minority groups. **Tables 4A through 4D** in Appendix D provide details of inclusion from FY 11 to FY 16 of male and female participants in clinical research who are members of minority groups. **Tables 4L through 4O** provide a detailed breakdown of enrolled participants by race and ethnicity of male and female enrollees for FY 15 and FY 16.

Racial and Ethnic Breakdown of Participants Enrolled in NIH-Funded Clinical Research at U.S. Sites

Figures 11 and 12 provide an overview of self-reported race and ethnicity for participants enrolled in all NIH-Defined Phase III Clinical Trials at U.S. sites for FY 15 and FY 16.

Figure 9: Percentage of Female Participants in NIH-Defined Phase III Clinical Trials that are Members of Minority Groups FY 15 and FY 16

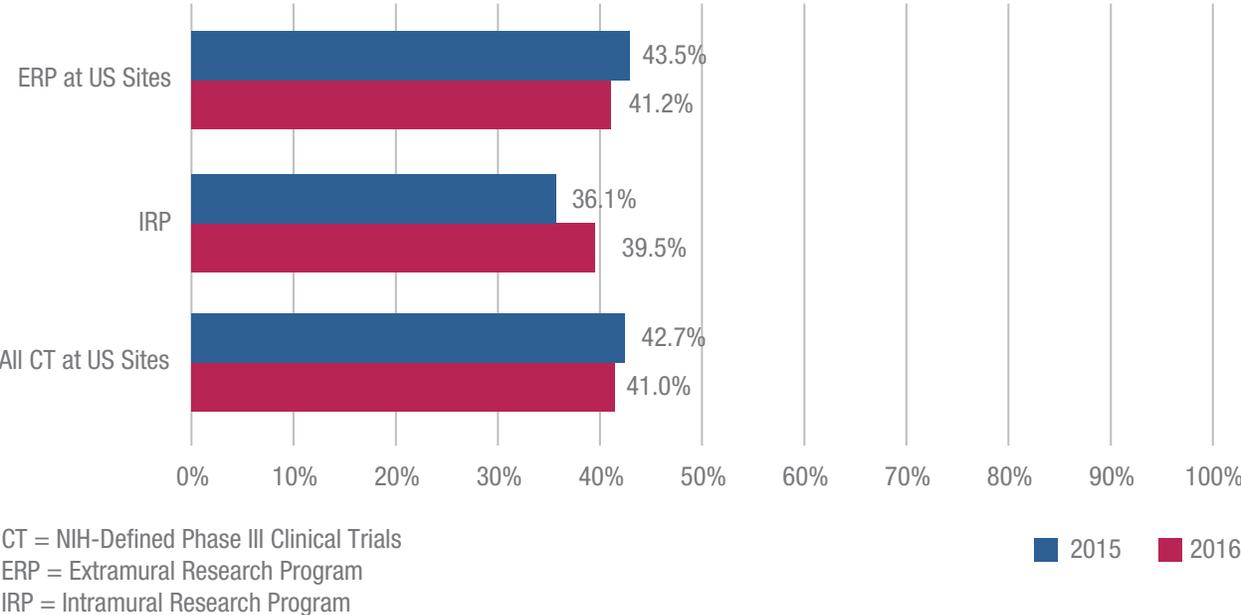


Figure 10: Percentage of Male Participants in NIH-Defined Phase III Clinical Trials that are Members of Minority Groups FY 15 and FY 16

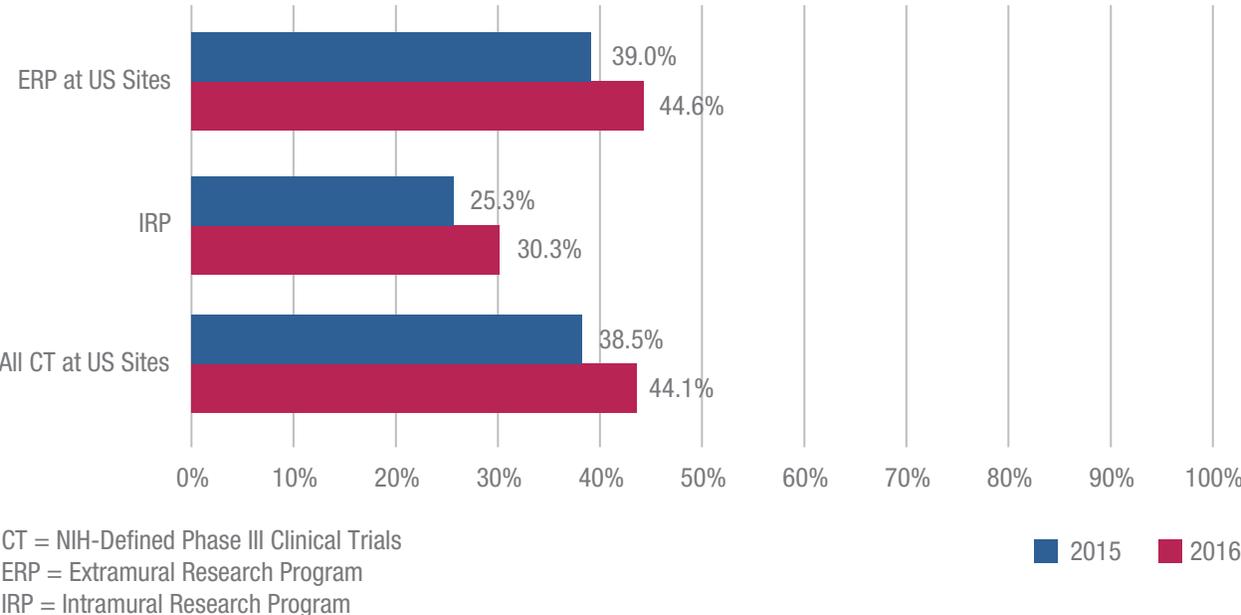


Figure 11: Enrollment for All NIH-Defined Phase III Clinical Trials at U.S. Sites Racial Categories FY 15 and FY 16

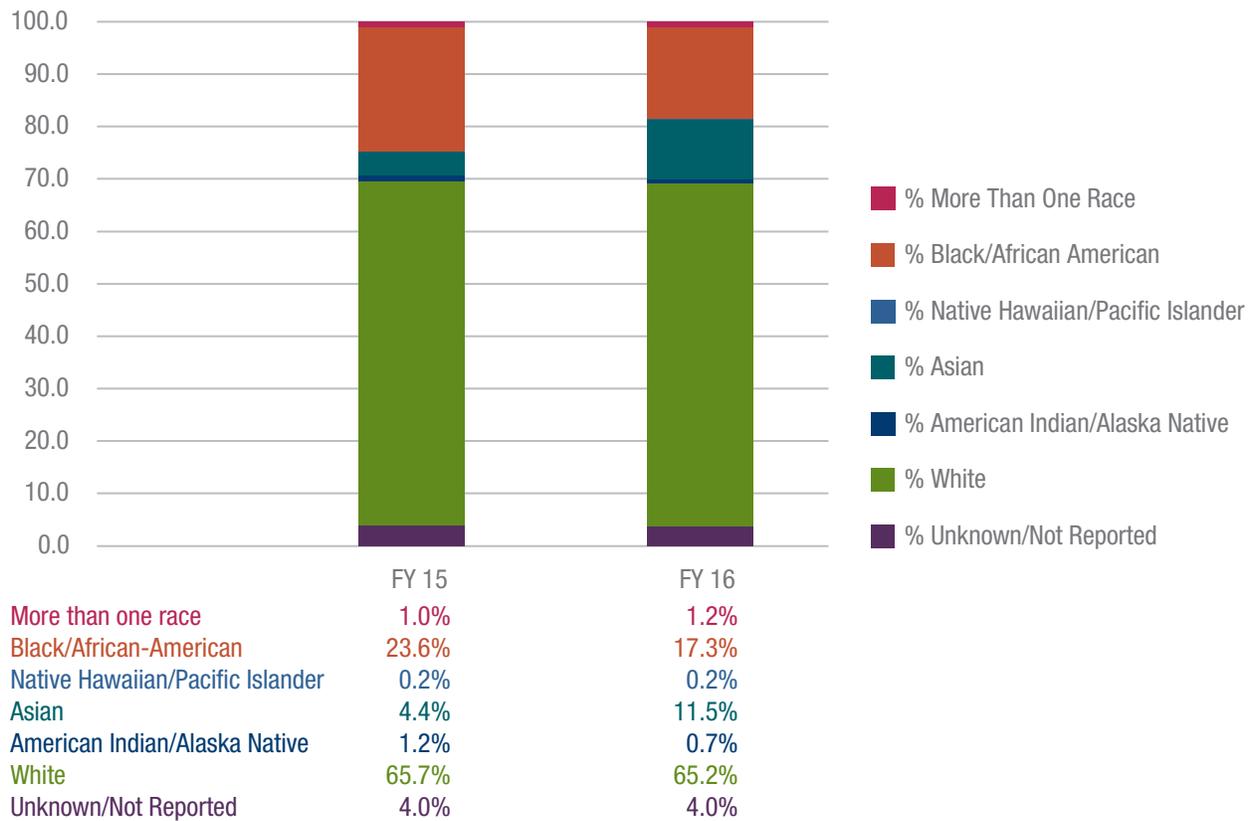
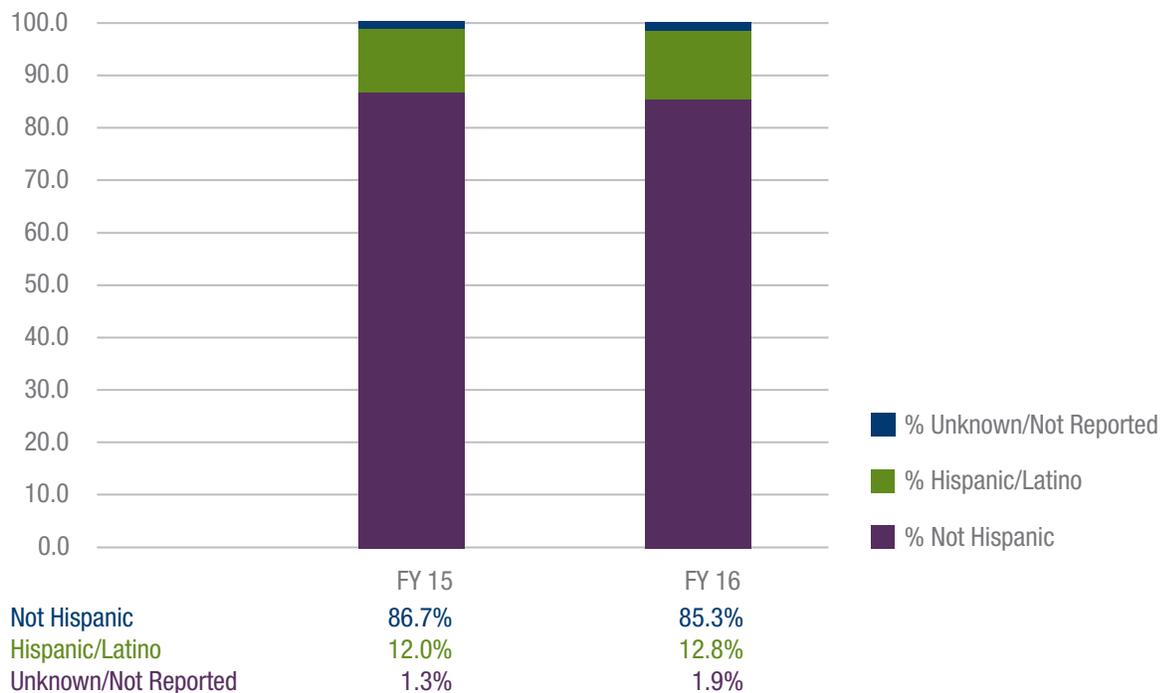


Figure 12: Enrollment for All NIH-Defined Phase III Clinical Trials at U.S. Sites Ethnic Categories for FY 15 and FY 16





Summary

In summary, recent improvements in the system of data collection on inclusion of women and minorities in NIH-funded clinical research have helped to streamline reporting over previous manual reporting processes. The Inclusion Management System has also provided an opportunity to allow for greater accuracy in reporting. Overall trends in the data show a consistent pattern of 50 percent or greater enrollment of women in NIH-Funded clinical research and in NIH-defined Phase III clinical trials since 2006. In FY 15 and FY 16, Minority enrollment for Phase III clinical trials is approximately 40% for U.S. sites overall; lower levels of minority enrollment are seen in the NIH Intramural Research Program, especially for inclusion of minority men.

ORWH Activities Related to NIH Inclusion Policies and Reporting

“Raising the Bar” Project

U.S. citizens have shorter years of life expectancy and suffer from more illness than residents in other high-income nations. In 2013, the National Research Council and Institute of Medicine released a report, *“U.S. Health in International Perspective: Shorter Lives, Poorer Health.”*³⁷ Through a systematic examination of the relevant data and studies, this report demonstrates that socioeconomic factors, racial-ethnic diversity, health insurance coverages and other related factors only partially explain the health disadvantages of the United States. Controlling for person-level

³⁷ National Research Council and Institute of Medicine. (2013). *U.S. Health in International Perspective: Shorter Lives, Poorer Health*. Panel on Understanding Cross-National Health Differences Among High-Income Countries, Steven H. Woolf and Laudan Aron, Eds. Committee on Population, Division of Behavioral and Social Sciences and Education, and Board on Population Health and Public Health Practice, Institute of Medicine. Washington, DC: The National Academies Press.



risk factors such as smoking and obesity, even for Americans in the higher socioeconomic stratum, has shown no effect on the life expectancy over the past decades. The finding that U.S. women's health is significantly worse than their counterparts in the peer countries is particularly disturbing. To improve U.S. women and people's health, there is an urgent need to study the underlying causes and associated health outcomes using new data and analyses. ORWH has been examining available disease prevalence and mortality data through a sex/gender lens and performing our own analyses to look for trends and areas of concern that would inform our research priorities and strategic planning going forward.

Grounded on the "*Shorter Lives, Poorer Health*" report, in September 2015, ORWH and the National Academies of Sciences jointly organized the "Raising the Bar: The Health of Women in America" workshop in Washington, D.C. Rather than reiterate U.S. women's health disadvantages relative to other economically-advanced nations, the Workshop situated its scope of discussion within the United States. In this event, attendees identified the causes and pathways of disease development, assessed the magnitudes of health disparities between different subgroups of the population, and articulated how

patient and provider-level determinants, health care service systems, as well as policies may result in intended and unintended consequences for U.S. women's health. The presentation contents from invited speakers were collated and published in 2016, entitled "Improving the Health of Women in the United States: Workshop Summary"³⁸ for future references.

As science evolves, it is imperative for the NIH community to adjust its scientific priorities accordingly. To guide the trans-NIH endeavors on women's health research, ORWH will update the current strategic plan, incorporating lessons learned through the Raising the Bar Workshop. To better understand the current status of women's health in the United States, ORWH will conduct descriptive data analyses and pinpoint key research areas that can be targeted to decrease mortality and morbidity in women. These analyses will take socioeconomic and contextual effects into consideration. For example, early-life experiences can have a cumulative impact on physical health, mental health, and quality of life in the later years. Also, investigation of health across the lifespan will likely identify critical time windows for early disease detection, thereby increase the prospect for effective prevention, treatment, and cure.

³⁸ National Academies of Sciences, Engineering, and Medicine. (2016). *Improving the Health of Women in the United States: Workshop Summary*. Washington, DC: The National Academies Press.



V. NIH Budget for Women’s Health Research

NIH Budgetary Expenditures for Research on Women’s Health, FY 15 and FY 16

NIH funding in research during FY 15 and FY 16 is presented in this budget summary, which focuses on diseases and conditions relevant to women. Budget officials at the individual NIH ICs and the NIH Office of Budget contributed the data in the tables in this chapter.

“Women’s health conditions,” as defined in section 141 of the NIH Revitalization Act of 1993 (42 U.S.C. § 287d), include all diseases, disorders, and conditions—

1. That are unique to, more serious, or more prevalent in women.
2. For which the factors of medical risk or types of medical intervention are different for women, or for which it is unknown whether such factors or types are different for women.
3. With respect to which there has been insufficient clinical research involving women as subjects or insufficient clinical data on women.

Research on women’s health conditions includes research on preventing such conditions and applies to women of all ages and racial and ethnic groups.

In collaboration with the HHS Coordinating Committee on Women’s Health (CCWH), ORWH reports the budgetary expenditures on women’s health throughout HHS. The reporting effort is coordinated by the Office on Women’s Health in the Office of the Assistant Secretary for Health. The HHS Office of the Assistant Secretary for Financial Resources and other women’s health offices and programs across HHS agencies contributed to the effort.

A collection of spending categories for diseases or disorders relevant to women is used for data collection and budgetary reporting on women’s health research. The spending categories are periodically updated to reflect (1) new disease categories, (2) new methods to standardize the proportion of the budget accounted for by women’s health research when enrollment data are not available, and (3) the inclusion of men as a comparison for those women’s health categories in which both men and women may be affected. For this latter point, the data collection process has evolved to account for studies in which men and women are both included and reported. For example, in some of the reports prior to FY 03 and FY 04, the budgetary reporting on women’s health expenditures focused on single-gender studies; studies to evaluate sex/gender differences; and studies of diseases, disorders, and conditions that are unique to women. Previous reporting also used prevalence data as part of the reporting criteria and included research on diseases, disorders, and conditions that are not unique to one sex but for which there is documented evidence of greater prevalence in one sex by a ratio of at least two to one, or for which a specific gender-related consideration exists.

For this report, budgetary expenditures are categorized as either inseparably combined, as supporting research on women’s health only, or supporting research on men’s health only. As a result of discussions with the CCWH and the NIH Coordinating Committee on Research on Women’s Health, uniform procedures for determining the appropriate categorical allocations were established. The guidelines for budget calculations are—

1. All funding for projects that focus primarily on women, such as the Nurses’ Health Study, the Mammography Quality Standards Act, and the Women’s Health Initiative, should be attributed to women.
2. For research, studies, services, or projects that include both men and women, recommended

methods to calculate the proportion of funds spent on women’s health are as follow:

- a. If target or accrual enrollment data are available, multiply the expenditure by the proportion of female subjects included in the program. For example, if 50 percent of the subjects enrolled in a trial, study, service, or treatment program are women, then 50 percent of the funds spent for that program should be counted as for women’s health. On the other hand, for diseases, disorders, or conditions without enrollment data, expenditures can be calculated based on the relative prevalence of that condition in women.
- b. Where both males and females are included, as may be the case for many basic science research projects, multiply the expenditure by 50 percent.

ORWH, with its advisory and coordinating committees, monitors the methodology used by the ICs for collecting budget data and provides input

to the CCWH’s efforts to optimize budget data collection methods.

Table 2 lists the overall NIH research expenditures in FY 15 and FY 16 for specific diseases, disorders, and conditions by women only, men only, and for both women and men. The health categories and subcategories in this table were developed to accommodate all agencies in HHS. The table will show zeros across all columns for subcategories that are not applicable to the NIH mission. Because the table is additive, zeros may be shown even for relevant subcategories. Even though conceptually a budget expenditure can apply to more than one subcategory, the funding must be applied to a single primary subcategory. When a budget expenditure overlaps multiple subcategories, the IC assigns the expenditure to the most scientifically appropriate subcategory. Because no overlap in reporting is allowed by the prescribed method of data collection for this report, the amounts listed for each individual topic area are potentially understated.

Table 2. HHS–NIH Research Budget for Women’s and Men’s Health by Disease, Condition, and Special Initiatives, FY 15 and FY 16 (Dollars in Thousands)^{38,39}

Disease, Condition, or Initiative	FY 15 Women	FY 15 Men	FY 15 Both	FY 15 Total	FY 16 Women	FY 16 Men	FY 16 Both	FY 16 Total
I. Cancer								
Breast cancer (including mammography and other services)	700,106	3	3,275	703,384	688,957	151	5,054	694,162
Reproductive cancers								
Cervical	85,542	1,013	10,483	97,038	90,491	705	9,384	100,580
Ovarian	108,816	0	474	109,290	120,189	87	430	120,706
Vaginal, uterine, and other	26,577	2	0	26,579	25,439	21	38	25,498
Lung cancer	149,512	190	131,593	281,295	180,600	318	135,655	316,573
Colorectal cancer	134,496	1,704	140,914	277,114	118,658	1,525	143,000	263,183
Other neoplasms	22,359	63,281	4,034,908	4,120,547	26,459	56,071	4,032,881	4,115,410
Subtotal	1,227,408	66,193	4,321,646	5,615,247	1,250,793	58,877	4,326,442	5,636,112

³⁸ These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas.

³⁹ Figures shown in this table do not include NIH Buildings and Facilities program spending.

Disease, Condition, or Initiative	FY 15 Women	FY 15 Men	FY 15 Both	FY 15 Total	FY 16 Women	FY 16 Men	FY 16 Both	FY 16 Total
II. Cardiovascular/Pulmonary								
Blood diseases	42,299	73,413	368,602	484,314	76,199	75,921	403,730	555,850
Heart disease	140,233	84,951	417,014	642,198	166,058	124,132	786,209	1,076,399
Stroke	22,154	135	215,361	237,650	23,028	371	234,874	258,273
Other cardiovascular diseases/disorders	148,563	111,486	1,152,724	1,412,773	94,809	50,286	892,039	1,037,134
Pulmonary diseases	71,060	74,667	405,500	551,227	108,886	98,684	386,208	593,778
Asthma	35,209	37,605	155,633	228,447	50,157	38,178	142,807	231,142
Other	700	0	350,952	351,652	496	0	373,715	374,211
Subtotal	460,218	382,257	3,065,786	3,908,261	519,633	387,572	3,219,582	4,126,787
III. Reproductive and Maternal/Child/Adolescent Health								
Contraception	20,117	10,317	61,519	91,953	22,016	7,705	76,071	105,792
Infertility	3,026	1,953	9,118	14,097	3,446	1,863	10,955	16,264
Female reproductive physiology	75,334	0	250	75,584	72,307	133	256	72,697
Hysterectomy	0	0	0	0	0	0	0	0
Endometriosis/leiomyomas (fibroids)	13,914	0	396	14,310	7,558	0	419	7,977
Pregnancy/pregnancy prevention/maternal health	228,126	280	15,503	243,910	233,765	765	2,051	236,581
Diseases related to diethylstilbestrol exposure	0	0	0	0	0	0	0	0
Female genital cutting	0	0	0	0	0	0	0	0
Pelvic floor disorders	1,199	0	0	1,199	1,132	0	0	1,132
Other	5,252	12,731	583,027	601,010	11,435	10,960	539,028	561,422
Subtotal	346,968	25,282	669,813	1,042,063	351,659	21,427	628,780	1,001,865
IV. Aging								
Menopause	23,884	0	0	23,884	24,880	0	0	24,880
Menopausal hormone/nonhormone therapy	10,437	0	0	10,437	9,946	0	0	9,946
Alzheimer's disease	129,697	110,287	278,036	518,020	293,215	195,494	288,395	777,104
Malnutrition in the elderly	69	46	0	115	72	48	0	120
Osteoarthritis	52,497	3,643	57,340	113,480	55,444	4,864	52,264	112,572
Osteoporosis (including fractures)	88,979	7,246	16,198	112,423	79,622	6,344	4,736	90,702
Women's Health Initiative	2,070	0	0	2,070	0	0	0	0
Demography of aging	25,800	21,142	7,470	54,412	49,197	25,392	0	74,589
Aging economics	17,029	16,681	7,985	41,695	19,752	15,854	13,032	48,638
Other	147,938	129,775	490,389	768,102	162,784	150,900	594,526	908,210
Subtotal	498,400	288,820	857,418	1,644,638	694,912	398,896	952,953	2,046,761

Disease, Condition, or Initiative	FY 15 Women	FY 15 Men	FY 15 Both	FY 15 Total	FY 16 Women	FY 16 Men	FY 16 Both	FY 16 Total
V. Metabolism, Endocrinology, and Gastrointestinal								
Diabetes	106,964	80,746	105,122	292,833	161,397	119,798	178,443	459,638
Obesity	161,823	106,421	103,672	371,916	179,068	97,349	110,504	386,921
Hepatobiliary diseases	1,935	3,028	232,685	237,648	1,938	2,973	239,654	244,565
Thyroid diseases/conditions	11,364	2,844	0	14,208	11,756	2,939	0	14,695
Fecal incontinence	936	623	0	1,559	1,273	849	0	2,122
Irritable bowel syndrome	5,728	2,015	667	8,410	4,288	1,391	17	5,696
Other	2,472	1,382	114,717	118,571	2,359	1,627	145,966	149,952
Subtotal	291,222	197,059	556,863	1,045,145	362,079	226,926	674,584	1,263,589
VI. Substance Abuse								
Etiology (<i>unspecified</i>)	8,064	9,293	89,809	107,166	8,927	10,335	98,104	117,366
Epidemiology (<i>unspecified</i>)	29,253	26,622	72,020	127,895	33,212	33,430	58,808	125,450
Prevention (<i>unspecified</i>)	26,871	25,335	42,691	94,897	28,092	28,571	43,222	99,885
Treatment (<i>unspecified</i>)	81,213	80,850	157,023	319,086	84,679	91,895	150,895	327,469
Alcohol	19,074	21,957	114,322	155,353	20,117	22,842	127,949	170,908
Illegal drugs	115,506	108,227	212,144	435,877	112,233	115,211	202,384	429,828
Prescription drugs	11,375	10,916	21,713	44,004	11,514	12,114	21,328	44,956
Tobacco products	26,456	24,138	64,801	115,394	25,975	25,881	62,415	114,271
Other substances	841	925	1,514	3,280	1,354	1,090	11,360	13,804
Co-occurring substance abuse and mental disorders	1,110	719	2,895	4,724	1,207	1,017	3,968	6,192
Subtotal	319,763	308,982	778,933	1,407,677	327,310	342,385	780,433	1,450,128
VII. Behavioral Studies/Programs								
Violence (<i>including domestic, abused women, spouse abuse, elder abuse, violence against women, trafficking, and bullying</i>)	4,081	2,130	14,730	20,941	5,139	2,305	15,679	23,123
Tobacco use cessation	162	103	2,849	3,114	380	110	2,636	3,126
Physical activity/exercise/nutrition (<i>promoting healthy behavior</i>)	2,772	1,439	224,791	229,002	3,081	1,782	228,914	233,777
Other behavior change/risk modification	17,317	9,170	456,761	483,248	18,210	14,998	491,877	525,085
Caregiving	300	0	12,234	12,534	455	239	17,949	18,643
Other	5,724	3,581	396,707	406,012	23,481	4,366	540,549	568,396
Subtotal	30,356	16,423	1,108,072	1,154,850	50,746	23,800	1,297,604	1,372,150

Disease, Condition, or Initiative	FY 15 Women	FY 15 Men	FY 15 Both	FY 15 Total	FY 16 Women	FY 16 Men	FY 16 Both	FY 16 Total
VIII. Mental Health								
Etiology (<i>unspecified</i>)	1,046	1,254	32,953	35,253	531	882	29,443	30,857
Epidemiology (<i>unspecified</i>)	498	0	19,721	20,219	0	0	925	925
Prevention (<i>unspecified</i>)	102	91	642	836	151	118	208	478
Treatment (<i>unspecified</i>)	767	249	3,205	4,221	270	231	2,441	2,942
Depression/mood disorders	20,797	592	110,066	131,456	24,326	647	114,021	138,994
Suicide	1,816	642	25,210	27,668	1,916	156	32,140	34,212
Schizophrenia	764	84	103,228	104,076	3,695	99	101,251	105,045
Anxiety disorders	2,299	1,018	39,907	43,224	4,946	1,076	39,695	45,717
Eating disorders	5,894	0	5,513	11,407	6,619	0	5,625	12,244
Psychosocial stress	4,538	701	20,175	25,414	4,948	650	24,188	29,786
Posttraumatic stress disorder	2,843	1,379	11,936	16,158	2,282	579	14,080	16,941
Other mental disorders (<i>excluding Alzheimer's</i>)	31,323	4,772	786,090	822,185	50,896	6,665	808,889	866,451
Autism	3,713	32,288	91,399	127,400	5,439	35,261	93,497	134,197
Subtotal	76,400	43,070	1,250,047	1,369,517	106,020	46,365	1,266,403	1,418,789
IX. Infectious Diseases								
AIDS/HIV	188,024	120,895	1,988,859	2,297,779	185,901	126,696	2,253,331	2,565,928
Tuberculosis	9,397	26,767	171,940	208,105	14,094	30,290	165,828	210,212
Sexually transmitted diseases	24,120	19,210	157,685	201,015	26,054	19,032	115,571	160,657
Topical microbicides	95,168	0	2,059	97,227	89,665	0	4,398	94,063
Toxic shock syndrome	461	0	0	461	1,003	0	0	1,003
Tropical diseases (<i>including malaria</i>)	24,063	26,192	501,332	551,586	36,165	33,017	541,557	610,738
Other	687	97	709,762	710,547	908	326	596,292	597,526
Subtotal	341,921	193,162	3,531,637	4,066,720	353,790	209,360	3,676,978	4,240,128
X. Immune Disorders								
Rheumatoid arthritis	37,602	1,407	139,953	178,962	43,729	1,501	144,110	189,339
Lupus erythematosus	43,818	4,779	25,951	74,548	56,060	4,590	22,594	83,244
Multiple sclerosis	30,934	2,192	46,407	79,533	16,973	2,485	62,532	81,990
Myasthenia gravis	262	223	514	999	67	52	513	632
Scleroderma	11,131	566	950	12,647	9,212	358	1,679	11,249
Sjögren's syndrome	9,923	92	495	10,510	18,693	0	182	18,875
Takayasu disease	0	0	0	0	0	0	0	0
Other	502	197	177,807	178,506	2,846	2,685	191,356	196,888
Subtotal	134,172	9,456	392,077	535,705	147,580	11,671	422,966	582,217

Disease, Condition, or Initiative	FY 15 Women	FY 15 Men	FY 15 Both	FY 15 Total	FY 16 Women	FY 16 Men	FY 16 Both	FY 16 Total
XI. Neurologic, Muscular, and Bone								
Trauma research								
Brain	8,569	0	221,400	229,969	12,615	0	233,976	246,591
Other neurologic trauma	100	0	17,302	17,402	0	0	13,243	13,243
Bone fracture (<i>non osteoporotic</i>) and muscle injury	23	40	18,839	18,902	24	41	24,404	24,469
Muscular dystrophy	709	31,286	27,650	59,645	1,360	31,016	33,136	65,512
Chronic pain conditions	6,664	13	131,200	137,877	10,639	44	134,732	145,415
Temporomandibular disorders	14,787	0	174	14,961	13,645	0	146	13,791
Vulvodynia	1,537	0	227	1,764	1,586	0	227	1,813
Fibromyalgia and eosinophilic myalgia	3,675	0	0	3,675	3,850	0	0	3,850
Migraine	88	0	3,024	3,112	3,738	0	7,559	11,297
Sleep disorders	1,102	383	53,424	54,909	1,826	432	59,582	61,840
Paget's disease	0	0	899	899	0	0	1,029	1,029
Parkinson's disease	2,465	775	120,464	123,704	5,217	797	127,372	133,386
Seizure disorders	5,726	45	112,765	118,536	7,494	171	115,935	123,600
Other	27,708	7,463	1,089,992	1,125,163	25,828	7,784	1,199,360	1,232,972
Subtotal	73,153	40,005	1,797,360	1,910,518	87,823	40,286	1,950,700	2,078,809
XII. Kidney and Urologic								
Urinary tract infections (<i>cystitis, pyelonephritis</i>)	8,498	2,586	25,455	36,539	8,673	3,653	26,173	38,499
End-stage renal disease/transplantation	2,656	8,717	100,810	112,183	7,498	10,333	97,995	115,826
Urinary incontinence	7,391	0	0	7,391	9,647	0	0	9,647
Painful bladder, interstitial cystitis	8,911	923	546	10,380	10,099	1,038	900	12,037
Other	649	4,043	415,692	420,384	482	3,129	434,244	437,855
Subtotal	28,105	16,269	542,503	586,877	36,399	18,153	559,312	613,864
XIII. Ophthalmic, Otolaryngologic, and Oral Health								
Eye diseases and disorders	23,440	14,897	698,049	736,386	20,088	11,556	737,885	769,529
Ear diseases and disorders	12,784	0	204,403	217,187	12,519	0	203,140	215,659
Dental and oral health	0	245	358,264	358,509	4,063	314	371,910	376,287
Other	317	268	1,861	2,446	513	313	1,961	2,787
Subtotal	36,541	15,410	1,262,577	1,314,528	37,183	12,183	1,314,895	1,364,261

Disease, Condition, or Initiative	FY 15 Women	FY 15 Men	FY 15 Both	FY 15 Total	FY 16 Women	FY 16 Men	FY 16 Both	FY 16 Total
XIV. Health Effects of the Environment								
Environmental estrogens	13,411	370	9,720	23,501	11,252	0	11,216	22,468
Health effects of toxic exposure (excluding cancer)	103	3	109,740	109,846	1,302	2	110,411	111,716
Toxicological research and testing program	0	0	94,566	94,566	0	0	97,560	97,560
Chemical/biological warfare agents	100	0	1,473	1,573	0	0	2,708	2,708
Other	0	7	5,121	5,128	429	12	5,739	6,179
Subtotal	13,614	380	220,619	234,614	12,983	14	227,634	240,631
XV. Cross Cutting Categories and Special Initiatives								
Treatment, prevention, and services	4,071	10,020	423,329	437,420	5,819	12,257	449,854	467,930
Access to health care and financing	260	252	35,662	36,174	744	319	7,511	8,574
Education and training for health care providers	7,818	1,842	91,486	101,145	3,599	1,740	67,862	73,201
Health literacy and bilingual information	477	532	25,614	26,623	407	264	25,986	26,657
Cultural influences	2,596	1,429	70,598	74,623	2,584	2,294	97,207	102,085
Disability research and services	10	313	111,453	111,776	620	1,409	105,246	107,275
Homelessness	65	328	384	777	20	320	390	730
Chronic fatigue syndrome	2,854	1,052	1,264	5,170	3,581	1,257	2,730	7,568
Breast feeding	0	0	0	0	0	0	0	0
Organ donation	417	0	1,283	1,700	0	0	1,411	1,411
Genetic services/counseling	11,415	8,937	10,954	31,306	10,829	8,047	14,680	33,556
Unintentional injury	76	347	43,085	43,509	113	428	53,282	53,823
Alternative and complementary therapies	31,726	25,028	114,628	171,382	33,229	30,038	134,779	198,046
Health statistics and data collection	1,824	1,559	55,110	58,493	2,454	2,395	59,225	64,074
Programs/Offices on/of Women's Health	31,244	6,195	1,436,041	1,473,480	118,826	5,767	1,577,247	1,701,839
Global health	14,805	77,879	1,519,525	1,612,209	16,814	79,363	1,842,012	1,938,188
Drug metabolism (sex differences, pregnancy, etc.)	1,396	305	5,665	7,366	1,405	625	4,788	6,818
Other cross-cutting ⁴⁰								
Subtotal	111,054	136,017	3,946,082	4,193,153	201,043	146,524	4,444,209	4,791,777
Total	3,989,295	1,738,786	24,301,433	30,029,514	4,539,952	1,944,440	25,743,476	32,227,868

⁴⁰ Category is no longer valid. Programs/Offices on/of Women's Health acts as a replacement.

Table 3 shows the dollar amounts and percentages of the NIH research budget in FY 15 and FY 16 for women and for men only as well as for research including both women and men. Overall, the proportion of the research budget supporting women only was 14 percent for both FY 15 and

FY 16. The proportion of the research budget supporting men only was 6 percent for both FY 15 and FY 16, which likely reflects bias in the construction of data categories on diseases, conditions, and disorders relevant to women or occurring only in women.

Table 3. FY 15 and FY 16 Summary: NIH Research Budget by Sex (Dollars in thousands)

Category	FY 15, \$	FY 16, \$	FY 15, %	FY 16, %
Women	3,989,295	4,539,952	14%	14%
Men	1,738,786	1,944,440	6%	6%
Both	24,301,433	25,743,476	80%	80%
Total	30,029,514	32,227,868	100%	100%

Reference

NIH Reform Act of 2006, H.R. 6164, 109th Congress. (2007).







REPORT OF THE
NIH INSTITUTES
AND CENTERS

National Cancer Institute (NCI)

Executive Summary

There is encouraging news for the American public—deaths due to all cancers combined for both sexes declined by 13 percent over the 10-year period through 2013. The death rates continue to fall. For women, this reflects a 12 percent decrease in deaths due to all cancers. Yet, in 2017, 282,500 women are expected to die from cancer in the United States, with lung cancer being the leading cause of cancer death in women.

Breast, lung, and colon cancers are the three most commonly diagnosed cancers among U.S. women, accounting for approximately 50 percent of all estimated new cases each year. These same three cancers also are the leading causes of cancer deaths in women of all ages. However, in women ages 20 to 39 years, breast cancer and cervical cancer are the first and second leading causes of cancer deaths. Thus, female-specific cancers are the leading cause of cancer deaths among young women.

The declines in cancer mortality noted are attributable to the progress made in our basic understanding of cancer and to advances in cancer prevention, screening, and treatment. However, improvement has not been equal in all cancers, nor among all populations, with minority and underserved women burdened by increased rates of cancer incidence and mortality. Additional research and more progress are needed to reduce cancer disparities.

The National Cancer Institute (NCI) coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and the families of cancer patients. This report highlights progress being made in the basic understanding of cancer, cancer control (including primary prevention),

and treatment that has helped to reduce cancer morbidity and mortality in women.

Over the past 2 years, NCI-supported researchers have made significant strides in understanding a variety of cancers that affect women. Some of the most promising results include initial findings from the TAILORx clinical trial, which showed that women with early-stage hormone receptor-positive breast cancer with a low risk of recurrence could be spared chemotherapy. Additionally, combined data from two large clinical trials have shown that fewer doses of the human papillomavirus (HPV) vaccine (one or two doses) are as efficacious as the standard three-dose regimen at preventing HPV-16/18 infections, which cause the majority of cervical cancers.

NCI also is enabling basic and translational research related to women's health, as well as population-based studies aimed at identifying cancer risks and improving outcomes. To this end, in 2016, NCI-supported research led to the development of a new tool to assess breast cancer risk specifically for Hispanic women. This tool will be incorporated into NCI's online breast cancer risk assessment tool (www.cancer.gov/bcrisktool), which currently lacks risk assessment for this group. In addition, NCI remains dedicated to expediting the dissemination of research advances, knowledge, and beneficial interventions to the scientific community and diverse public audiences via numerous resources related to women's health. Additional information on women's health issues related to cancer can be found on NCI's website, www.cancer.gov.

Introduction

Based on recent statistics, it is estimated that 852,630 women in the United States will be diagnosed with cancer and that 282,500 women will die from the disease during 2017. The most commonly diagnosed cancers among U.S. women are breast, lung, and colon cancer. Collectively,

these cancers account for about half of the new cancer cases and are the three major causes of cancer-related deaths in women. Although breast cancer is the most prevalent, lung cancer is the deadliest cancer among women.

To understand our Nation's progress in fighting cancer, epidemiologists measure cancer incidence rates and mortality rates each year and compare these rates over time. The incidence rate reflects how many new cases of cancer appeared in the population, whereas the mortality rate reflects how many people have died as a result of cancer. NCI collects data on every case of cancer reported in 20 U.S. geographic areas covering about 30 percent of the U.S. population through the Surveillance, Epidemiology, and End Results (SEER) cancer registry program. This information is used by thousands of researchers, clinicians, public health officials, legislators, policymakers, community groups, and the public.

According to the 2016 *Annual Report to the Nation on the Status of Cancer* (Ryerson et al., 2016), between 2003 and 2012, the overall cancer incidence rates for women remained stable, whereas the overall cancer mortality rates decreased by 1.4 percent on average annually, which signifies real progress in cancer control for our Nation. Primary prevention, early detection, and improved treatments are the main contributors to this progress. Improved treatment strategies include combination therapy, targeted drugs, and use of genetic testing to determine treatment.

Lung cancer is the leading cause of cancer-related death in women, with a projected 105,510 new cases, and 71,280 deaths in 2017. Due primarily to reduced smoking in the population, incidence rates for lung cancer in women decreased by about 1.3 percent between 2003 and 2012, while mortality rates decreased by 1.4 percent per year. Smoking cigarettes is still the major contributing risk factor for developing lung cancer, with an estimated 80 percent of lung cancer deaths in the United States attributed to smoking. The website women.smokefree.gov is a resource designed specifically

for women to help prevent and stop tobacco use among women. It is anticipated that further decreases in lung cancer will occur in future years because of reduced tobacco use among women.

Breast cancer is the second-leading cause of cancer-related death in women. An estimated 252,710 women will be diagnosed with breast cancer in 2017, and 40,610 women will die from the disease. Risk factors for developing breast cancer include inherited mutations and family history of breast cancer, although most breast cancers are sporadic and nonhereditary. From 2003 to 2012, incidence rates for breast cancer among women were stable, whereas mortality rates declined by 1.9 percent per year. Improved treatments contributed significantly to this decline.

Colon cancer is the third-leading cause of cancer-related death in women. In 2017, an estimated 64,010 women will be diagnosed with colon cancer, and 23,110 women are projected to die from colon cancer. From 2003 to 2012, both the incidence rate and the mortality rate for colorectal cancer in women declined by 2.9 percent per year. One reason for this progress is higher uptake of screening in the population, which enables doctors to find and excise polyps and precancerous lesions, preventing their progression to cancer.

In addition to lung, breast, and colon cancers, cervical and ovarian cancers are female-specific cancers that impact women's health. In 2017, approximately 12,820 new cases of cervical cancer will be diagnosed and more than 4,000 deaths are projected. For ovarian cancer, an estimated 22,440 new cases are projected, with 14,080 deaths from the disease in 2017.

NCI supports numerous research programs and projects that address cancers specific to or primarily affecting women, especially those cancers with high incidence or mortality among women, as well as cancers that affect both sexes to a similar degree. These endeavors focus on all stages of disease, from prevention through cancer survivorship, and range from laboratory investigation of the basic mechanisms of cancer biology to community-based

interventions to prevent cancers and improve outcomes.

It is an exciting time in cancer research, with two major initiatives started in 2015 and 2016—the Precision Medicine Initiative® (PMI) in oncology and the Beau Biden Cancer MoonshotSM, respectively. The PMI in oncology launched the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) clinical trial. NCI-MATCH is the first of its kind—a large, nationwide precision medicine oncology trial enrolling patients regardless of where in the body their cancers originated (e.g., breast, colon, lung). NCI-MATCH is enrolling patients with any type of solid tumor or lymphoma who are no longer responding to standard therapy and seeking to “match” them with one or more of the many targeted drugs being studied in the trial. To accomplish this, DNA from the patient’s tumors is sequenced to identify any actionable genetic alteration for which a targeted trial drug is available. This clinical trial design illustrates the essence of precision medicine for cancer patients—individualized treatment based on the specific molecular characteristics of the patient’s disease. This trial marks the realization of the era of precision oncology treatment.

The Beau Biden Cancer MoonshotSM seeks to accelerate progress in cancer research, accomplishing in 5 years what would normally take 10 years. Ten areas of cancer research were recommended for acceleration by a Blue Ribbon Panel of leading experts from a broad range of scientific areas, as well as representatives of cancer advocacy groups and pharmaceutical and biotechnology companies. These recommendations include expanding the use of proven prevention and early detection strategies. This calls for boosting prevention research to increase tobacco control, colon cancer screening, and HPV vaccine uptake. These actions would greatly benefit women’s health by reducing their risk for developing numerous types of cancer. The recommendation also calls for increasing testing for Lynch syndrome—which is associated with increased risk of several cancers,

including colon and endometrial cancers—and for hereditary breast and ovarian cancer syndromes.

NCI also is committed to disseminating research advances to the scientific community and the public and sustains numerous resources related to women’s health. The award-winning NCI website, www.cancer.gov, serves a diverse range of audiences, including Spanish speakers (www.cancer.gov/espanol). NCI’s Cancer Information Service provides the latest, most accurate information about cancer treatment, clinical trials, early detection, and prevention for cancer patients, their families, and the public at 1-800-4-CANCER (1-800-422-6237). An instant-messaging service called LiveHelp also is available on the NCI website.

Although far from comprehensive, the following summary provides a representative sample of the accomplishments and activities of NCI related to women’s health in fiscal years (FY) 15 and 16. Disease areas included in this report are breast, cervical, ovarian, and uterine cancers and melanoma.

Accomplishments by Cancer Type

Breast Cancer

The TAILORx Clinical Trial Uses a Genomic Profiling Assay to Identify Low-Risk Breast Cancer Patients and Spare Them Chemotherapy.

Previous studies have shown that gene expression profiles of tumor samples can provide valuable prognostic information. Sparano et al. (2015) reported the first results from the randomized, Phase III, TAILORx clinical trial, in which gene expression profiles were used to calculate a score that indicates the risk of breast cancer recurrence in women with hormone receptor-positive, *HER2*-negative, node-negative disease. Women with low recurrence scores were randomized to endocrine therapy alone without chemotherapy and had very low rates of recurrence at 5 years. These results reaffirm the prognostic value of gene expression

profiling in choosing the right therapy for women with certain types of breast cancer.

Combination of Docetaxel and PANVAC Increases Progression-Free Survival in Patients with Metastatic Breast Cancer. Preclinical data have shown that docetaxel can make tumor cells more amenable to T cell-mediated killing. Previous trials of PANVAC have suggested that this poxvirus-based cancer vaccine shows clinical efficacy in some patients with breast, ovarian, and colon cancer. The results of this Phase II clinical trial by Heery et al. (2015) suggest that the combination of docetaxel and PANVAC in metastatic breast cancer may provide a clinical benefit.

Extending Aromatase Inhibitor Adjuvant Therapy to 10 Years Reduces the Risk of Breast Cancer Recurrence. The Canadian Cancer Trials Group conducted a Phase III, randomized, double-blind, placebo-controlled trial designed to evaluate the effect of extending letrozole treatment for an additional 5 years following 5 years of treatment with an aromatase inhibitor or after tamoxifen therapy in postmenopausal women with primary breast cancer. Goss et al. (2016) reported that extending treatment with an aromatase inhibitor to 10 years resulted in significantly higher rates of disease-free survival and a lower incidence of contralateral breast cancer, compared to women treated with placebo. However, the rate of overall survival was not higher with the additional 5 years of an aromatase inhibitor compared with placebo.

Phase I Trial of Targeted T-Cell Therapy in Stage IV Breast Cancer. Effective treatments are urgently needed for patients with metastatic breast cancer with *HER2*-negative disease. Lum et al. (2015) conducted a Phase I clinical trial using activated T cells (aATC) armed with an anti-*HER2* × anti-CD3 bispecific-antibody (HER2Bi) to target *HER2*-negative and *HER2*-positive metastatic breast cancer in combination with IL-2 and GM-CSF. The study demonstrated that infusions of HER2Bi aATC are feasible and safe and did not cause dose-limiting toxicities. Two follow-up Phase II trials are ongoing.

Creating Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. Invasive lobular carcinoma is the second most prevalent histologic subtype of invasive breast cancer. Ciriello et al. (2015) reported that the investigators in the University of North Carolina's Specialized Program of Research Excellence (SPORE) in breast cancer comprehensively profiled 817 breast tumors, including 127 invasive lobular carcinomas, 490 invasive ductal carcinomas, and 88 mixed tumors. The investigators identified several mutations specific for invasive lobular or invasive ductal carcinoma. Proliferation and immune-related signatures determined three invasive lobular carcinoma transcriptional subtypes associated with survival differences.

Surgery at the Primary Tumor Site Improves Patient Survival for Stage IV Breast Cancer. A retrospective cohort study using SEER data by Thomas et al. (2015) found that women who received surgery at the primary tumor site as an initial treatment for stage IV breast cancer were 2.8 times more likely to survive at least 10 years than those who did not. Factors associated with longer survival included smaller tumor size, being married, age 65 or older, and race/ethnicity other than black. Black women represented a disproportionately high 16.1 percent of the study population, but they were less likely to undergo surgery.

Modeling Predicts Optimal Mammography Screening Frequency. A collaborative study by Mandelblatt et al. (2016) used national data on incidence, digital mammography performance, treatment effects, and other-cause mortality to evaluate screening outcomes, taking into account advances in mammography and treatment of breast cancer. Using six simulation models, the authors determined that biennial screening strategies for breast cancer are the most efficient for average-risk populations. Decisions about starting ages and intervals will depend on population characteristics and the decision-makers' determination, given the harms and benefits of screening. The results of this study helped to inform the U.S. Preventive Services

Task Force recommendations for breast cancer screening.

Optimal Frequency of Screening Mammograms Depends on Relative Risk. Biennial screening mammograms are recommended for women ages 50–74. However, in addition to age, higher breast density increases the risk of developing breast cancer. A study by Trentham-Dietz et al. (2016) found that triennial screening is equivalent to biennial screening for women with non-dense breasts and low relative risk. But for women with higher risk, yearly mammograms are more beneficial, irrespective of their breast density. Interestingly, a separate study by Sprague et al. (2016) found that radiologists who interpreted breast density from mammograms disagreed widely on what qualifies as “dense breasts.”

Factors Underpinning Improved Survival for Women with Invasive Breast Cancer. Since the 1970s, breast cancer survival rates have increased for all women diagnosed with local and regional disease. Park et al. (2015) investigated whether the parameters of tumor size and estrogen receptor status are associated with the increase in survival rates. They showed that for women younger than age 70, these parameters explained only 17 percent of the improvement, which suggests that the majority of improvements resulted from new or improved treatments.

A Serum-Based Assay Establishes Peptide Profiles for *BRCA1* Breast Cancer. Mutations in *BRCA1* genes increase the risk for developing breast cancer. Capturing circulating peptides that correlate with breast cancer occurrence can provide a useful strategy to assess risk among *BRCA1* carriers. Fan et al. (2016) used nanoporous silica thin films (NanoTraps) to enrich circulating peptides and found two putative peptide candidates and corresponding peptidases that differentiate between *BRCA1* mutant breast cancer, sporadic breast cancer, and cancer-free *BRCA1* mutant carriers.

A Molecular Marker in Normal Breast Tissue Predicts Breast Cancer Risk. Ki67 is a molecular marker that identifies proliferating cells. Huh et al.

(2016) examined biopsies from women with benign breast disease and found that women with high levels of Ki67 in normal mammary epithelium are five times more likely to develop cancer. Doctors already test breast tumors for Ki67 levels, which can inform decisions about treatment, but this is the first time researchers have linked Ki67 to precancerous tissue and identified it as a possible predictive tool.

Mitotic Gene Network Activity Predicts Therapeutic Outcome in Breast Cancer. A systems biology approach by Hu et al. (2016) combined genetic data, drug responses from breast cancer cell lines, and patient samples to identify a genomic amplification-based mechanism for response to inhibitors targeting the mitotic apparatus. Experimental validation of the computational predictions led to the identification of 22 additional therapeutic targets in patients with high mitotic activity.

Actin-binding Protein Mena^{INV} Promotes Invasive Migration of Breast Cancer Cells. Metastasis requires the coordinated action of several intracellular signaling pathways involving extracellular growth factor receptors, adhesion molecules, and the actin cytoskeleton, which underpins cell migration. The actin-binding protein Mena interacts directly with these components and recruits phosphatases that control growth factor receptor signaling. In two separate studies, Hughes et al. (2015) and Oudin et al. (2016) describe molecular mechanisms by which a prometastatic isoform of Mena dysregulates these signaling pathways and promotes invasive cell migration.

Estrogen May Contribute to Brain Metastasis in Triple-Negative Breast Cancers. Brain metastases are a frequent and devastating consequence of triple-negative breast cancers. As young age is a risk factor for brain metastases, Sartorius et al. (2015) tested the idea that circulating estrogens in premenopausal women could exert paracrine effects on the brain. The authors demonstrated that the estrogen 17- β -estradiol stimulates the release of astrocyte-derived paracrine factors that promote

proliferation, migration, and invasion of metastatic triple-negative breast cancer cells. These findings suggest that adjuvant treatment with aromatase inhibitors, which can cross the blood-brain barrier, could prevent brain metastases in women with triple-negative breast cancers, but more research is needed.

Potential New Target for Treatment of Estrogen Receptor Positive Breast Cancer. The most commonly diagnosed type of breast cancer is estrogen receptor positive (ER+). Previous studies showed that tamoxifen treatment of ER+ tumors stimulates the unfolded protein response (UPR), which reinforces cell survival and drug resistance. GRP78 protein regulates UPR, a normal pathway used by cells to eliminate aberrantly folded proteins. A study by Cook et al. (2016) demonstrated that GRP78 also controls lipid metabolism of breast cancer cells. Down-regulating GRP78 restored response to tamoxifen in ER+ breast cancers, suggesting that GRP78 may be a new target for treatment of ER+ tumors.

Response and Resistance to BET Bromodomain Inhibitors in Triple-Negative Breast Cancer. Triple-negative breast cancer is a clinically aggressive disease with limited options for targeted therapy. Although BET bromodomain (BRD) inhibitors have shown efficacy in several models of cancer, they have not been evaluated in triple-negative breast cancer. These inhibitors displace BET bromodomain proteins from chromatin, leading to inhibition of oncogenic transcriptional programs. Shu et al. (2016) reported preferential sensitivity of triple-negative breast cancers to BET bromodomain inhibition *in vitro* and *in vivo*, and resistance was associated with *MED1* and hyperphosphorylation of BRD. These studies provide a rationale for BET inhibition in triple-negative breast cancer and present mechanism-based combination strategies to anticipate clinical drug resistance.

Inhibition of Phosphatidylinositol-3 Kinase (PI3K) as a Strategy to Abrogate Antiestrogen Resistance in Breast Cancer. Approximately 30

percent of triple-negative breast cancers harbor molecular alterations in PI3K/mTOR signaling, but therapeutic inhibition of this pathway has not been effective. Bholra et al. (2016) showed that treatment of triple-negative breast cancer cell lines with a PI3K/mTOR inhibitor or a TORC1/2 inhibitor increases the expression of cancer stem cell markers, Notch1 activity, and mammosphere formation. Furthermore, blockage of *Notch1* abrogated cancer stem cell markers, suggesting that targeting the FGFR-mitochondrial metabolism-Notch1 axis may prevent resistance to TORC1/2 inhibitors by eradicating drug-resistant cancer stem cells in triple-negative breast cancer. This may represent an attractive therapeutic strategy to improve drug responsiveness and efficacy.

Breast and Ovarian Cancers

A Phase I/Ib Study of Olaparib Tablets and Carboplatin in Women's Cancer. Recurrent or refractory gynecologic or breast cancer is an incurable disease with limited treatment options. Subsets of these cancers respond to therapies targeting DNA repair, such as PARP inhibitors or platinum agents. NCI researchers previously reported that intermittent administration of olaparib capsules with carboplatin yields clinical benefit in women with germline *BRCA* mutation-associated ovarian or breast cancer. Lee et al. (2017) reported that this combination also has activity outside of *BRCA* mutation-associated cancers and that carboplatin given prior to olaparib increased olaparib clearance due to intracellular olaparib accumulation. This study also showed that olaparib, in a new tablet formulation, given with carboplatin is a well-tolerated and active combination. These findings suggest carboplatin should be administered prior to olaparib, and they support evaluation of the combination more broadly in breast and ovarian cancer patients.

Identification of a MicroRNA that Targets Myc-Driven Breast and Ovarian Cancers. Seviour et al. (2015) performed an integrated proteogenomic

analysis of breast and ovarian cancer patients that identified a set of candidate microRNAs that contribute to poor patient prognosis. These mechanistic studies led to the discovery of a unique RNA-activating function of microRNA mir-124. Expression of mir-124 arrested cell growth and led to decreased proteins levels of the oncogene myc. Results of the study suggest that targeting mir-124 in breast and ovarian cancer could increase sensitivity to chemotherapy and lead to better patient outcomes.

Cervical Cancer

Fewer Doses of HPV Vaccine Are Efficacious.

Kreimer et al. (2015) analyzed data from two large trials—the Costa Rica Vaccine trial and the PATRICIA trial—to demonstrate that only one or two doses of the HPV-16/18 vaccine appear to protect women ages 15–25 against cervical HPV-16/18 infections to a similar degree as the standard three-dose schedule. Two doses separated by 6 months provided some cross-protection for other HPV types.

Recommended Revision of the Guidelines for Cervical Cancer Screening in Women Vaccinated for HPV.

Guidelines established in 2012 by various medical organizations recommend cervical cancer screening with a Pap test starting at age 21 for all U.S. women, regardless of their HPV vaccination status, with an option to switch, at age 30, to “co-testing” with cytology and HPV testing every 5 years. Using an individual-based mathematical model of HPV and cervical cancer, J. Kim et al. (2016) found that less frequent cervical cancer screening that starts at a later age may be appropriate for women who have been vaccinated against HPV and thus have a lower cervical cancer risk. The study’s results suggest that cervical cancer screening policies in HPV-immunized women should be reassessed.

Novel HPV Therapeutic Vaccine Decreases Viral Load. Cervical cancer is almost always attributable to HPV infection. However, available prophylactic

vaccines are not effective in women already infected with HPV. Coleman et al. (2016) conducted a Phase I clinical trial and demonstrated that the HPV therapeutic vaccine, PepCan, can decrease HPV-16 viral load in women who were HPV-16 positive. A Phase II trial currently is enrolling patients to assess efficacy, including immune stimulation.

A Novel Therapeutic Target for Prevention and Treatment of Cervical Cancer.

He et al. (2015) found that the expression of the Yes-associated protein (YAP), a downstream effector of the Hippo pathway, increased with cervical cancer progression and that elevated levels of YAP protein are associated with a poor prognosis for cervical cancer. The authors also reported that the HPV E6 protein, a major etiological molecule of cervical cancer, maintained high YAP protein levels in cervical cancer cells by preventing proteasome-dependent YAP degradation *in vitro*. *In vitro* studies also suggest that the Hippo and the EGFR signaling pathways regulate cervical cancer cell proliferation and progression. Results from human cervical cancer genomic databases and a transgenic mouse model strongly support the clinical relevance of this signaling loop as a novel therapeutic strategy for prevention and treatment of cervical cancer.

Melanoma

An Association Between Indoor Tanning and Melanoma in Young Women.

Melanoma incidence is rising more steeply among women younger than age 50 than among men of the same age. Lazovich et al. (2016) reported that younger women who had tanned indoors were six times more likely to develop melanoma than any other age groups of women or men. The researchers analyzed data on 681 patients diagnosed with melanoma between 2004 and 2007 and before age 50 and compared them to people without skin cancer between ages 25 and 49. Nearly 80 percent of women said they had been indoor tanning, compared to 44 percent of the men. The results suggest that the rising rates of melanoma among younger women compared to men are likely due to indoor tanning.

Ovarian Cancer

Associations of Risk Factors with Ovarian Cancer Subtypes. An understanding of the etiologic heterogeneity of ovarian cancer is important for improving prevention, early detection, and therapeutic approaches. Wentzensen et al. (2016) evaluated 14 hormonal, reproductive, and lifestyle factors by histologic subtype in the Ovarian Cancer Cohort Consortium. They found that most risk factors exhibited significant heterogeneity by histology. Most established risk factors were more strongly associated with nonserous carcinomas; however, serous cancers are the most fatal subtype. These findings emphasize the importance of conducting etiologic studies by ovarian cancer subtype.

Metformin Inhibits Ovarian Cancer Growth and Increases Sensitivity to Chemotherapy in Preclinical Studies. Studies by Lengyel et al. (2015) and Litchfield et al. (2015) investigated the use of metformin, a diabetic medication, as an ovarian cancer therapeutic. Lengyel and colleagues reported that pretreatment of mice with metformin reduced ovarian tumor growth by 60 percent, compared with controls. Combination treatments of paclitaxel plus metformin showed a 60 percent reduction in tumor weight, compared with controls, suggesting that metformin increases sensitivity to chemotherapy. Litchfield and colleagues reported a reduced sensitivity of ovarian tumors to metformin treatments in hyperglycemic compared to normoglycemic mice, suggesting the hyperglycemia inhibits the anticancer effects of metformin. Additional clinical testing is needed to investigate the effect of metformin treatment in patients without diabetes.

Long-circulating, Self-Assembled Core-Shell Nanoscale Coordination Polymer Nanoparticles Promise More Effective Chemotherapeutic Treatments for Ovarian Cancers. Many ovarian cancer patients become resistant to the standard platinum- and paclitaxel-based treatment within several months, which reduces their long-term

survival. He et al. (2016) developed long-circulating, core-shell nanoscale coordination polymer nanoparticles that deliver multiple therapeutics to enhance synergistic drug effects. These particles contain high payloads of chemotherapeutics and short interfering RNAs (siRNA) that target multidrug-resistant genes. Intraperitoneal injections of these nanoparticles caused long-lasting tumor regression or even eradication in xenograft mouse models of cisplatin-resistant ovarian cancer.

Caspase 8 Expression May Determine Survival of Women with Ovarian Cancer. Ovarian cancer is a disease characterized by high rates of relapse, frequently due to ovarian cancer cells being resistant to apoptosis-inducing chemotherapies. Using genome-wide RNAi technologies, Hernandez et al. (2015) identified Caspase 8 as a key regulator of pro-survival NF- κ B activity in ovarian cancers. In three large data sets containing gene expression profiles from women newly diagnosed with ovarian cancer, NCI researchers found that ovarian cancer patients whose tumors expressed low levels of Caspase 8 had shorter overall survival, compared to those with higher Caspase 8 expression. M. Kim et al. (2016) hypothesized that a subset of cells with insufficient Caspase 8 expression may be resistant to apoptosis, but targetable via necroptosis. The authors suggest that necroptosis-inducing therapies might be a new avenue for treatment of ovarian cancer patients whose tumors express low levels of Caspase 8.

A Multiplex Bio-Nanochip That Measures Early Biomarkers of Ovarian Cancer Rapidly. Shadfan et al. (2015) configured a programmable bio-nanochip to quantify novel biomarkers related to early expression in ovarian cancer. This allows point-of-care, low-cost, early detection screening for patients to receive immediate results and to avoid extra follow-up clinic visits. The nanochip assay delivers results in less than 45 minutes. A programmable bio-nanochip is a promising diagnostic tool for large-scale screening of ovarian cancer that has high sensitivity and specificity for biomarker expression.

Activation of Phosphoinositide-3 Kinase (PI3K) in Oocyte Induces Ovarian Granulosa Cell Tumors. Granulosa cell tumors constitute approximately 5 percent of human ovarian tumors. Granulosa cells secrete factors to support oocyte development and ovulation. In a study by S.-Y. Kim et al. (2016), PI3K was overexpressed in the oocytes of mice during development to cause granulosa cell tumors months following birth. Once transformed, the granulosa cell tumors grew independently of oocytes. The authors propose that overactive phosphoinositide signaling within the oocyte perturbs the normal communication with granulosa cells to cause transformation, and later tumor growth becomes auto-stimulatory and independent of oocyte signals.

Health Disparities

New Breast Cancer Risk Prediction Model for Hispanic Women. The Hispanic risk model developed by Banegas et al. (2016), with support from NCI, is the first breast cancer risk model to be based exclusively on data from Hispanic women. This model permits a more accurate estimate of invasive breast cancer risk for Hispanic women considering different risk factors, including their country of birth. The model will become part of the Breast Cancer Risk Assessment Tool, an online NCI tool that helps providers calculate invasive breast cancer risk in individual patients.

HPV-16 and Cancer Risk. HPV-16 is a common sexually transmitted infection that causes half of cervical cancers worldwide; however, only a small proportion of infections lead to cervical precancer/cancer. Currently, we do not have the ability to predict which infections will lead to cancer and which will not. Mirabello et al. (2016) sequenced the HPV-16 genome of 3,200 infected women to determine if different variants (HPV-16 has 4 variant lineages) could predict risk of developing cancer. The study found that specific HPV-16 variants strongly influenced risk of precancer and cancer. Moreover, the risk of precancer and cancer for specific variants varied by a woman's race/ethnicity.

Other Activities

Clinical Trials

NCI Supports Clinical Trials Through the National Clinical Trials Network (NCTN).

Currently, there are numerous active clinical trials in women's cancers. Examples from 2015–2016 include three major randomized clinical trials led by the NRG Oncology Network, a member of the NCTN. Two of the trials are registration studies evaluating the role of the combination of cediranib and olaparib in ovarian cancer (NRG GY004 and NRG GY005). Both are accruing ahead of schedule and will be expanded to include the Canadian Clinical Trials Group of NCTN. The third study (NRG GY006) is examining the role of addition of the experimental agent NTO-1151 to cisplatin and radiation for newly diagnosed cervical cancer patients (*U10CA180868*).

In 2016, the U.S. Food and Drug Administration (FDA) approved the use of the anti-angiogenic therapy bevacizumab in combination with chemotherapy for women with recurrent platinum-sensitive ovarian cancer. The results of the NCI-sponsored Gynecologic Oncology Group (GOG) 0213 trial contributed the primary data that led to this approval (*U10CA180868*). Another GOG study (GOG 0218) is seeking to determine if there is an association between angiogenic factors, survival, and bevacizumab resistance. Bevacizumab is the most effective form of biologic therapy developed thus far for epithelial ovarian cancer. However, this therapy is expensive, response is variable, and significant toxicity may occur. Therefore, it is critical to identify patients who will truly benefit from this treatment (*5R21CA185730-02*). Additionally, NCI continues efforts to increase clinical trial enrollment for all underrepresented groups. At the interim analysis of the NCI MATCH trial, women represented 62 percent of the first 795 patients enrolled.

Funding Initiatives

Breast Cancer Genetic Study in African-Ancestry Populations. In 2016, NCI launched the Breast Cancer Genetic Study in African-Ancestry Populations, the largest study ever to investigate how genetic and biological factors contribute to breast cancer risk among black women. This collaborative research project will identify genetic factors that may underlie breast cancer disparities and will build on years of cooperative research among investigators who are part of the African-American Breast Cancer Consortium, the African-American Breast Cancer Epidemiology and Risk Consortium, and the NCI Cohort Consortium. These investigators will share biospecimens, data, and resources from 18 previous studies, resulting in a study population of 20,000 black women with breast cancer (*1R01CA202981-01*).

African Organization for Research and Training in Cancer (AORTIC) Beginning Investigator Grant for Catalytic Research Awards. The cancer burden in Africa is predicted to rise, with breast and cervical cancers as the most common types of cancers afflicting African women. Since 2009, NCI has partnered with AORTIC, a nongovernmental organization promoting cancer control, to support exploratory data collection by African cancer researchers. This collaboration focuses on furthering research related to cancers prevalent in Africa. NCI provides funding support through the Center for Global Health (CGH), while AORTIC administers the grants.

The following is a list of FY 15 research projects:

- Survival from genetic and nongenetic susceptibility to invasive breast carcinoma in HIV-positive and HIV-negative black South African women.
- Cold coagulation versus cryotherapy for immediate treatment of women who test positive to VIA and VILI in rural African settings.
- Sociocultural factors on health behavior toward early detection of breast cancer among women

who were exposed to breast cancer education in Ghana.

United States–Latin America Cancer Research Network. In 2009, CGH established the United States–Latin America Cancer Research Network (US-LA CRN) to increase cancer research capacity in Latin America. In 2011, US-LA CRN launched a breast cancer research study titled, “Molecular Profiling of Stage II and III Breast Cancer in Latin American Women Receiving Standard of Care Treatment.” In 2016, CGH provided funding to complete the primary study and continue the effort for 2 additional years to complete data collection, research assays, and correlative biology studies that will use data and specimens from the primary study.

Pink Ribbon Red Ribbon (PRRR)—A Global Partnership Fighting Women’s Cancers. CGH partnered with Pink Ribbon Red Ribbon (PRRR) to help countries in sub-Saharan Africa develop and implement comprehensive, evidence-based, well-resourced, and operational cancer control plans that translate commitments to health into action. In FY 15 and 16, NCI funded a cancer registrar in Zambia for 3 years. NCI continues to provide technical assistance in strengthening the registry and cancer control planning. In Botswana, NCI supported a survey of cervical cancer screening services to identify best practices for scale-up of new treatment facilities and to develop strategies for cervical cancer control. CGH also is providing technical assistance for the evaluation of national cervical cancer strategies in Botswana.

Science, Technology, Engineering, and Mathematics (STEM) Efforts

Sallie Rosen Kaplan Postdoctoral Fellowship for Women Scientists. Recent observational, longitudinal, and intervention studies have shown that women in science are significantly more likely to leave research careers earlier than men, specifically at the transition from a mentored scientist to an independent investigator. The Sallie Rosen Kaplan Fellowship is equipping NCI’s women postdoctoral fellows for the competitive nature

of the job market and helping them transition to independent research careers through a highly competitive, annual, 1-year program to strengthen leadership skills by providing additional mentoring opportunities, networking, seminars, and workshops. The program is for current women NCI postdoctoral fellows training at NCI's intramural research locations in Bethesda, Rockville, Gaithersburg, and Frederick, Maryland.

Technology

NCI Supports Technology Development for Women's Cancers and by Women-Owned Small Businesses Through the Small Business Innovation Research (SBIR) Program. Selected examples follow:

- Lumicell, Inc., is developing a hand-held imaging system to assist surgeons in detecting tumor margins during surgical excision. The system is intended to reduce incidence of residual tumor left in patients. Lumicell was funded by the NCI SBIR program to refine its technology for use in removal of ductal carcinoma *in situ* (DCIS). DCIS is a non-invasive form of breast cancer commonly removed by lumpectomy (surgical excision). Margin detection in DCIS is critical because tumor cells left behind after lumpectomy have the potential to re-grow. (R44CA11013)
- Acoustic MedSystems, Inc., is developing a focused, ultrasound device for ablation of uterine fibroids. Current fibroid ablation technologies can potentially damage neighboring healthy tissues during the ablation procedure. Acoustic MedSystems device is minimally invasive and is designed to limit damage to neighboring organs. (R44CA121740)
- For-Robin, Inc., is a woman-owned small business developing treatments for breast cancer. The company was named in honor of the founder's sister, who died of breast cancer at age 31. For-Robin's lead technology product is a monoclonal antibody that targets many subtypes of breast cancer, including

triple-negative breast cancer. The NCI SBIR program is providing funding to complete translational studies necessary for filing an application with FDA to begin a clinical trial. (R44CA136033)

- Phoenica Biosciences, Inc., is a woman-owned small business developing therapeutics for Epstein-Barr Virus (EBV) -associated cancers, such as lymphoma. Phoenica Biosciences was funded by the NCI SBIR program to refine its lead technology to create an orally available, potent therapeutic for patients with EBV-associated cancers that do not respond well to conventional therapies. (R44CA153474)

Workforce

NCI Women's Health Officer. The NCI Women's Health Officer facilitates communication across the Institute and promotes collaboration between NCI and other National Institutes of Health (NIH) Institutes and Centers, Federal agencies, and nongovernmental organizations. The Women's Health Officer develops and disseminates reports and information on NCI's research and research progress on cancers in women and coordinates NCI's responses to agency requests for information.

Clinical Trials Steering Committees for Women's Cancers. The NCI NCTN supports steering committees with disease-specific strategic priorities. The steering committees increase information exchange at early stages of trial development, increase efficiencies of collaboration among trial sites, and reduce trial redundancy. This ensures a nationally coordinated effort to implement optimally designed, high-priority, clinical trials. The NCTN steering committees include representatives from NCTN disease committee groups, NCI Community Oncology Research programs, SPORE groups, NCI-funded consortia, biostatisticians, patient advocates, special expert clinicians, and NCI staff. Among the NCTN steering committees, the Breast Cancer Steering Committee and the Gynecologic Cancers Steering Committee develop, evaluate, and prioritize concepts for large Phase II

and all Phase III clinical trials related to breast and gynecological cancers, respectively.

Workshops and Conferences

Designing Trials for Endometrial Cancer Populations Using Targeted Agents. The NCTN Gynecologic Cancer Steering Committee held a clinical trials planning meeting in January 2016 to discuss development and validation of diagnostic strategies for molecular subtypes of uterine carcinomas, including biomarkers in various stages of clinical development. Participants developed a research agenda that included seven Phase 0 to Phase III trials of agents that target molecularly defined pathways, alone or in combination with standard chemotherapy in uterine carcinoma. Trials will be developed by members of the NCTN.

The Breast and Cervical Cancers Advocacy, Education, and Outreach Summits. CGH plays an important role in NCI's efforts to build capacity for women's cancer control in low- and middle-income countries. In FY 15 and 16, CGH partnered with the Women's Empowerment Cancer Action Network to coordinate regional Women's Cancer Summits in Peru (March 2015), Romania (October 2015), and Kenya (April 2016) to help build regional networks of advocates and health care providers who can facilitate breast and cervical cancer education and awareness efforts. The summits train health care professionals and community advocates about breast and cervical cancer, key elements of cancer control programs, and the role of advocates in working with health care professionals and policymakers.

Cervical Cancer Control Workshop 2016. CGH partnered with the *Instituto Nacional de Enfermedades Neoplásicas* in Peru to hold a workshop focused on developing strategies for implementing the Asia-Pacific Economic Cooperation (APEC) cervical cancer recommendations. The workshop was held in Lima, Peru, in August 2016. Outcomes include the development of a roadmap for implementing the cervical cancer recommendations in APEC

economies, including specific action steps regarding cervical cancer prevention and control, and engagement of economies of non-APEC Latin American countries.

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National Eye Institute (NEI)

Executive Summary

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90-489, with the mission to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

Clinical research demonstrates that nearly two-thirds of all visually impaired and blind people in the world are women. More women than men are affected by eye diseases such as [cataracts](#) and [macular degeneration](#), and studies have shown that there are gender-specific symptoms, conditions, and risks associated with this vision loss. One reason is that the visual changes are linked to hormonal changes. For instance, dry eye syndrome, which is believed to be linked to hormones, is two to three times more common in women than in men. Hormonal changes across the life span of a woman, from pregnancy to postmenopause, can influence vision changes. Women also have higher rates of autoimmune diseases, such as lupus, rheumatoid arthritis, and multiple sclerosis. These conditions often have serious effects on the eyes, causing vision loss. Another explanation is that women generally live longer than men and are, therefore, more likely to be affected by conditions such as [cataracts](#), [macular degeneration](#), and [diabetic retinopathy](#). The rates of these diseases are increasing as the population ages, especially among women.

NEI's research and initiatives in fiscal years (FY) 15–16 addressed the National Institutes of Health (NIH) *Strategic Plan for Women's Health and Sex Differences*. For example, Objective 3: "Actualize Personalized Prevention, Diagnostics and Therapeutics for Girls and Women, including (i) conducting developmental and developmentally framed research to understand the role of

hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan (3.1); (ii) studying sex/gender differences in the aging process (3.6); and (iii.) conducting research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life (3.8)."

NEI studies of hormone factors in such conditions as dry eye and Sjögren's syndrome, glaucoma, corneal dystrophies, myopia, cataracts, eye diseases of aging women, and the role of dietary supplements in eye health in aging women are also examples that satisfy the goals and objectives of the Office of Research on Women's Health (ORWH). Below is a summary of vision research findings for which significant sex/gender differences were reported during FY 15–16.

NEI's Women's Health Research Report

Accomplishments—Highlights

A. Corneal Diseases

Corneal Endothelial Dystrophy

Corneal dystrophies are a group of genetic and progressive eye disorders in which abnormal material accumulates in the clear outer layer of the eye (cornea); they are more common in women than in men. Corneal dystrophies may not cause symptoms in some individuals; however, in others, they may cause significant vision impairment. The age of onset and specific symptoms vary among the different forms of corneal dystrophy. The disorders have some similar characteristics—most forms of corneal dystrophy affect both eyes and progress slowly, do not affect other areas of the body, and

tend to run in families. Most forms are inherited as autosomal-dominant traits, while a few are inherited as autosomal-recessive traits. Corneal transplants are the only treatment; however, in some cases, cornea specialists are able to treat these conditions by performing limbal stem cell transplants to repopulate the damaged corneal epithelial cells. Clinical trials are expected to begin in the near future.

Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus (HZO) is a form of *Herpes zoster* (HZ), or shingles affecting the eye, which is a common and serious disease caused by reactivation of the chicken pox virus that can result in chronic eye disease and incapacitating pain. HZ in general, and HZO in particular, can be associated with serious complications that result in diminished quality of life, chronic eye disease, reduced vision, and even death. Most studies find that women are affected significantly more frequently than men with regard to HZ incidence, hospitalizations, and mortality. NEI is currently funding a clinical trial to determine if prolonged treatment with a low dose of the antiviral valacyclovir improves outcomes by reducing eye disease and/or chronic pain in HZO patients. This study is currently recruiting patients.

B. External Ocular Diseases

Dry Eye

Tears are necessary to maintain the health and comfort of the eye. A lack of sufficient tear fluid is a very common and frequently debilitating condition that may feel like a stinging or burning sensation in the eye and, if left untreated, may result in blurred vision and/or vision loss. Dry eye disease (DED) results from a reduction in secretion of fluid by the lacrimal glands, or from defects in the surface of the eye, mucin or mucous production, or the lipid or fatty components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders, such as Sjögren's syndrome, lupus, and rheumatoid arthritis, but it also occurs in association with aging, medications, environmental

exposures, and eye surgery, including laser correction surgery. DED affects roughly 2 million Americans and is the most common complaint to present in the ophthalmologist's office, with 10 to 20 percent of adults in the United States reporting dry eye. It appears to be more common in women than in men, particularly among postmenopausal women.

Despite the prevalence of DED treatments have met with limited success. Restasis®, a drug that has been approved by the U.S. Food and Drug Administration (FDA), has been shown to increase natural tear production in the eye; however, this drug is not very effective and only works for some people. Another treatment for severe DED is the surgical insertion of lacrimal or punctal plugs to block the eye's drainage ducts, keeping the tears in place. Supporting better treatments for DED. NEI has funded a Small Business Innovation Research Grant for an FDA-approved Phase II clinical trial to evaluate the efficacy and safety of a new drug, P-321 Ophthalmic Solution, in relieving the symptoms of moderate to severe DED.

Dry Eye Assessment and Management Study (DREAM)

NEI is currently funding DREAM, a Phase III clinical trial, which will examine the effectiveness of omega-3 supplementation treatment for DED. Despite being a widespread and a growing problem with serious consequences, DED is inadequately treated. Because omega-3 fatty acids have been shown in laboratory studies, animal models, and some human studies to ameliorate inflammatory reactions and they are widely available over the counter, they are gaining in popularity to combat or prevent diseases associated with inflammation, including DED. As with any treatment, however, results of a large, randomized double-blind clinical trial are needed to assess efficacy and safety. The study recently completed the recruitment of participants. Patient follow-up will continue.

Sjögren's Syndrome Registry

Sjögren's syndrome is a chronic autoimmune disease that occurs primarily in women and attacks the salivary and lacrimal glands, resulting in severe DED. NEI is currently funding studies aimed at investigating the effects of FDA-approved immunosuppressant drugs to treat Sjögren's syndrome. This includes a study using a class of protein polymer nanomedicines to determine if the drugs can be more efficiently targeted to treat inflamed lacrimal glands without increasing the toxicity of the immunosuppressant.

NEI also continues to co-fund, with the National Institute of Dental and Craniofacial Research and ORWH, the [Sjögren's Syndrome International Collaborative Clinical Alliance](#), a group developing an international Sjögren's syndrome registry. The purpose of this registry is to promote cutting-edge research in the area of Sjögren's syndrome, with emphasis on diagnosis, epidemiology, causes, prevention, and treatment. The coordinating center is at the University of California, San Francisco, and multiple international sites in the United States, Argentina, China, Denmark, Japan, India, and the United Kingdom have been established. Enrollment is complete, with 301 people successfully enrolled.

Thyroid Eye Disease

Graves' eye disease, also known as thyroid eye disease, is an autoimmune condition that causes hyperthyroidism and tends to affect 2 percent of all women (7 to 1, compared to men) between the ages of 20 and 40. Excessive thyroxine is produced from the enlarged thyroid glands and causes swelling of the muscle and other tissues around the eye, resulting in proptosis (bulging of the eye), corneal exposure, optic nerve compression, and, ultimately, loss of vision. NEI is currently funding three research project grants to identify immune cells—including T cells, B cells, and fibrocytes—that are unique to Graves' eye disease and are being used to develop new therapeutics.

C. Lens

Cataracts

Cataracts are the leading cause of blindness, with more than 20 million people affected worldwide. Epidemiological evidence indicates that cataracts are more prevalent in women than in men. For example, a study on the Swedish population reported that cataracts are more prevalent in postmenopausal women than in men of similar ages. Moreover, the study showed that women who receive hormone replacement therapy (HRT) were at greater risk for developing cataracts. The longer a woman used HRT, the greater the severity of the cataract.

The biological basis of these intriguing findings is not certain. However, estrogen receptors have been detected in the ocular lens, and naturally occurring (endogenous) estrogen appears to protect the eye from cataracts. In fact, estrogen is known to exert anti-aging effects that may also explain the longer lifespan seen in women. Another angle is the role of oxidative damage in cataracts. Studies in animal subject models showed a protective role for estradiol against oxidative stress. In sum, the data suggest a provocative potential role for gender differences in this age-related disease. Clearly, more studies are warranted.

D. Retinal Diseases

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of blindness and visual impairment among elderly individuals in the United States. The macula is a specialized region near the center of the retina responsible for the high-resolution vision that permits activities such as reading. Several genetic and environmental risk factors have been identified with this condition; among those is female sex, which has been associated with a higher prevalence of AMD in many population-based studies.

One study in the *Archives of Ophthalmology*, looking at AMD in women participating in the Nurses' Health Study (NHS), showed an association between women who received HRT after menopause and 34 percent higher risk of early AMD, whereas, a 48 percent lower risk of the late-stage neovascular form of the disease was observed. Another study by the Korea National Health and Nutrition Examination Survey revealed that age, duration of lactation, and duration of oral contraceptive pills are associated with late AMD. These findings suggest a role for estrogen in the pathogenesis of AMD as well as the importance of screening and prevention among postmenopausal women and other patients at higher risk of developing AMD.

Age-Related Macular Degeneration—Age-Related Eye Disease Study (AREDS)

AREDS is a multicenter clinical trial/epidemiological study designed to assess the clinical course, prognosis, and risk factors of AMD and to evaluate the effects of antioxidants and zinc in slowing the progression of the disease. The study demonstrated that high-dose antioxidant supplements (beta-carotene, vitamins C and E, and zinc) can slow the progression of AMD. Data from AREDS and other studies suggested that lutein/zeaxanthin and omega-3 long chain polyunsaturated fatty acids might also have benefit in AMD and cataracts. A second study, AREDS 2, confirmed this hypothesis. A multicentered clinical trial, the Complications of Age-Related Macular Degeneration Prevention Trial, assessed the safety and efficacy of laser treatment in preventing vision loss in patients in whom the disease is manifested bilaterally. This study recently reported that low-intensity laser treatment was ineffective in preventing complications of AMD or loss of vision.

Second Carotenoids in Age-Related Eye Disease (CAREDS2)

The dietary plant pigments lutein (L) and zeaxanthin (Z) and the lutein metabolite meso-zeaxanthin comprise macular pigment in the

macula of the retina. A large body of evidence suggests that these pigments can protect against damage that contributes to AMD. The CAREDS2, an ancillary study of the Women's Health Initiative (WHI), indicates that individuals with low optical density of macular pigment are more likely to develop AMD and that older women who had the lowest 20 percent of macular pigment optical density (MPOD) were about 40 percent more likely to have died over 14 years of follow-up. These results may be due to multiple shared risk factors for low MPOD and common chronic diseases, which are also risk factors for AMD.

Moreover, concentrations of L and Z in the central retina and lens epithelium are also shown to protect against ultraviolet light damage, oxidative stress, and, subsequently, cataract development. Data from this CAREDS2/WHI study demonstrate an increased risk of cataract development among women (53%) with high MPOD.

E. Optic Neuropathies

Glaucoma

Glaucoma is a group of conditions that damage the optic nerve, which is the bundle of nerve fibers connecting the eye to the brain. Primary open-angle glaucoma (POAG) is the most common and is a leading cause of irreversible blindness worldwide, yet the pathogenesis of this condition remains unknown. The NHS, supported by various branches of NIH, has contributed considerably to research on POAG. These studies suggest that HRT use in postmenopausal women may be beneficial in reducing intraocular pressure or the incidence of glaucoma. These studies, however, have been limited by methodological issues, particularly small sample size. The results support the notion that there are unique, sex-specific risk factors for glaucoma in women, and the risk associations between reproductive factors—including menopause, late menarche, oophorectomy, oral contraceptive use—and POAG continue to be studied.

NEI is currently funding a consortium involving 12 institutions in the United States called the **NEI Glaucoma Human Genetics Collaboration** (NEIGHBOR) to identify genes linked to POAG. DNA samples were collected from women in the NHS and the Genetic Etiology of POAG, and genotyping was done in collaboration with the Glaucoma Genes and Environment Initiative. Genome-wide association study results identified common variants near *FOXCI*, *ATXN2*, and *TXNRD2* as new risk loci for POAG. These genes suggest new pathways that may contribute to glaucoma development, including abnormal ocular development (*FOXCI*), neurodegeneration (*ATXN2*), and mitochondrial dysfunction secondary to accumulating reactive oxygen species (*TXNRD2*). These findings open avenues for the pursuit of new strategies to screen for, prevent, and treat glaucoma.

F. Myopia

Nearsightedness, or myopia, is the most common refractive error of the eye and has become more prevalent in recent years. Epidemiological data in children indicate that myopia is more common and progresses more quickly in girls than in boys. These findings have traditionally been attributed to gender-specific behavioral differences, but new research examines the degree to which sex hormones play a role. NEI is continuing to work with ORWH by co-funding projects to investigate the influence of systemic sex hormones on ocular growth and myopia in animal models. NEI is currently funding 20 grants on refractive error, including one administrative supplement through the Women's Health Program.

Initiatives

NEI and the National Advisory Eye Council (NAEC) have established a 5-year strategic plan: *Vision Research, Needs, Gaps, and Opportunities*, a report completed in August 2012. This report provides a comprehensive review of the highlights of recent progress in vision research and the emerging

needs, gaps, and opportunities that lie ahead for improving visual health and preventing blindness. This includes research on diseases that are known to have a higher incidence and prevalence in women than men.

The NEI Audacious Goal Initiative (AGI; see www.nei.nih.gov/audacious) is focused on regenerating neurons and neural connections in the eye and visual system. In consultation with the 2016 NAEC, the NEI initiative is targeting the photoreceptor and retinal ganglion cells, because the loss of either cell type by disease or injury leads to severe visual disorders and blindness. This includes loss of photoreceptor cells, as in AMD, or damage to retinal ganglion cells (RGC) resulting in glaucoma or optic nerve pathologies, all of which are conditions that are more pronounced in women. One challenge in vision research is how to restore vision by promoting photoreceptor cell and RGC survival, as well as optic nerve regeneration. In addition to therapies that may slow or prevent the death of these cells, retinal stem cell replacement therapies also hold promise and may be used to integrate rod and cone photoreceptors and/or retinal ganglion cells into diseased retinas and form the appropriate connections with the remaining neurons. Studies that promote research aimed at restoring these connections to visual centers of the brain are encouraged.

Moreover, NEI encourages studies that (1) gather comprehensive knowledge of the molecular basis of ocular health and disease and use that knowledge to improve diagnosis, treatment, and prevention of eye disease; (2) further translational basic research into clinical studies; (3) use clinical, epidemiological, and statistical tools to identify populations at risk of blinding eye diseases and visual disorders; and (4) evaluate new therapeutics to improve vision. However, all proposed projects should include a group of animals/humans of the opposite sex (female) for comparative analyses of gender-mediated effects and treatment outcomes.

National Heart, Lung, and Blood Institute (NHLBI)

Executive Summary

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for research, training, and education to improve prevention and treatment of heart, lung, blood, and sleep diseases. For many of these diseases, men and women face differences in risk, signs and symptoms, progression, and responses to treatment. For example, some types of coronary heart disease are more common in women than in men, and women are more likely to experience atypical symptoms of heart disease (such as neck, abdominal, or back pain) (NHLBI, 2014). Since its establishment in 1948, NHLBI has recognized both the profound impact that such sex differences can have on clinical research findings and conclusions and the importance of ensuring the full participation of women in research. Indeed, the Framingham Heart Study, which was launched in 1948 as one of the first epidemiological studies to address cardiovascular disease (CVD), was designed to include women and men from the beginning (History of the Framingham Heart Study, 2017).

Beyond inclusion of women in clinical research, NHLBI also recognizes the importance of addressing sex as a biological variable at all stages of research. This includes appropriate analyses and reporting of sex-specific risks and outcomes for clinical studies and for preclinical studies involving animal or cell models of disease. Accounting for sex as a biological variable is important not only for investigating known or suspected sex differences in disease, but for ensuring rigor and reproducibility in study design. It may hint at completely unknown mechanisms through which sex hormones, sexual development, or other sex-related factors influence health and disease in women and men.

To reduce the burden of disease for all Americans, NHLBI supports a vast portfolio of basic, clinical,

and translational studies that address sex as a biological variable. This report highlights the Institute's recent scientific efforts, as well as its work in education and outreach to increase awareness about women's health risks and options for intervention. These highlights include identification of a potential biomarker for preeclampsia, a potentially serious rise in blood pressure that can affect pregnant women. We highlight studies that examine risk factors for heart failure in women, and a trial of blood pressure management for pregnant women, using the same blood pressure target recommended for non-pregnant adults. We also discuss studies conducted as part of 25+ year Women's Health Initiative, including a trial to evaluate the benefits of physical activity for reducing CVD events in older women.

This report also addresses the health disparities experienced by minority women. For example, African-American women face a prevalence of CVD (47.7%) higher than that of African-American men and white, Hispanic, and Asian men and women (Benjamin et al., 2017). Below, we summarize NHLBI's support for diverse population studies that explore the intersection between women's health and minority health.

Finally, this report notes the importance of ensuring that women are appropriately represented in the scientific workforce, and it highlights NHLBI's recent efforts to improve the recruitment and retention of female scientists in heart, lung, blood, and sleep research.

NHLBI's Strategic Vision, completed in fiscal year 2016, reaffirms and expands the Institute's commitment to understanding sex as a biological variable, to appropriate inclusion of women and minorities in research, and to improving opportunities for women in science (NHLBI, n.d. [a]).

- Objective I of the Vision is to “understand normal biological function and resilience,” and NHLBI explicitly notes the need for “reliable and diverse investigational models—from single cells to animals—that reflect...sex/gender-based differences” to achieve this objective.
- Objective III is to “investigate factors that account for differences in health among populations,” as defined by age, sex, race, and ancestry. To that end, NHLBI will make it a priority to continually improve inclusion of women and minority groups in clinical research.
- Objective VIII is to “further develop, diversify, and sustain a scientific workforce capable of accomplishing NHLBI’s mission,” which encompasses efforts to recruit and retain women in science.

Scientific Accomplishments and Activities

Reproductive Health and Pregnancy

Oral Contraceptives and Mortality

NHLBI-funded investigators recently studied more than 121,500 women to determine the effect of oral contraceptives on rates of disease and mortality. Just over half of the participants had never used oral contraceptives while 48 percent had used them (with no minimum use defined). There was no significant difference in all-cause mortality rates between ever-users and never-users. However, oral contraception was associated with differences in specific causes of death, including increased mortality from violence/accidents and breast cancer, and decreased mortality from ovarian cancer. A limitation is that the study used oral contraceptive formulations with higher hormone doses rather than third- and fourth-generation formulations with lower estrogen doses (Charlton et al., 2014).

Improving Postpartum Care

Women with pregnancy complications may benefit from closer monitoring after giving birth (postpartum). In a recent study, researchers evaluated how often women visited the emergency room (ER) for care during the first 6 months postpartum. Through a prospective analysis of Medicaid claims, the researchers identified 26,074 pregnancies in Maryland from 2003–2010, of which 20 percent were complicated by gestational diabetes, gestational hypertension, or preeclampsia. They found that women with complicated pregnancies, especially those under 25 years old, were more likely to have at least one postpartum visit to the ER compared to women with uncomplicated pregnancies. Interventions that improve discharge planning and early postpartum care may decrease the need for ER care among these women (Harris et al., 2015).

Preeclampsia

Preeclampsia affects 2–8 percent of pregnant women and is characterized by high blood pressure and elevated protein in urine (Jeyabalan, 2013). Preeclampsia usually develops after the 20th week of pregnancy and resolves after delivery. However, it can evolve into eclampsia—characterized by seizures or coma—which is a leading cause of maternal morbidity and mortality. Moreover, complications from preeclampsia—such as kidney failure, hemorrhage, and stroke—can lead to lasting health problems.

Assessing Preeclampsia Mechanisms and Risk

A number of NHLBI-funded studies have found that the hormone vasopressin, which causes blood vessel constriction, may play a role in triggering preeclampsia. Levels of copeptin, a byproduct of vasopressin, are significantly elevated in blood throughout pregnancy in women with preeclampsia. Moreover, low-dose infusion of vasopressin in pregnant mice is sufficient to induce signs of preeclampsia. These findings provide insights into the mechanisms of preeclampsia, and

suggest that copeptin could serve as a biomarker to help identify women at risk for preeclampsia (Sandgren et al., 2015).

Insulin Resistance and Preeclampsia

NHLBI-funded researchers have found that insulin resistance is a risk factor for developing preeclampsia. Among 1,100 first-time expectant mothers, those with higher insulin resistance during the second trimester were more likely to develop preeclampsia later in pregnancy, even after factors such as body mass index, race, ethnicity, blood pressure, and gestational age of the fetus were taken into account. In addition, Hispanic and African-American women had a higher percentage of elevated scores on insulin resistance tests, as did obese women (Hughes et al., 2016).

Safe Drug Delivery for Preeclampsia

While treatment of chronic hypertension is standard practice for the general population, there is no equivalent standard of care during pregnancy due to the concern that drug treatments may cross the placenta and harm the developing fetus. NHLBI-funded investigators have developed a new drug delivery system using elastin-like polypeptides (ELP), which are synthetic proteins derived from human elastin. Using ELP as a drug carrier prevented drugs from crossing the placental barrier when tested in rats. With further development, this approach could minimize fetal exposure and potential developmental effects of drug treatments given during pregnancy (George et al., 2014).

Linking Preeclampsia to Other Health Outcomes

NHLBI, together with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, is supporting the nuMoM2b Heart Health Study, which is following mothers for 2 to 5 years after giving birth to evaluate potential links between preeclampsia, sleep, and future maternal cardiovascular health. ORWH and the Office of Behavioral and Social Sciences Research (OBSSR) are each supporting subprojects that focus on

comparing biomarkers, stress, physical activity, sleep, and nutrition in 750 women with adverse pregnancy outcomes, including preeclampsia, and 750 women without adverse pregnancy outcomes to better understand the impact on women's health after pregnancy.

Protein Misfolding in Preeclampsia

NHLBI-supported investigators have found that urine from women with preeclampsia contains misfolded proteins, including β -amyloid, a fragment of the amyloid precursor protein (APP) that accumulates in the brain during Alzheimer's disease. The abundance of these proteins in urine correlates with preeclampsia severity. The placenta expresses APP, and its expression is up-regulated in preeclampsia, as is the expression of β -amyloid. These findings suggest that preeclampsia should join the growing list of protein conformational disorders. Further characterization may lead to new treatments for preeclampsia (Buhimschi et al., 2014).

Cardiovascular Disease (CVD)

Menopausal Hormone Therapy Ineffective Against Atherosclerosis

The NHLBI-funded Women's Health Initiative established that hormone replacement therapy (HRT) does not protect older postmenopausal women from CVD, but left open the possibility that hormone therapy might be protective for younger women in early menopause. NHLBI-funded scientists recently studied the effects of hormone therapy on atherosclerosis among healthy menopausal women aged 42–58 years between 6 and 36 months from last menses, who had no history of CVD events and had not received estrogen or lipid-lowering therapy for at least 90 days. Study participants were given either oral estrogen, transdermal estrogen, or placebo for 48 months and evaluated with respect to carotid artery thickness and CVD markers, such as hypertension and LDL-cholesterol. When compared to placebo over the 4-year course of the study, HRT did not

affect the progression of atherosclerosis, although some markers of CVD risk improved (Harman et al., 2014).

Breast Arterial Calcifications and CVD

Although breast arterial calcifications (BAC) found during mammography are not associated with breast cancer risk, they are associated with some risk factors for CVD. NHLBI is funding a study to gain insight into ethnic differences in BAC incidence, severity, and association with CVD risk factors. This work will shed light on the potential value of BAC mass as a new tool for CVD risk stratification and, thus, for CVD prevention (Iribarren, n.d.).

Risk Factors for Heart Failure

Heart failure is a growing health problem, affecting 6.5 million Americans from 2011 to 2014. A recent study of postmenopausal women explored differences in the risk factors for heart failure with preserved ejection fraction (HFpEF) versus heart failure with reduced ejection fraction (HFrEF). (Ejection fraction is the percentage of the blood volume in the heart that is pumped out with each contraction.) The investigators tracked the incidence of hospitalized HFpEF and HFrEF in a multiracial cohort of more than 42,000 women for approximately 13 years. They found that risk factors for both types of heart failure include older age, white race, diabetes, cigarette smoking, and high blood pressure. Obesity, coronary heart disease, anemia, and atrial fibrillation were associated with HFpEF, but not with HFrEF. History of myocardial infarction was associated with HFrEF, but not with HFpEF. Obesity was a more potent risk factor for HFpEF among African-American women than among white women (Eaton et al., 2016).

Hypertension

Chronic Hypertension During Pregnancy

Due to concerns about potential adverse effects on the fetus, some medical associations recommend against treating mild chronic hypertension during

pregnancy. The risks from uncontrolled mild hypertension during pregnancy are not clear. The NHLBI-funded Chronic Hypertension and Pregnancy Trial is designed to evaluate the efficacy and safety of treating pregnant women toward the same blood pressure target recommended for nonpregnant reproductive-age adults (< 140/90 mmHg). This treatment will be compared to usual care, that is, no treatment except for severe hypertension. The primary outcome measures are small fetal size for gestational age, and a composite adverse pregnancy outcome that includes one or more of the following: fetal or newborn death, severe preeclampsia, and placental rupture before birth (Tita, n.d.).

Pulmonary Arterial Hypertension (PAH)

PAH is 2 to 4 times more common in women than men, but the reasons are unclear (Pugh et al., 2010). A recent NHLBI-funded study showed how estrogen and estrogen metabolites might contribute to the disease and revealed a potential target for therapy. The investigators focused on hereditary PAH, which has been linked to several genetic factors, including mutations in the gene-encoding bone-morphogenetic protein receptor type II (BMP2). They conducted a mass unbiased screen to look for changes in the levels of small regulatory RNAs (microRNAs) in lung tissue from women with hereditary PAH and from mice with BMP2 mutations. They found that hereditary PAH is associated with increased levels of microRNA-29 and that levels of miR-29 increased further when the mice were given estrogen metabolites. Treatment with an inhibitor of miR-29 reduced right ventricular systolic blood pressure and other markers of PAH in the mice. Thus, miR-29 represents a novel therapeutic target for PAH (Chen et al., 2016).

Venous Thrombosis (VT)

Estrogen and Thrombosis Risk

Oral use of exogenous estrogen/progesterone is associated with altered levels of hemostatic factors—factors that stop bleeding and promote

coagulation (blood clotting). These hormone treatments also are known to increase the risk of VT (a blood clot in a vein). However, the extent to which estrogens produced by the body can influence hemostatic factors has not been fully characterized. NHLBI-supported investigators addressed this issue in a recent study of postmenopausal women with no history of VT or hormone therapy. The investigators found that higher levels of estrone, an estrogenic hormone secreted by the ovaries and fatty tissue, were associated with lower levels of a natural anticoagulant called protein S antigen (Harrington et al., 2016a).

Impact of Hysterectomy on Risk of VT

Hysterectomy and bilateral salpingo-oophorectomy (BSO; removal of the uterus, ovaries, and fallopian tubes) are associated with changes in endogenous hormone levels, but their effects on the risk of VT have not been well characterized. NHLBI-supported investigators evaluated the risk of VT among postmenopausal women. Compared to a control group of women who had not had a hysterectomy and were not using hormone therapy, women with a prior hysterectomy but without BSO had a similar risk for VT, whether using hormone therapy or not. Women with a prior hysterectomy and BSO who were using hormone therapy also had a similar risk to the control group. The investigators concluded that there is no substantial impact of hysterectomy, with or without BSO, on the risk of VT in postmenopausal women (Harrington et al., 2016b).

VT Risk, Factor XI Gene Variants, and Statin Use

Factor XI is an essential protein in the blood coagulation system. Certain variants in the Factor XI I gene, *F11*, are associated with an increased risk of VT. Prior research suggested that this risk might be diminished by statin use. A recent NHLBI-supported study addressed this issue by evaluating the association between two *F11* gene variants and VT risk among female statin users and nonusers. The study found no significant difference

in VT risk estimates between the two groups of women (Smith et al., 2016).

Sleep Disorders

NHLBI houses the National Center for Sleep Disorders Research (NCSDR), established by Congress in 1993 to address sleep as a public health concern. To advance sleep science, the Center supports research, training, technology transfer, and coordination across Federal agencies. NCSDR activities are supported by the Trans-National Institutes of Health (NIH) Sleep Research Coordinating Committee, which comprises representatives from 13 NIH Institutes, Centers, and Offices, including NHLBI and ORWH.

Sleep Apnea and Markers of Cardiovascular Disease

NHLBI's Multi-Ethnic Study of Atherosclerosis (MESA) has examined the relationship between obstructive sleep apnea and pathological changes in the heart. The analysis involved more than 1,400 participants under age 65 from six U.S. communities who underwent sleep assessments and cardiac magnetic resonance imaging. The investigators found that the severity of untreated, abnormal breathing patterns during sleep is associated with greater left ventricular (LV) mass and LV mass/volume ratio in both men and women. Prior studies had demonstrated associations in men, but not women, or found stronger associations in men. These findings support the need to consider obstructive sleep apnea as a contributor to cardiac dysfunction in women (Jahaveri et al., 2016).

Sleep Apnea and Heart Failure

The impact of obstructive sleep apnea in midlife on cardiovascular risk in late life varies by sex. Although obstructive sleep apnea is more prevalent in men than women, a recent study found that apnea severity was associated with incident heart failure in women, but not men. More than 750 men and 890 women received an objective assessment of sleep apnea at baseline (midlife), and were followed for 13 to 15 years to identify incident cardiovascular

risk/disease. In women, but not men, the severity of obstructive sleep apnea was associated with elevated levels of cardiac troponin (a biomarker used to diagnose myocardial infarction), incident heart failure, and death during the follow-up. In study participants without a cardiovascular event, obstructive sleep apnea was associated with higher LV mass in women, but not in men. The findings suggest that, in midlife, the risk of heart failure associated with untreated sleep apnea is higher in women than in men (Roca et al., 2015).

Sleep and Maternal Health

The nuMoM2b Sleep Disordered Breathing Study was designed to determine whether sleep-disordered breathing during pregnancy is a risk factor for adverse pregnancy outcomes. The study has recruited 3,702 women from the nuMomM2b cohort to undergo overnight in-home sleep-disordered breathing assessments in early pregnancy (6–15 weeks) and mid-pregnancy (22–31 weeks). The study will examine whether sleep-disordered breathing is associated with preeclampsia, gestational hypertension, gestational diabetes, fetal growth restriction, or preterm birth (Facco et al., 2015).

Scientific Workshops

Understanding Sarcoidosis

Sarcoidosis is an enigmatic disease characterized by inflammation in the lung, heart, brain, eyes, skin, liver, and other organs. Disease manifestations, severity, and long-term prognoses vary from person to person, with significantly higher prevalence and mortality among African-Americans and women. To address these issues, NHLBI held a workshop to discuss how to better understand sarcoidosis disease mechanisms and how to identify and treat patients at high risk for severe sarcoidosis. The workshop took place from August 31 to September 1, 2015, in Bethesda, Maryland, and brought together researchers, patient advocates, and NIH program staff. The participants recommended (1) establishing a cohort of rigorously phenotyped sarcoidosis patients, (2) standardizing definitions

of disease phenotypes, (3) establishing standards of care for different phenotypes of sarcoidosis patients, (4) developing innovative prevention and therapeutic approaches, (5) prioritizing clinical trials that evaluate interventions for life-threatening complications, (6) applying “omics” and systems biology research to improve the characterization of sarcoidosis phenotypes, (7) developing animal models that more closely reproduce features of chronic sarcoidosis, and (8) integrating and using electronic medical records systems to assess the impact of sarcoidosis (NHLBI, 2015).

Addressing Sex Differences in Cardiovascular Health

CVD is the leading cause of morbidity and mortality in the United States. However, it can present and progress differently in men and women. To address the biological bases for these sex differences, NHLBI assembled a working group on “Sex Bias in Cardiovascular Research,” comprising leaders in the field and program staff from NIH and the U.S. Food and Drug Administration (FDA). The group convened in Bethesda on September 22, 2014, and reported preliminary recommendations in January 2015. These recommendations are to (1) educate scientists about the importance of sex balance in research, (2) develop tools and resources for studying sex differences in CVD, (3) foster basic research on sex differences in health and disease, (4) develop guidelines for sex-based clinical and basic/translational research design, and (5) develop metrics for tracking implementation of these recommendations (NHLBI, 2014). The group also published an analysis of critical questions and research gaps to be addressed regarding sex differences in CVD. These include understanding differences in immune modulation of blood pressure and the potential impact of sex-linked genes and epigenetic differences. The group concluded that understanding similarities and differences between the sexes may lead to the development of sex-specific therapies for prevention and treatment of CVD (Maric-Bilkan et al., 2016).

Education and Engagement

NHLBI sponsors a national health education program, *The Heart Truth*[®], to promote heart disease prevention among women.¹ It seeks to raise awareness that heart disease is the leading cause of death for women in the United States, increase knowledge of the risk factors that render women susceptible to heart disease, and encourage women to talk to their doctors, learn their personal risk, and take action to reduce it. *The Heart Truth*[®] collaborates closely with other components of the U.S. Department of Health and Human Services (HHS), including ORWH, the Centers for Disease Control and Prevention's Million Hearts[®] initiative, and the HHS Office on Women's Health.

The program uses the iconic *Red Dress*[®] to impart the awareness message. Awareness of the *Red Dress*[®] symbol has grown considerably since its launch in 2002. In 2010, about 60 percent of women were aware of the *Red Dress*[®], and those who reported awareness of the *Red Dress*[®] or *The Heart Truth*[®] campaign were more likely than other women to take at least one risk-reducing action as a result (up from 35% in 2008 to 57% in 2010).

Raising awareness about risk has done more than just inform women—it motivates them to act. Women who know that heart disease is their leading cause of death were 35 percent more likely to be physically active and 47 percent more likely to report weight loss than those who are unaware (Mosca et al., 2013).

The Heart Truth's strategic framework is built on three pillars: national awareness-raising activities, community activation, and partnerships. National-level partnerships and activities, such as National Wear Red Day[®], are designed to raise awareness of heart disease and its risk factors among American women. Community activation, including *The Heart Truth* Community Action Grant Program (supported by a public-private partnership between NHLBI and the Foundation

for the NIH), and Champions Trainings (supported by the HHS Office on Women's Health), provides community-level education to women of color and low income. Using multicultural, science-based resources, these programs help motivate women to make healthy lifestyle and behavior changes. These programs also equip health educators and women's health advocates to plan and implement heart health awareness and education programs in their communities.

Partnerships with a wide variety of organizations—community, media, corporate, government, nonprofit, and health professional—leverage *The Heart Truth*'s outreach to its target audience, amplify the program's key evidence-based, public health messages, and support national activities and community programming. Over the past decade, the program has contributed to an increased awareness among women that heart disease is their leading cause of death—a recent American Heart Association survey showed that such awareness nearly doubled between 1997 and 2012, from 30 percent to 56 percent (Mosca et al., 2013). Despite the increase of heart disease awareness in women, disparities remain among African-American women and Latinas. *The Heart Truth*[®] continues to work to support outreach to these priority populations to reduce disparities and promote healthy behavior changes.

In developing the Strategic Vision, NHLBI engaged scientific, professional, and patient advocacy communities that align with our mission, including organizations that represent women's health issues (e.g., Women's Heart Alliance). To leverage the energy and wealth of ideas from these groups, in February 2015, NHLBI convened a "Scientific Roundtable on Cardiovascular Health in Women" involving about two dozen experts in cardiovascular research—including basic and clinical scientists, epidemiologists, patient advocates, Federal officials, and others. The aims were to (1) assess the current state of research on women's cardiovascular health, spanning basic to clinical to implementation

¹ *The Heart Truth*[®], its logo, *The Red Dress*[®], *Red Dress*[®], and Million Hearts[®] are registered trademarks of HHS. National Wear Red Day[®] is a registered trademark of HHS and the American Heart Association.

science; (2) work toward a shared vision of future research to advance women's cardiovascular health; and (3) further shape priorities within the NHLBI Strategic Vision with regard to women's health.

Inclusion

NHLBI is committed to inclusion of women in research across its research portfolio. In fiscal year 2015, women made up 64 percent of participants in all NHLBI-funded cardiovascular clinical trials, including WHI. Excluding WHI, 46 percent of participants in such trials were women. Over the last few years of monitoring these data, the number of women enrolled in NHLBI-funded cardiovascular clinical trials has been stable.

Through its strategic visioning process, academic roundtables, and other outreach efforts, NHLBI has engaged scientific, professional, and patient communities to further enhance the participation of women in clinical research and to facilitate appropriate reporting of research outcomes by gender. One of the priorities identified through the Strategic Vision is to probe the risk factors and systemic mechanisms that determine sex-related differences in heart, lung, blood, and sleep health.

Women's Health Initiative (WHI)

NHLBI's WHI is a major, long-term research program designed to address the most frequent causes of death, disability, and diminished quality of life in postmenopausal women. Launched in 1991, this project originally recruited nearly 162,000 women ages 50 to 79, and was one of the most definitive, far-reaching clinical trials of women's health ever undertaken in the United States. The WHI had two major parts: a randomized controlled Clinical Trial and an Observational Study.

The Clinical Trial enrolled 68,132 postmenopausal women ages 50 to 79 into three trials testing unique prevention strategies. If eligible, women could choose to enroll in one, two, or all three of the following trial components. The components were:

- **Hormone Therapy Trial (HT):** This component examined the effects of combined hormones or estrogen alone on the prevention of coronary heart disease and osteoporotic fractures, and associated risk for breast cancer. There were more than 27,000 participants, who were randomized to receive either hormone pills or a placebo.
- **Dietary Modification Trial:** This component evaluated the effect of a diet low in fat and high in fruits, vegetables, and grains on the prevention of breast and colorectal cancers and coronary heart disease. Nearly 49,000 participants followed either their usual eating pattern or the low-fat dietary pattern. Study participants were followed for 8 to 12 years, with clinical exams every 6 months.
- **Calcium/Vitamin D Trial:** This component began 1 to 2 years after a woman joined one or both of the other clinical trial components. It evaluated whether calcium and vitamin D supplementation could help prevent osteoporotic fractures and colorectal cancer. More than 36,000 participants were randomized into two groups, who received calcium and vitamin D or a placebo.

The Observational Study is examining the relationship between lifestyle, health, and risk factors and specific disease outcomes. This component involves tracking the medical history and health habits of 93,676 women. Recruitment for the observational study was completed in 1998 and participants were followed for 8–12 years.

Recruitment began in September 1993 and continued through October 1998 for the WHI Clinical Trial. Close-out of the three trials occurred between October 2004 and March 2005. Observational study enrollment continued through December 1998.

WHI continued to follow the first consenting participants from each of the original WHI study components for an additional 5 years (2005–2010), and the second consenting participants from an Extension Study for an additional 5 years

(2010–2015). In 2015, WHI was awarded additional funding to continue following participants through 2020. Annual updates on health outcomes are collected by mail from the participants enrolled in each extension study.

Ongoing WHI Studies

Women’s Health Initiative Strong and Healthy (WHISH) Study

The WHISH study is examining the benefits of physical activity for reducing major cardiovascular events in older women. WHISH is a large-scale, randomized controlled trial embedded within the WHI Extension cohort (now ages 63 to 99 years). The study will also evaluate the safety of the intervention by examining risks of bone fractures, falls, and non-CVD mortality (Stefanick, n.d.). Preliminary screening indicates that 50,500 WHI women will meet eligibility criteria.

COcoa Supplement and Multivitamin Outcomes Study (COSMOS)

COSMOS, a component of WHI, is testing whether cocoa flavonoids or multivitamins might reduce cancer and CVD. There is no previous large-scale randomized clinical trial in either men or women for cocoa flavonoids or in women for multivitamins (COSMOS Trial, n.d.). Current projections for the number of WHI participants expected to be randomized into COSMOS range between 6,000 and 7,000 women.

TransOmics for Precision Medicine (TOPMed)

NHLBI’s TransOmics for Precision Medicine (TOPMed) program will leverage existing NHLBI cohorts, including WHI, to identify genetic factors that contribute to heart, lung, blood, and sleep disorders. More than 11,000 whole-genome sequences will be derived from WHI to explore genes that contribute to stroke, hypertension, and venous thromboembolism. These genomic data will be combined with clinical and environmental data, as well as other omics data, to gain a better

understanding of mechanisms that contribute to chronic diseases in women and to explore new targets for therapy (NHLBI, n.d. [b]).

Women’s Health and Minority Health

Recent U.S. health statistics provide the following snapshot of racial/ethnic similarities and differences in the burden of leading causes of death relevant to NHLBI’s mission (CDC, 2015).

- Diseases of the heart account for 22 percent of deaths (first or “leading” cause) in non-Hispanic white women, 23 percent (first) in non-Hispanic black women, 20 percent (second) in Hispanic women, 20 percent (second) in non-Hispanic Asian or Pacific Islander women, and 17 percent (second) in non-Hispanic American Indian or Alaska Native women.
- Cerebrovascular disease (stroke) accounts for 6 percent of deaths (fifth) in non-Hispanic white women, 6 percent (third) in non-Hispanic black women, 6 percent (third) in Hispanic women, 8 percent (third) in non-Hispanic Asian or Pacific Islander women, and 4 percent (seventh) among non-Hispanic American Indian or Alaska Native women.
- Chronic lower respiratory diseases account for 7 percent of deaths (third) in non-Hispanic white women, 3 percent (sixth) in non-Hispanic black women, 3 percent (seventh) in Hispanic women, 3 percent (eighth) in non-Hispanic Asian or Pacific Islander women, and 6 percent (fifth) among non-Hispanic American Indian or Alaska Native women.

NHLBI supports an extensive portfolio of research focused on the health of racial and ethnic minorities and on addressing health disparities that exist between these groups and the majority white population in the United States. Of particular relevance are large epidemiological studies that enable detailed study of diseases and their associated risk factors in defined groups. The Jackson Heart Study, launched in 1998, addresses

CVD prevalence, morbidity, and mortality among black women and men living in the Jackson, Mississippi, area. MESA, launched in 1999, is investigating predictors and progression of subclinical CVD in a cohort that includes white, black, Hispanic, and Asian Americans living in six urban and suburban areas of the United States. Since 1988, NHLBI has supported the Strong Heart Study to understand CVD mortality and risk factors among Native Americans, with sites in Oklahoma, Arizona, and the Dakotas.

Since 2006, the Hispanic Community Health Study/ Study of Latinos has monitored disease risk factors and outcomes in a Latino cohort that comprises self-identified Mexican Americans, Puerto Ricans, Cuban Americans, and Central/South Americans. Disease outcomes under study include CVD, stroke, asthma, chronic obstructive pulmonary disease, sleep disorders, dental disease, hearing disorders, diabetes, kidney and liver disease, and cognitive impairment. Pregnancy-related complications—including pre-eclampsia, eclampsia, and gestational diabetes—were added as outcome measures in 2013. The study has found that CVD risk factors vary among distinct Latino groups. The prevalence of three or more CVD risk factors is highest among participants with lower socioeconomic status, those with higher levels of acculturation to the United States (as determined by years of residence, generational status, and language preference), and those of Puerto Rican background. For example, 51 percent of Puerto Rican women in the study are obese, a higher rate than among Puerto Rican men or any other Latino group (Daviglius et al., 2012).

Women in Science

One of NHLBI's enduring principles is to enable and develop a diverse biomedical workforce. Increasing the representation of underrepresented groups, including women, in this pipeline is a top priority. NHLBI has explicitly addressed its commitment to workforce diversity in its Funding

and Operating Guidelines. In FY 16, NHLBI adopted a more flexible funding strategy for competing grant applications. For some grant types, including R21 exploratory grants, the Institute now evaluates all applications that fall within a particular score range, rather than focusing narrowly on the payline.² NHLBI also has the flexibility to fund R01 grants that score outside the payline. In both cases, NHLBI makes final award decisions based on a variety of criteria, including its goal to maintain and enhance workforce diversity (NHLBI, 2017).

NHLBI participates in the NIH-funded National Research Mentoring Network (NRMN), a nationwide consortium of institutions collaborating to provide mentorship and career development to biomedical researchers from diverse backgrounds. Funding for this program was predicated on the goal of improving recruitment and training of researchers from underrepresented groups, as defined in the National Science Foundation's *Report on Women, Minorities, and Persons with Disabilities in Science and Engineering (RFA-RM-13-017)*. The NRMN emphasizes the benefits of diversity and inclusivity within mentoring relationships and within the research workforce (National Research Mentoring Network, n.d.).

In January 2016, NHLBI's Office of Science Policy, Engagement, Education, and Communications coordinated a 1-day seminar as part of a Women in STEM Policy program (The Public Leadership Education Network, 2017). This week-long program was organized by the Public Leadership Education Network, a national nonprofit organization whose mission is to prepare women for public leadership. The program's goals were to increase participants' understanding of the public policy dimensions of science and technology and to prepare women for active roles as leaders in science and technology policy. NIH's seminar included presentations by women in science policy leadership positions at NHLBI, the National Institute on Aging, the

² The payline is the percentile score above which grant applications are generally not funded.

National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute on Drug Abuse.

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National Institute on Aging (NIA)

Executive Summary

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer's disease (AD) and other dementias, implications of ovarian aging, menopause and menopausal hormone therapy, osteoporosis, physical disability, and other diseases and conditions. During fiscal years (FY) 15–16, NIA-supported researchers made important progress in a number of women's health-related areas, including the following:

Reproductive health and menopause.

Research continued through the Study of Women's Health Across the Nation (SWAN) and other studies on health across the menopausal transition. For example, SWAN investigators found that regular exposure to environmental tobacco smoke is associated with the development of uterine fibroid tumors, and that women who experience hot flashes are more likely than those who do not to have high blood pressure. Investigators also explored the effects of blood pressure-lowering drugs on bone mineral density (BMD) and found that users of one class of drugs, thiazide diuretics, had a slower annual percent decline in BMD than nonusers. Neither ACE inhibitors nor beta blockers appeared to have a significant effect on BMD.

Menopausal hormone therapy. Investigators with the NIA-supported Early versus Late Intervention Trial with Estradiol (ELITE) showed that when initiated early in menopause (< 6 years postmenopause), menopausal hormone therapy (MHT) slows the progression of subclinical atherosclerosis. However, MHT initiated early in menopause shows no effect on cognition at 2.5 years of treatment.

Cognitive health. Investigators reported on vascular risk factors for age-related cognitive decline in women. For example, a recent

observational study by researchers with the Baltimore Longitudinal Study of Aging showed that cognitive ability in some, but not all, domains declines at a steeper rate for men than for women.

Alzheimer's disease. Recent estimates suggest that nearly two-thirds of individuals diagnosed with AD are female, possibly because women, on average, live longer than men. At the same time, most studies conducted in the United States have not observed sex differences in the incidence of AD, although some studies have shown a higher incidence of AD among women after around age 80. Recent reviews have explored possible reasons for these phenomena, including differences in brain structure, differential effects of the APOE ε4 genotype (the most common genetic risk factor for late-onset disease), and differences in education between men and women in the age cohorts currently at greatest risk.

Behavioral and social research. NIA-supported longitudinal studies provided insights into how early life experiences influence later-life health in women. For example, childhood stress may be a driver of later-life increase in body mass index (BMI) in women, but not in men. In addition, higher childhood conscientiousness is associated with longer leukocyte telomere length measured 40 years later. Leukocyte telomere length, which shortens with age, has been used as a marker of premature aging, and these results offer the first evidence that childhood personality prospectively predicts telomere length.

Ongoing research initiatives focusing on women's health include the Women's Health Initiative Memory Study (WHIMS) suite of studies, which assesses the effects of MHT on memory, cognition, and mood in participants ages 65 and older, without dementia, who had been randomized to

hormone therapy or placebo within the original Women's Health Initiative (WHI) trial; a Specialized Center of Research on Sex Differences, co-funded with ORWH, to explore the intersection of sex, vascular dysfunction, and cognitive decline; and the SWAN Sleep Study, in which investigators from four SWAN sites are examining sleep patterns and factors that may affect sleep during the menopausal transition.

In addition, NIA supports communication and education activities related to women and aging, career development activities, and research on the specific health concerns of minority women.

Introduction

Older women outnumber older men in the United States, and the proportion of the population that is female increases with age. In 2014, women accounted for 56 percent of the population ages 65 and older and for 66 percent of the population ages 85 and older. Despite living longer, however, older women are more likely to report depressive symptoms or limitations in physical function, are more likely to live alone (a potential indicator or risk factor for isolation, lack of caregivers, or lack of support), and live in poverty at a disproportionately high rate (Federal Interagency Forum on Aging-Related Statistics, 2016). American women also lag significantly behind their counterparts in other higher income nations in terms of longevity, and since 1980, the pace of gains in life expectancy of older U.S. women has slowed markedly, compared to that in other industrialized countries (National Research Council, 2011). In fact, life expectancy has fallen 3 to 5 years behind other developed nations, including France, Italy, Spain, Switzerland, Australia, and Japan (National Research Council and Institute of Medicine, 2013).

NIA supports a diverse portfolio of research on older women's health, including studies on the following subjects:

- Cognitive and emotional aging.
- AD and other types of dementia.

- Menopause and MHT.
- Osteoporosis and hip fracture.
- Physical disability.
- Caregiver burden.
- Decline in function of older women.
- Age-related muscle loss.
- Cancer in older women.
- Demography and economics of aging.
- Ovarian hormone influences on brain structure and function.
- Mechanisms of ovarian aging, including premature ovarian failure.
- Sex differences in aging and age-related health conditions.

A Women's Health Liaison in the Office of Planning, Analysis, and Evaluation coordinates communication and reporting on NIA activities related to women's health and serves as liaison to the NIH Coordinating Committee on Research on Women's Health. Recent accomplishments in women's health, as well as ongoing and new research initiatives with a particular emphasis on women, are described below.

Accomplishments

Women's Aging and Health: Findings from the SWAN

NIA's flagship study of women's health is SWAN, an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from pre- to postmenopause. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in White, African-American, Chinese, Japanese, and Hispanic women. Findings from SWAN have greatly enhanced our understanding of women's health across the menopausal transition. For example, SWAN investigators recently identified four distinct

trajectories of vasomotor symptoms (VMS): (1) onset early (11 years before the final menstrual period) with decline after menopause (early onset, 18.4%); (2) onset near the final menstrual period with later decline (late onset, 29.0%); (3) onset early with persistently high frequency (high, 25.6%); and (4) onset early with persistently low frequency (low, 27.0%). Relative to women with persistently low frequency of VMS, women with persistently high and early-onset VMS had a more adverse psychosocial and health profile. Black women were overrepresented in the late-onset and high VMS subgroups relative to white women. Obese women were underrepresented in the late-onset subgroup. (Tepper 2016)

In 2016, SWAN became part of the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) project, a global research collaboration that aims to advance understanding of women's reproductive health in relation to chronic disease risk by pooling individual participant data from some 20 cohort and cross-sectional studies. InterLACE pooled data from 229,054 midlife women (ages 41 to 58). Variables were harmonized across studies to create a new and systematic synthesis of life-course data.

Selected findings from SWAN in 2015–2016 include:

Uterine Fibroids. SWAN investigators found that regular exposure to environmental tobacco smoke is associated with the development of new uterine fibroid tumors—benign tumors of the uterine lining that typically develop during premenopause and perimenopause. Separately, investigators found that high circulating levels of testosterone and estradiol are associated with the development of new, but not recurrent, fibroids.

Cardiovascular disease. SWAN investigators evaluated whether biomarkers, such as high-sensitivity c-reactive protein (HSCRP), fibrinogen, plasminogen-activator inhibitor 1, tissue plasminogen activator antigen, and circulating factor vii (factor viic) were associated with coronary artery calcification (CAC)—a sign of coronary

artery disease—in healthy midlife women. They found that apart from factor viic, all the biomarkers were associated with CAC presence and extent. In addition, HSCRP was associated with CAC only among African-American women, suggesting that hscrp may have a role in coronary heart disease prevention in this population. Elsewhere, SWAN investigators found that prior-year exposures to air pollution (fine particles and ozone) are associated with adverse effects on these pathways.

Separately, SWAN investigators found that women experiencing VMS early in the menopausal transition had higher mean and maximal intima media thickness—a marker for atherosclerosis of the carotid artery—than those with consistently low VMS across the transition. Investigators also found that women with VMS may be more likely to develop hypertension than women who do not experience these symptoms.

Bone health. SWAN participants with fasting plasma triglycerides (TG) of at least 300 mg/dl had a 2.5-fold greater risk of nontraumatic fracture 2 years later and onward, compared to those with TG less than 150 mg/dl. Investigators also explored the effects of blood pressure-lowering drugs on bmd and found that users of one class of drugs, thiazide diuretics, had a slower annual percent decline in BMD than nonusers. Neither ACE inhibitors nor beta blockers appeared to have a significant effect on BMD.

Sleep. Investigators found that chronic stress is associated with sleep disturbance in midlife women, even after adjusting for acute stressors at the time of the sleep study and other factors known to disrupt sleep. Separately, they found that frequent shifts in sleep timing may be related to poor metabolic health, even among non-shift-working midlife women.

Health disparities. Psychosocial predictors of allostatic load—a measure of physiological dysregulation thought to indicate disease risk—were examined in midlife women using data from SWAN. Researchers found that African-American race, lower income, and lower education predicted

higher levels of allostatic load. These associations were partially explained by higher experiences of discrimination, perceived stress, and hostility.

Novel Treatments for Menopausal Symptoms: The MsFLASH Network

Researchers with the Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) Network, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition, recently published a comprehensive overview of results of clinical trials for menopausal VMS (e.g., hot flashes). They found that the antidepressants escitalopram and venlafaxine, as well as low-dose estradiol, provide comparable, modest reductions in VMS frequency and bother among women with moderate hot flashes. Aerobic exercise, yoga, and omega-3 supplements had no effect on symptom frequency or perceived discomfort in these studies. Network investigators also found that speaking on the phone with a “sleep coach” and keeping a nightly sleep diary significantly improved sleep quality and reduced insomnia in women through all stages of menopause. The intervention also reduced the degree to which hot flashes interfered with daily functioning. Because many women experience sleep disturbances at some point during the menopausal transition, the development of effective nondrug interventions to improve sleep could help millions of women each year.

MHT and the Timing Hypothesis: Results from ELITE

The question of whether the effects of MHT on cognitive and physical health outcomes depend on the timing of initiation of MHT relative to menopause, age, or both, has long been of interest to researchers. Investigators with the NIA-supported Early versus Late Intervention Trial with Estradiol (ELITE) showed that when initiated early in menopause (< 6 years postmenopause), MHT slows the progression of subclinical atherosclerosis, a condition leading to the narrowing or complete

obliteration of blood vessels. This result may provide reassurance to women who are prescribed MHT early in menopause, but are concerned about possible adverse effects on the heart. Conversely, the ELITE investigators found that MHT initiated within 6 years of menopause does not affect cognition at 2.5 years differently than when initiated more than 10 years postmenopause (Henderson 2016). Although these findings do not support the timing hypothesis with respect to cognition, healthy younger postmenopausal women considering MHT for other reasons may be reassured that treatment should not adversely affect cognitive abilities in the short term.

The Menopausal Transition, Menopausal Hormone Therapy, and Cognitive Health

Although the number of women prescribed MHT continues to decline, a recent nationally representative survey showed that more than 8 million American women continue to use MHT, with women older than age 60 continuing to account for more than one-third of MHT use in the United States. Meanwhile, the long-term effects of estrogen-containing MHT on cognition, including the association between MHT use and AD, remain the subject of intense scientific scrutiny. The question of whether MHT promotes, protects against, or does not influence risk of cognitive decline and/or AD and related dementias has proven to be extremely complex, with timing and duration of treatment, specific hormones prescribed, and environmental factors all implicated to some degree in each woman’s individual risk profile.

Observational studies have long suggested that use of estrogen-containing MHT is associated with a reduced risk of AD. However, among participants in the WHIMS, conjugated equine estrogens plus the progestin (progesterone-related hormone) medroxyprogesterone acetate (CEE/MPA) increased dementia risk, although not the risk of mild cognitive impairment (MCI), in women ages 65 years and older. While the WHI Study of Cognitive

Aging showed that CEE/MPA worsens verbal memory, it found that CEE alone had no influence on cognition. These findings have been replicated in several randomized clinical trials. The apparent negative effect of CEE/MPA on verbal memory does not appear to be age-dependent. Studies testing the long-term effects of natural estrogen and progesterone on dementia and cognitive outcomes are in progress.

In the past several years, National Institutes of Health (NIH)-supported investigators have begun to explore whether hormone use by younger postmenopausal women near the time of menopause reduces dementia risk, or whether WHIMS findings should be generalized to younger women. Some research suggests that some forms of MHT may be beneficial if taken during a critical window near menopause, but when initiated in later life it may be associated with increased dementia risk. Recent results from the NIH-supported Cache County Study support this “window of opportunity” hypothesis. In this study, women who used any type of hormone therapy within 5 years of menopause had a 30 percent lower risk of AD, especially if use was for 10 or more years. By contrast, AD risk was not reduced among those who had initiated MHT 5 or more years postmenopause. Instead, rates were increased among those who began estrogen-progestin compounds within the 3 years preceding the Cache County Study baseline evaluation. At the same time, however, NIA intramural researchers with the Women’s Health Initiative Study of Younger Women found no cognitive benefit or risk associated with estrogen therapy (CEE) in women who started treatment when they were between the ages of 50 and 55 and continued it for an average of 7 years. Research is ongoing in this area.

Age-Related Cognitive Decline and Cognitive Impairment

Midlife vascular risk factors influence later cognitive decline and AD. The decrease in serum estradiol levels during menopause has been associated with cognitive impairment and increased vascular risk,

such as high blood pressure, which independently contributes to risk of cognitive dysfunction and AD. Recently, investigators with the NIA-supported Kronos Early Estrogen Prevention Cognitive and Affective Study (KEEPS-Cog) reported on the extent to which various vascular risk factors relate to cognition in healthy, middle-aged, recently postmenopausal women. They found that higher systolic blood pressure early in the postmenopausal period was weakly related to poorer performance in auditory working memory and attention, although other cognitive domains were not affected by blood pressure. This relationship was not associated with hormone levels. KEEPS investigators also developed a model that stratified risk for cardiovascular disease and cognitive decline, incorporating education level, age, ethnicity, and genetic indicators. They noted that these differences may point to phenotypes for cardiovascular disease risk. Evaluating the evolution of phenotypes could, in turn, clarify preclinical disease, as well as screening and preventive strategies.

Sex Differences Identified in Cognitive Aging.

Previous research has shown that aging affects cognitive ability, and that subtle sex differences in cognition exist across the lifespan. A recent observational study by researchers with the Baltimore Longitudinal Study of Aging, in NIA’s Intramural Research Program, showed that cognitive ability in some, but not all, domains declines at a steeper rate for men than for women. Over 9 years, men outperformed women on the two tests of visuospatial ability, and women performed better than men on several other cognitive tests. Men showed overall steeper rates of cognitive decline in areas of mental status, perceptuomotor speed and integration, and visuospatial ability. None of the measures showed significantly steeper declines for women. This suggests that women have a greater resilience to age-related cognitive decline than do men.

The researchers note that societal changes may contribute to these sex differences, as they have resulted in greater improvements in cognitive stimulation, financial prosperity, and health for

women. In addition, sex differences in cognitive aging may be affected by differences in brain structure and function, which tend to show more favorable outcomes for women at advanced ages. Further research is needed to link longitudinal brain changes to cognition in older men and women.

Other Risk Factors for Age-Related Cognitive Decline

Alzheimer's Disease

AD is the most common cause of dementia among people ages 65 and older, and it is a major public health issue for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. As many as 5.1 million people ages 65 and older in the United States are affected by AD, depending on how the condition is measured, and scientists agree that unless it can be effectively treated or prevented, the numbers will increase significantly if current population trends continue (Hebert et al., 2013).

The prevalence of AD is significantly higher among women than among men. Recent estimates suggest that nearly two-thirds of individuals diagnosed with the disease are female (Hebert et al., 2013), perhaps because women, on average, live longer than men. At the same time, the majority of studies conducted in the United States have not observed sex differences in the incidence of AD—that is, in the rate of developing the disease. However, several American studies, and most European and Asian studies on the subject, have shown a higher incidence of AD among women after around age 80 (Mielke et al., 2014). The potential reasons for this are complex and may include differences in brain structure, differential effects of the APOE $\epsilon 4$ genotype (the most common genetic risk factor for late-onset disease), and differences in education between men and women in the age cohorts currently at greatest risk (Mielke et al., 2014; Rocca et al., 2014). Notably, a recent study of amnesic mild cognitive impairment (MCI), often

a precursor condition to AD, indicated that it was more common in men than in women, suggesting that sex differences in disease course may exist. For example, the investigators hypothesized that women may transition from MCI to dementia later in life than men, but more abruptly (Petersen, 2010).

Behavioral and Social Research

Midlife in the United States Study (MIDUS).

MIDUS follows 7,000 midlife adults (ages 25–74), including a large national twin sample, first assessed in 1994. MIDUS exemplifies innovation in NIA-supported longitudinal biosocial surveys, incorporating in-depth laboratory assessments into large social surveys, with substudies targeting cognitive functioning, daily stress, clinical biomarkers, and neuroscience assessments of emotional function. The unique design of the MIDUS study enables, broadly, (1) the investigation of the role of long-term, cumulative psychosocial factors on mid- and later-life health, (2) the identification of the neurobiological mechanisms and pathways through which psychosocial factors contribute to health, and (3) the advancement of knowledge of protective psychosocial factors (those that promote positive health and resilience). NIA renewed funding for MIDUS in 2016 to support completion of a 20-year follow-up of the sample and expansion into new research on gene expression and efforts to re-enlist participants lost to follow-up in prior waves. Several new studies of women's health have resulted from use of MIDUS data, which are publicly available.

There is increasing scientific interest in understanding the long-term health impacts of early life adversity. A study reported in *JAMA Psychiatry* found that in the MIDUS sample, women who reported emotional or physical abuse in childhood were at increased risk for all-cause mortality over a 20-year follow-up period, as compared with those who did not—an effect that was not accounted for by childhood socioeconomic status, personality traits, or depression. Similar effects were not found in men.

A study examining sexual satisfaction among over 2,000 midlife and older women in MIDUS found that a considerable portion of women remained sexually active if they had a partner available. Such psychosocial factors as relationship satisfaction and communication with a partner were more important contributors to sexual satisfaction than age.

In another study using MIDUS data, researchers found that although divorce has been associated with poor health outcomes, women in lower quality marriages (e.g., reporting less support from their spouses and the presence of more marital strain) report increases in life satisfaction following divorce, while women in high-quality marriages experience much lower levels of life satisfaction after divorce.

Early Life Influences on Later Life Outcomes.

Childhood predictors of adult health were examined in two additional studies:

- Using 15-year data from the Americans' Changing Lives study, researchers found that although childhood stress predicts adult stress in both men and women, relationships between stress and BMI differ by sex. Women with higher adult stress had higher BMI, and women who retrospectively reported higher levels of childhood stress gained weight more rapidly over the study period, suggesting that childhood stress may be a driver of long-term BMI increase in women. These associations were not found in men.
- The link between early life personality traits—especially conscientiousness and neuroticism—and later life morbidity and mortality has been widely reported. Leukocyte telomere length, which shortens with age, has been used as a marker of premature aging. A 2015 study of a subsample of 60 women in the Hawaii Personality and Health Cohort found that higher childhood conscientiousness was associated with longer leukocyte telomere length measured 40 years later, offering the first evidence that childhood personality prospectively predicts telomere length.
- Using data from the longitudinal U.S. Health and Retirement Study, researchers examined relationships between women's exposure to midlife work/family demands and subsequent mortality risk. They first identified common patterns in how U.S. women born between January 1936 and February 1956 combined work, marriage, and children between the ages of 16 and 50. The researchers found that women spending most of their adult lives as single mothers (working and nonworking) were at greatest risk of dying during follow-up, followed by nonworking married mothers. Married women out of the workforce when their children were young were at lowest risk. Effects were partially explained by behavioral factors (e.g., smoking and obesity) and household wealth in later adulthood. In a cross-national analysis of comparable data, researchers found that differences between the United States and Europe in women's work-family patterns explained only a small fraction of the health disadvantage of U.S. women relative to European women.

Improving Functional Outcomes after Stroke.

Causes of poorer functional outcomes after stroke in women than in men are unknown. In a study of 439 ischemic stroke survivors, of whom 51 percent were women, functional outcomes among women were significantly worse than among men. The most important factor contributing to worse functional outcomes in women was prestroke function, suggesting that prevention efforts aimed at maintaining functional status in aging women could improve stroke outcomes.

Informal Caregiving: Who Experiences Most Stress?

Informal caregiving—providing regular support to an infirm friend or relative—can vary in intensity, and many report it to be a stressful experience. Women in the Caregiver-Study of Osteoporotic Fractures whose caregiving intensity increased over time reported higher stress levels than those who had sustained high-intensity caregiving over an equivalent time period, while

cessation of caregiving resulted in lower reports of perceived stress.

Initiatives

Ongoing Research Initiatives

Menopause and Beyond: SWAN. SWAN is an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from pre- to postmenopause. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in White, African-American, Chinese, Japanese, and Hispanic women. SWAN is unique in that the period of follow-up spans the menopausal transition, the final menstrual period, and postmenopause to characterize how the menopausal transition influences health outcomes at older ages. Over two decades, SWAN investigators have collected a wealth of clinical data and biospecimens that represent an important research resource for further studies of menopause.

Initially funded in 1994, SWAN is a cooperative agreement consisting of seven clinical field sites, a central reproductive hormone laboratory, a coordinating center, an advisory panel, and a repository of blood, urine, and DNA specimens. The study is supported by NIA, the National Institute of Nursing Research, and the NIH Office of Research on Women's Health (ORWH), and supports Objective 3.1 of the ORWH Strategic Plan, "Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan."

The SWAN Sleep Study. SWAN investigators from four sites are examining sleep patterns and factors that may affect sleep during the menopausal transition. Although sleep disruptions, insomnia, and breathing-related sleep disorders increase as women age, little is known about

how sleep changes as women progress through the menopausal transition. The goals of Sleep I, the baseline phase, were to (1) characterize sleep disturbances in a large, multiethnic sample of midlife women; (2) characterize relationships among menopausal characteristics (e.g., vasomotor symptoms and bleeding) and sleep disturbances; (3) evaluate the influence of psychobiological factors on the sleep-menopause relationship; and (4) establish baseline data for Sleep II, the longitudinal phase of this research study. The major goals of Sleep II, currently in progress, are to identify (1) potential predisposing, precipitating, and perpetuating factors for chronic sleep disturbances during the menopausal transition and (2) adverse effects of sleep disturbances on subsequent health status during the early postmenopausal period.

MsFLASH Network. In 2008, NIA—in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Center for Complementary and Integrative Health, and ORWH—established the MsFLASH initiative, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition. The Network's current focus is on such postmenopausal vaginal problems as dryness, itching, irritation, burning, or pain with sexual activity, but the investigators also have studied a variety of approaches for efficacy against hot flashes and night sweats, as well as for other symptoms, including sleep disturbance, mood disorder, and sexual function.

Hormones, Menopause, and the Aging Brain. NIA-supported investigators continue to study the mechanisms through which estrogen and related hormones work on the brain, as well as the effects of different forms of MHT on cognition. These efforts support ORWH Strategic Plan Objective 1.5, "Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders." Ongoing initiatives exploring

the effects of age-related hormone changes and menopausal hormone therapy on the brain include the following:

- **The Women’s Health Initiative Memory (WHIMS) Suite of Studies.** NIA intramural researchers also conduct and manage the WHIMS suite of studies, which assess the effects of MHT on memory, cognition, and mood in participants ages 65 and older, without dementia, who had been randomized to hormone therapy or placebo within the original WHI trial.
- **Perimenopause in Brain Aging and Alzheimer’s Disease.** The goal of this large, long-running Program Project, which was renewed in FY 16, is to determine how the brain changes during the perimenopausal transition and how these changes can lead to development of early risk factors for developing AD. Currently, investigators are exploring the impact of the *APOE4* allele—strongly associated with risk for AD—among perimenopausal women.
- **Estrogen and the Aging Brain.** In this Program Project, researchers are investigating the interplay of aging with estrogen and progesterone on key brain regions in animal models. The researchers are exploring the cognitive and neurobiological effects of different hormone treatment regimens. Proposed studies will investigate the “window of opportunity” hypothesis and the duration of beneficial effects after treatment has ended. These results will provide critically important information on brain aging and will aid in the design of hormone treatments that provide maximal neurological benefits for postmenopausal women.

Bone Health. NIA continues to support the multicenter Study of Osteoporotic Fractures (SOF), which has collected 20 years of prospective data about osteoporosis that have served as the basis for many findings about osteoporosis and aging in women ages 65 and older. In addition to fractures, SOF has tracked cases of breast cancer, as well

as total and cause-specific mortality. The data include measures of BMD, hormones, strength and function, cognition, sleep, medication use, and health habits. Although most of the initial study participants were White, in 1997 SOF enrolled an additional 662 African-American women who now are seen with the original cohort. The participants, who are now in their 80s and 90s, continue to be assessed every 2 years, and data are available to qualified researchers for further analysis.

In a separate study, NIA-supported researchers are working to determine if and how a variant of the amyloid precursor protein, already implicated in the development of AD, contributes to bone loss and osteoporosis. Frequently, AD patients have lower BMD and higher rates of hip fracture, compared with the same-age normal population, and several newly identified AD risk genes/loci encode proteins critical for bone health. Results from this research may not only provide a potential link between AD and osteoporosis/osteopenia, but also identify unrecognized functions of APP and reveal new pathological mechanisms underlying both disorders.

Early Versus Late Intervention Trial With Estradiol (ELITE). Understanding the effect of MHT on the progression of subclinical atherosclerosis, especially in young postmenopausal women, continues to be an important public health issue. Investigators with ELITE evaluated whether 17 β -estradiol (estrogen) reduces the progression of early atherosclerosis if initiated soon after menopause when the vascular endothelium (lining of blood vessels) is relatively healthy, versus later, when the endothelium has lost its responsiveness to estrogen. The investigators also tested whether 17 β -estradiol reduces the progression of cognitive decline if initiated soon after menopause.

Sex and Gender Analyses

NIA supports research to identify and elucidate sex and gender differences in aging and age-related disease and dysfunction. New and ongoing initiatives, which are broadly responsive to ORWH

Strategic Plan Objective 3.6, “Study sex/gender differences in the aging process,” include the following:

- A Funding Opportunity Announcement (“Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of Alzheimer’s Disease Risk and Responsiveness to Treatment,” R01) soliciting research to increase our understanding of the impact of sex differences on the trajectories of brain aging and phenotypes of AD risk and on the responsiveness to pharmacologic and nonpharmacologic interventions.
- A large program project grant that innovatively combines informative animal models, high-quality human data, and sophisticated demographic analyses to generate a deeper understanding of the basis for sex differences in health and survival, as well as opportunities to reduce these differences.
- A Specialized Center of Research on Sex Differences, co-funded with ORWH, to explore the intersection of sex, vascular dysfunction, and cognitive decline. By focusing on women who have experienced a hypertensive pregnancy event, preeclampsia, and menopause, these studies will identify women who might benefit from early treatments to sustain cognitive health across their life transitions.

Sex and gender analyses are included in many NIA basic and clinical studies, and several studies focus specifically on sex and gender differences in older age, including the following:

- The Interventions Testing Program, which supports the testing of compounds with the potential to extend the lifespan and delay disease and dysfunction in a genetically heterogeneous mouse model of aging. All interventions are tested in both male and female animals, and sex differences in responses to several compounds have been identified.

- A study to identify the genetic and gene expression mechanisms that mediate the apparent sex differences in AD presentation.
- A study exploring the intersection of sex, genotype, and air pollution in the development of AD in a mouse model.

Communications and Education Initiatives

Many topics covered by NIA publications and online health information are of special interest to women. Recent communications activities include the following:

- Email, online, and social media outreach to promote NIA women’s health research.
- NIA staff outreach to Federal and non-Federal organizations interested in caregiving and other women’s issues.
- Development and distribution of evidence-based consumer publications on women’s health topics, including the new tip sheet *Menopause: Treatments for Symptoms*.
- Development and outreach for the NIHSeniorHealth page within the new topic “Health Immunizations and Screenings, Recommended Screenings for Women 50+.”
- A feature article on menopause treatments for *Medline Plus* magazine (Winter 2017).
- Support for the Women of Color Research Network.
- Support for the U.S. Food and Drug Administration’s Office of Women’s Health Diverse Women in Clinical Trials campaign.

Health Disparities

Demographic projections predict a substantial change in the racial and ethnic makeup of the older population, heightening the need to examine and reduce differences in health and life expectancy. NIA is committed to addressing health disparities, with many initiatives supported in partnership

with the National Institute on Minority Health and Health Disparities. Minority aging research is conducted throughout NIA's programs, and much of this research has relevance to the health needs of minority women, including the following current programs and projects:

- SWAN, which explores a number of health parameters among White, African-American, Chinese, Japanese, and Hispanic women.
- The MsFLASH initiative, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition, which has successfully recruited sufficient numbers of African-American women to gather baseline data to analyze for differences by race and ethnicity in perimenopause/menopause characteristics.
- The Healthy Aging in Neighborhoods of Diversity across the Life Span study, a community-based research effort designed to focus on evaluating health disparities in minority and socioeconomically diverse populations.

Career Development

NIA actively encourages participation of women in its training and career development initiatives. The Institute supports a research study examining the barriers women face in careers in biomedical research in universities and research centers and also co-funds the University of Maryland Building Interdisciplinary Research Careers in Women's Health Program, which has a research emphasis on women and aging. The NIA Deputy Director also co-chairs the NIH Women of Color (WOC) Committee of the trans-NIH Working Group on Women in Biomedical Careers. The WOC Committee sponsors the Women of Color Research Network LinkedIn site, which provides women of color and supporters of their advancement in the biomedical sciences information about the NIH grants process, advice on career development, and a forum for networking and sharing information.

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National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Executive Summary

The mission of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is to generate and disseminate fundamental knowledge about the effects of alcohol on health and well-being and apply that knowledge to improve the diagnosis, prevention, and treatment of alcohol-related problems, including alcohol use disorder (AUD), across the lifespan.

NIAAA provides leadership in the national effort to reduce alcohol-related problems by—

- Conducting and supporting alcohol-related research in a wide range of scientific areas, including genetics, neuroscience, epidemiology, prevention, and treatment.
- Coordinating and collaborating with other research institutes and Federal programs on alcohol-related issues.
- Collaborating with international, national, state, and local institutions, organizations, agencies, and programs engaged in alcohol-related work.
- Translating and disseminating research findings to health care providers, researchers, policymakers, and the public.

Alcohol misuse refers to drinking in a manner, situation, amount, or frequency that could cause harm to an individual or those around them. It contributes to poor performance at school and work, family trouble, unprotected sex and sexually transmitted diseases, violence, memory blackouts, unintentional injuries, accidents, overdoses, and organ damage and disease. It also can lead to AUD, a serious condition that affects nearly 16 million people in the United States. The Centers for Disease Control and Prevention estimates that alcohol misuse costs the United States \$249 billion per year due to health care expenses, lost workplace productivity, crime, property damage, and other

adverse outcomes. An estimated 88,000 people (approximately 62,000 men and 26,000 women) die from alcohol-related causes annually, making alcohol the fourth leading preventable cause of death in the United States.

Studies indicate that women consume lower levels of alcohol and are less likely than men to drink daily or to engage in binge patterns of use. Women, however, are more sensitive than men to the physiological effects of alcohol, achieve higher blood alcohol concentrations, have a higher risk for the development of alcohol-related diseases, and show a higher vulnerability to alcohol dependence.

NIAAA-funded preclinical studies in animal models have begun to reveal the mechanisms underlying sex/gender differences in drinking behaviors and related problems. In the past two fiscal years, scientific areas related to Goal 1 and Goal 2 of the NIH Strategic Plan for Women's Health Research have benefited from significant advances in knowledge.

NIAAA also maintains a strong program of research that examines how the presence of other medical conditions, along with environmental and social factors, can lead to different patterns of alcohol abuse and health vulnerabilities in girls and women throughout their lives. Scientists now recognize that human biology and behavior continue to change throughout life, which, in turn, affects individuals' drinking patterns and their decisions to alter drinking habits or to seek help for alcohol use problems. A lifespan perspective will allow researchers to identify how the emergence and progression of drinking behavior is influenced by changes in biology, psychology, and exposure to social and environmental inputs over a person's lifetime, and vice versa. This approach will help discover life-stage-appropriate strategies for developing individualized prevention and treatment

programs for girls and women that fulfill Strategic Plan Goal 3.

This report highlights NIAAA's recent activities and accomplishments in biomedical and behavioral research related to women's health. The accomplishments fall into 11 research categories:

(1) consortia; (2) prevention and treatment for women; (3) comorbidity of AUD and other psychiatric disorders; (4) alcohol, aggression, and violence; (5) fetal alcohol exposure; (6) sex differences in basic research; (7) sleep; (8) women, alcohol use, and cancer; (9) women, alcohol use, and HIV; (10) women, alcohol use, and cardiac health; and (11) health disparities.

Accomplishments and Activities

Consortia

Adolescent Brain Cognitive Development (ABCD) Study (Objectives 1.8, 2.6, and 3.1).

The ABCD Study is a nationwide research consortium to investigate adolescent brain and behavior development and the effects of substance use on the normal developmental trajectory.

The ABCD Study includes 21 research project sites and is funded by several National Institutes of Health (NIH) Institutes and Centers (ICs), including NIAAA. Starting at ages 9–10 years, more than 10,000 participants (male and female) will be studied in a longitudinal design into early adulthood on a variety of brain imaging, behavior/cognitive, and social and clinical measures. The impact of sex differences on the measures acquired will be evaluated at both the research project site and consortium-wide levels (*U01 DA041106*).

Integrative Neuroscience Initiative on Alcoholism Neuroadaptation (INIA) Consortium (Objectives 1.5, 1.8, and 2.6). The INIA research consortium supports multidisciplinary collaborative research projects to find the underlying adaptations of chronic excessive alcohol use and dependence. The two funded INIA consortia are focused on

(1) neurobiological basis of excess drinking and (2) stress, anxiety, and alcohol abuse. Each consortium includes studies in research animals and human participants of both sexes to determine the effects of sex on alcohol abuse and dependence (*U24 AA025479*; *U24 AA013641*).

Collaborative Initiative on Fetal Alcohol Spectrum Disorders (Objective 3.1). This consortium comprises multiple international sites with high incidence of fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorders (FASDs). A Ukrainian cohort with moderate-to-heavy-drinking women examined nutritional factors in alcohol-related birth outcomes. Longitudinal studies expanded prenatal ultrasound measures, physical examination, and neurobehavioral testing of the offspring. In addition, consortium members are developing animal models of FAS and FASD. The long-term goals of this research consortium are to refine the diagnostic criteria for FAS/FASD, explore the underlying mechanisms of the disorder, and develop therapeutic interventions to provide relief to those affected (*U24 AA014811*).

Prevention and Treatment for Women

The Effects of Bariatric Surgery on Alcohol Consumption (Objective 2.5). Obesity represents a major medical and public health problem worldwide. An effective treatment for obesity is bariatric surgery, specifically Roux-en-Y Gastric Bypass (RYGB). Although clinical studies suggest an increased risk among RYGB patients for use of alcohol and risk for developing AUD, the neural mechanisms underlying this phenomenon remain poorly understood and have not been systematically investigated. This recently funded R21 grant proposes to use multiple techniques, including state-of-the-art *in vivo* micro-positron emission tomography (PET) imaging methods in female rats. This is the first study to examine the neural mechanisms underlying how RYGB increases susceptibility to alcohol addiction after an extended alcohol exposure in a female model (*R21 AA024490*).

Neurobiological Factors Underlying Sex Differences in Risk for Alcohol Abuse (Objectives 1.5, 2.3, and 3.1). This recently funded K01 career development award addresses neural and hormonal differences between the sexes that contribute to the differential risk for alcohol-related problems. The research project focuses on the role of ovarian hormones during response inhibition, a sexually dimorphic behavior. An innovative aspect of the application is the combined emphasis on both hormonal and neural factors that may contribute to the differential response of males and females. Findings from this study should help in understanding how deficits in inhibitory control affect women differently than men in response to drinking (*K01 AA024519*).

Gender Differences in Response to Naltrexone and Role of Family History of Alcoholism and Kappa Opioid Receptors (Objectives 1.5 and 2.6). Understanding how naltrexone, an opioid antagonist, can reduce abusive drinking in some individuals is necessary to further develop more effective medications. This R01 grant is using PET imaging with a novel radioligand to study occupancy of kappa opioid receptors in the brain by naltrexone in heavy drinkers with and without a family history of alcoholism. Previous work had suggested gender differences in baseline levels of kappa occupancy in healthy control individuals. A recent publication in the *American Journal of Nuclear Medicine and Molecular Imaging* (Vijay et al., 2016) is the first report of sex differences in the kappa opioid receptor system in humans *in vivo*. This study highlights the importance of understanding sex differences in the context of evaluating the efficacy of medications targeting the opioid receptor systems in treatments for pain and for addiction (*R01 AA021818*).

A Randomized Controlled Trial Targeting Alcohol Use and Sexual Assault Risk Among College Women at High Risk for Victimization (Objective 2.5). This study assessed the effectiveness of a Web-based program in a randomized control trial in 207 college women between the ages of 18 and 20. This is the first

intervention to target both alcohol use and sexual assault risk in college women. Women with higher severity of sexual assault at baseline experienced less incapacitated attempted or completed rapes, less severity of sexual assaults, and engaged in less heavy episodic drinking, compared to the control condition at the 3-month follow-up. Sexual assault risk reduction programs do not target alcohol use, despite the widespread knowledge that alcohol use is a risk factor for being victimized. This combined Web-based intervention could easily be disseminated to colleges to help reduce heavy episodic drinking and sexual assaults among women (Gilmore et al., 2015).

Tablet-Based Intervention to Prevent Substance-Exposed Pregnancy in Primary Care (Objective 3.3). The damaging consequences of fetal alcohol and tobacco exposure are well known, and recent research highlights the harmful effects (e.g., increased infant mortality) of prenatal marijuana use. Previous work on brief motivational interventions to prevent alcohol- and tobacco-exposed pregnancies has yielded favorable results, yet marijuana use at follow-up was consistently associated with significantly poorer intervention outcomes. Therefore, preconception marijuana use needs to be addressed for maximal reduction of substance-exposed pregnancies. Current research indicates participants are more likely to disclose substance use, particularly use of marijuana, in computer-based interventions than in face-to-face interventions. A randomized controlled study of 360 women of childbearing age within a primary care setting will compare the efficacy of the Choices4Health intervention delivered by a computerized tablet, the Choices4Health intervention delivered by a counselor, and Brief Advice (control group) from the research assistant about risk drinking, smoking, marijuana, and contraception. This work is aligned with the need to offer effective and efficient substance use screening and treatment in frontline medical settings and is expected to have significant impact on current standards of preconception care (*R01 AA022924*).

Comorbidity: AUD and Other Psychiatric Disorders

Comorbidity of Alcoholism and Post-Traumatic Stress Disorder-Induced Fear Memories: Neural Mechanisms (Objectives 1.4 and 1.5). Despite the high rates of comorbidity between AUD and post-traumatic stress disorder (PTSD), there is a gap in our knowledge concerning how these disorders interact to impair behavior and cognition. Furthermore, little is known about mechanisms underlying sex differences associated with co-occurring AUD/PTSD. Clinical evidence indicates that the prevalence of PTSD is twice as high in women as in men, with sex differences in the motives of alcohol use. This R01 grant examines the relationship of alcohol abuse and PTSD-related fear memories and the underlying neural mechanisms in the prefrontal cortex and amygdala in a rodent model. Preliminary data demonstrate that exposure to chronic intermittent ethanol (CIE) after fear conditioning leads to deficits in the extinction of fear-related behaviors, increased alcohol consumption in response to fear cues, and deficits in cognitive flexibility. One aim of the study is to investigate if and how sex affects CIE-induced deficits in extinction learning. Findings from this study will inform whether alcohol-induced deficits in extinction of fear memories are different in men and women. These findings will guide development of treatment programs for these commonly co-occurring disorders (*R01 AA024526*).

Sex and Hormonal Differences in Alcohol Drinking Behavior in Nonhuman Primates (Objectives 1.4, 1.5, 2.2, and 3.1). The nonhuman primate model closely approximates human drinking experiences and susceptibility for abuse. Using an open access self-administration model with male and female macaques, groups of heavy drinkers and non-heavy drinkers were classified, with initial drinking behavior predictive of long-term use outcome. Sex appeared to be a predictive factor; female macaques were biased toward heavy drinking, particularly during the luteal phase of menstruation. Future studies will determine the neurosteroid profile changes with alcohol during

menstruation, and functional magnetic resonance imaging studies will reveal sex differences in neural activation after chronic alcohol use (*U01 AA013510*).

Technology-Supported Physical Activity Intervention for Depressed Alcoholic Women (Objectives 2.5 and 3.7). The comorbidity of depression and AUD is much higher in women than in men, and depression more often precedes the onset of AUD in women than in men. Relapse rates are very high in both men and women, but significant gender differences emerge in the predictors of relapse. Women are more likely to relapse in unpleasant, negative emotional states, and depressive symptoms and negative affect mediate the relationship between these stressors and drinking outcomes. Previous research demonstrated benefits of exercise for decreasing depression, negative affect, and drinking urge. In this project, investigators are developing a 12-week lifestyle physical activity Fitbit®-mediated intervention that is simple, low cost, and easily transportable to a variety of clinical settings where women with AUDs receive treatment. The intervention may provide an alternate coping strategy that would reduce relapse risk and decrease the overall negative impact of alcohol use on women's health and well-being (*R34 AA024038*).

Alcohol, Aggression, and Violence

Effects of Alcohol on Arousal and Emotion-Regulation in Distressed Violent and Distressed Nonviolent Partners (Objective 1.5). Intimate partner violence (IPV) is a serious public health problem costing the United States \$5.8 billion per year, with more than \$4.1 billion spent annually in direct medical and mental health costs alone. Alcohol is present in most incidents of IPV and contributes to more frequent and severe IPV incidents, especially during heavier drinking episodes (e.g., binge drinking episodes). These facts make understanding the mechanisms through which alcohol is associated with IPV critical. This R21 grant application proposes to test the hypothesis that overarousal is a mechanism by which alcohol intoxication can increase risk for IPV.

Individuals who engage in IPV are hypothesized to experience greater increases in arousal when intoxicated than individuals in distressed relationships without IPV. This proposal is highly significant because it may lead to the development of interventions to reduce IPV. Recruitment of a distressed violent group of couples has been completed and recruitment and enrollment of a distressed nonviolent control group of participants is in progress (*R01 AA 22367*).

Precollege Predictors of Incapacitated Rape Among Female Students in Their First Year of College (Objective 1.8). The first year of college is an important transitional period for young adults; it also is a period associated with elevated risk of incapacitated rape (IR) for female students. The goal of this study was to identify prospective risk factors associated with experiencing attempted or completed IR during the first year of college. Using a prospective cohort design, 483 incoming first-year female students were recruited. Participants completed a baseline survey and three follow-up surveys over the next year. At baseline, precollege alcohol use, marijuana use, sexual behavior, and, for the subset of sexually experienced participants, sex-related alcohol expectancies were assessed. At the baseline and all follow-ups, sexual victimization was assessed. Approximately 1 in 6 women (18%) reported IR before entering college, and 15 percent reported IR during their first year of college. Precollege IR history, precollege heavy episodic drinking, number of precollege sexual partners, and sex-related alcohol expectancies (enhancement and disinhibition) predicted first-year IR. Among the subset of sexually experienced participants, both enhancement expectancies and precollege IR predicted IR during the study year. These findings suggest that IR during the first year of college is independently associated with a history of IR and with expectancies about alcohol's enhancement of sexual experience. Alcohol expectancies are a modifiable risk factor that may be a promising target for prevention efforts (Carey et al., 2015).

Fetal Alcohol Exposure

Epigenetic Modification of the Pituitary After Fetal Alcohol Exposure (Objective 3.4).

Prolactinomas are the most common type of tumors of the pituitary and lead to decreased production of sex hormones, including estrogen in women and testosterone in men. Prenatal alcohol exposure increases the susceptibility for developing prolactinomas. This R01 grant proposes an epigenetic mechanism for prolactinoma susceptibility. A rat model of fetal alcohol exposure confirmed increased pituitary weight and expression of prolactin mRNA and protein, indicators of tumor formation. A recent publication by the investigators reported increased levels of mRNA for genes that encode DNA methylation or acetylation (Gangisetty et al., 2015). Inhibitors of these epigenetic modifiers normalized pituitary weight and prolactin expression after fetal alcohol exposure, supporting an epigenetic mechanism. Fetal alcohol exposure alters post-transcriptional regulation D2 receptor, preventing normal growth control in the pituitary. Thus, fetal alcohol exposure has long-term consequences for adult female health (*R01 AA011591*).

Effects of Gestational Ethanol on the Neural Circuitry of Dorsal Striatum May Contribute to Behavioral Abnormalities in FASD (Objectives 1.4 and 1.5).

This K99/R00 project investigates the effects of prenatal ethanol exposure on dorsal striatal circuitry and the contributions to impaired decisionmaking, increased impulsivity, and motor deficits common in FASD. Mimicking the three trimesters of human development in a mouse model, embryonic and early postnatal mice are exposed to alcohol vapor. The synaptic specificity and subsequent striatal neurotransmission were studied to assess how disruptions of the GABAergic microcircuitry underlie many of the FASD behavioral abnormalities (*K99/R00AA021760*).

Prenatal Alcohol Exposure Among High-Risk Populations: Relationship to Sudden Infant Death Syndrome and Stillbirth (Objective 5.2).

NIAAA, the National Institute on Deafness and Other Communication Disorders, and the *Eunice*

Kennedy Shriver National Institute of Child Health and Human Development (NICHD) jointly funded a cooperative agreement to conduct community-linked studies on the underlying causes of sudden infant death syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and FAS, and the role of prenatal alcohol exposure. The Prenatal Alcohol in SIDS and Stillbirth (PASS) Network consists of two comprehensive clinical sites in the Northern Plains and Western Cape of South Africa, a developmental biology and pathology center, a physiology assessment center, and a data coordinating and analysis center. The PASS Network has completed enrollment of more than 12,000 pregnant women in a comprehensive longitudinal cohort study in which their infants will be followed for up to 1 year. In parallel, the network also has conducted a retrospective study to obtain additional SIDS cases occurring within the catchment areas that would not have been captured in the prospective study. Additionally, embedded studies have been designed to explore the role of (under-) nutrition in exacerbating the effects of maternal alcohol exposure on fetal and offspring development. The long-term goals of this initiative are to decrease fetal and infant mortality and improve child health in the affected communities (U01 AA016501).

Sex Differences in Basic Research

Adolescent Alcohol Drinking Increases Relapse-Like Drinking in Adulthood and This Effect Is Correlated to Sex-Dependent Loss of White Matter (Objectives 1.5, 2.2, and 3.1). Early onset of alcohol use in teenagers, especially binge drinking, is linked to reduced frontal white matter, cognitive deficits, and an increased lifetime risk of AUD. Studies in rats show that alcohol causes prefrontal myelin loss with heightened vulnerability in adolescence compared to adulthood, and in males compared to females. Voluntary binge drinking in early adolescence caused reduced myelin density in the medial prefrontal cortex of

male rats, but not female rats. High doses of alcohol induce brain damage through inflammation and oxidative stress, conditions that can be particularly toxic to oligodendrocytes and axons. Further studies are being conducted to understand the mechanisms of this sexual differentiation, especially the role of gonadal hormones in dampening inflammation and promoting the proliferation and survival of oligodendrocytes (R01 AA024774).

Understanding Greater Alcohol-Related Neuropsychiatric Disturbances in Females Versus Males (Objectives 1.4 and 1.5).

This study provides the first systematic investigation into sex, age, and alcohol withdrawal interactions with emotional behavioral disturbances as consequences of adolescent binge drinking. It addresses how early-life binge drinking perturbs the extended amygdala neural circuitry underpinning emotionality and how the extent of perturbation is more pronounced in female subjects than in males. The study focuses on understanding how the interaction of early onset of binge drinking and sex impacts the anxiety and depression associated with different periods of withdrawal (R01 AA024044).

Neuroendocrine Effects of Alcohol on Puberty (Objective 3.1).

This research is intended to further identify the effects of alcohol consumption on hormonal events and how their actions alter female pubertal maturation. The studies draw out the effects of chronic and acute alcohol upon the factors that regulate women's hypothalamic hormone release. Recent studies have demonstrated the importance of hypothalamic glial-neuronal communications for the activation of luteinizing hormone-releasing hormone (LHRH) secretion at puberty (Srivastava et al., 2015). Recently, low-dose manganese supplementation has been shown to partially ameliorate, at the level of LHRH release from the hypothalamus, the action of alcohol to delay the timing of puberty, suggesting a possible avenue for therapeutic intervention (Srivastava et al., 2016; Hiney et al., 2016) (R01 AA007216).

Sleep

Gender May Play an Important Role in Moderating the Relationship Between Sleep Problems and Alcohol Use/Abuse Among Children of Alcohol-Dependent Parents (Objectives 1.5 and 1.8)

This longitudinal study examines the sleep physiology of children of alcohol-dependent parents in two age groups: immediately preceding the onset of drinking (ages 8–12) and during onset of drinking (ages 12–14). One aim is to understand how gender moderates the relationship between sleep problems and alcohol use/abuse among children of alcohol-dependent parents. The study is under way, and findings will be available within next 2 years (*R01 AA020364*).

Sleep-Associated Slow-Wave Electroencephalogram Activity in Risky Behavior (Objectives 1.5 and 2.6). Adolescence is accompanied by changes in the sleep cycle, in particular a significant reduction in the slow-wave electroencephalogram activity. The loss of slow-wave activity in adolescents between the ages of 11 and 16 may lead to increased susceptibility of risky behaviors, including drinking alcohol. The known differences in impulsive behavior prompted analysis of male and female participants. Correlations between loss of slow-wave encephalogram activity, resting state functional connectivity, and impulsivity are expected. If the correlations are predictive of decreased impulse control and subsequent elevated reward-seeking and alcohol drinking, strategies to intervene and restore slow-wave activity will be investigated to decrease risky behavior (*R21 AA022339*).

Women, Alcohol Use, and Cancer

Alcohol and Breast Cancer (Objectives 1.7 and 5.2) (ORWH-Co-funded). Alcohol consumption is associated with an increased incidence of breast cancer. The association with alcohol is particularly pronounced in hormone-dependent

breast cancers. Cancers that are associated with alcohol consumption are more likely to be estrogen receptor-positive. A common hallmark of cancer cells is over-induction of polymerase III (Pol III), which is involved in expression of nonprotein coding RNAs, such as transfer RNAs. Alcohol induction of Pol III depends on estrogen receptor function, and the combination of estrogen plus alcohol synergistically increases the induction of Pol III activity. Built upon earlier ORWH-funded projects, the recent work focuses on signaling changes due to alcohol, in particular at the level of transcription factor modification. Transcription factor Runt-related gene 2 is altered, thereby affecting Pol III gene expression. Understanding the mechanism by which alcohol enhances tumor formation may lead to insights on prevention and therapeutic approaches and may inform women's decisions about drinking alcohol (*R21 AA023247*).

Alcohol and Breast Cancer (Objectives 1.7 and 5.2). The association of alcohol with breast cancer is epidemiologically well supported, but the mechanisms by which alcohol initiates and promotes breast cancer are poorly understood. This competitive renewal furthers the understanding of the changes in signaling pathways that occur in breast cancer and influence alcohol use. Alcohol consumption increases the risk of mammary tumors and is closely associated with advanced and invasive breast tumors. This work will extend the analysis of the erbB pathway by following up on an exciting preliminary observation that the p38gamma isotype (a component of the erbB pathway) is uniquely modified by ethanol. The work explores the downstream molecules activated by p38gamma that may mediate how alcohol enhances the promotion and aggressiveness of breast tumors (Xu et al., 2016). Knowledge of this type may provide more focused targets for intervention and help to inform women's decisions about consuming alcohol (*R01 AA017226*).

Women, Alcohol Use, and HIV

Reducing Alcohol-Related HIV/Sexually Transmitted Infection (STI) Risk for Women in Reproductive Health Clinics (Objectives 3.3 and 5.6). HIV and other STIs have harmful and costly consequences (e.g., infertility, cancer, AIDS). Young women who misuse alcohol are particularly vulnerable to HIV and other STIs. Single-focused interventions that focus primarily on sexual risk behavior or on alcohol use result in only modest reductions in alcohol-related sexual risk behavior. Lacking are integrated, gender-tailored interventions that address alcohol use in the context of intimate relationships and sexual behavior. This proposal is developing and pilot testing an integrated alcohol and sexual risk reduction intervention for use in reproductive health and family planning settings, where many young, at-risk women can be found. Based on feedback from several focus groups of young women (ages 18–29 years) at risk for alcohol misuse and STIs, the team will develop an integrated, individually delivered brief intervention (BI) that draws upon proven strategies (e.g., personalized feedback, normative comparisons, goal setting) to promote alcohol and sexual risk reduction. They also will develop a user-friendly website that will broaden the scope of the BI by promoting behavioral skills development and promote maintenance of initial intervention gains by extending the BI into the natural environment. If successful, this research will lead to an efficacious BI that can be disseminated to sexual health clinics across the Nation, and thereby reduce the incidence of HIV, STIs, harmful alcohol use, and related health consequences in young women (*R34 AA023158*).

Immune Dysregulation in HIV-Infected Women with Heavy Alcohol Consumption (Objective 3.3). Excessive alcohol consumption leads to a poorer outcome for all persons living with HIV/AIDS. This proposal investigates the mechanism underlying CD4 T-cell decline and HIV disease progression in HIV-infected women who engage in heavy alcohol consumption. One mechanism by which alcohol may cause immune dysfunction is by

inducing microbial translocation. The proposal tests the hypothesis that heavy alcohol consumption disrupts the gut barrier causing microbial translocation; all these events contribute to CD4 T-cell decline and HIV disease progression. The study is conducted retrospectively in biorepository specimens from the longitudinal cohort, the Women's Interagency HIV Study (*U01AA020800*).

Women, Alcohol Use, and Cardiac Health

Mechanisms for Estrogen-Dependent Myocardial Depressant Effect of Ethanol (ORWH-Co-funded) (Objectives 1.7 and 5.2). Moderate alcohol consumption provides a cardioprotective effect in men, but surprisingly, may cause cardiotoxicity in women. The underlying mechanism of this phenomenon is not well understood. Preclinical studies show that ethanol-derived acetaldehyde accumulation creates a conducive microenvironment that transforms estrogen into a proinflammatory hormone, which may be the basis for the cardiotoxicity of ethanol in females (Yao and Abdel-Rahman, 2016). This investigation is clinically relevant in view of the rise in acute alcohol consumption, especially by young women (*R01 AA014441*).

Health Disparities

Creating Support for Reservation-Based and Urban American Indian/Alaska Native Families Dealing with FASD (Objectives 5.1 and 5.2). Healthy Native Nation is an ongoing NIH Native American Research Centers for Health-funded study initiated in 2014. It was initially supported via a memorandum of understanding between NIAAA and the Indian Health Service, and now through the National Institute of General Medical Sciences (NIGMS). Healthy Native Nation will provide targeted support for individuals and families living with FASDs by developing a model National Organization on Fetal Alcohol Syndrome (NOFAS) affiliate with one reservation-based location and one urban location. The study will compare the

resulting affiliate structures in the two locations. It has been accepted as the first urban American Indian/Alaska Native affiliate by NOFAS (S06 GM106376/U261IHS0081).

Minority Stress and Alcohol Use Among Sexual Minority Women (Objective 3.9). Sexual orientation-related health disparities are now well recognized, and some of the largest disparities have been documented in comparisons of drinking behaviors among sexual minority women (SMW) and heterosexual women. This project is the longest-running and most comprehensive study of SMW drinking and health in the United States or elsewhere. This work capitalizes on historic opportunities to (1) evaluate the impact of the June 1, 2014, Illinois Marriage Fairness Act (which provides legal recognition of same-sex marriage) on SMW drinking and health and (2) take advantage of a unique longitudinal data set (including data on SMW drinking patterns over a nearly 20-year period) to examine the associations of long-term drinking trajectories with SMW health. Findings from the study will add significantly to the currently sparse knowledge about individual, interpersonal, and societal factors that contribute to elevated rates of physical and mental health problems in SMW, generating information that can guide the development of prevention, treatment, and policy to reduce health disparities in sexual minorities and potentially other minority groups. Furthermore, the study contains large subsamples of women younger than age 25 and older than age 50—as well as of bisexual women and African-American and Latina women—providing a rare opportunity to examine age, race/ethnicity, and sexual identity differences in the relationships between marriage recognition and drinking and between drinking and health (R01 AA013328).

Person-Level Factors and Daily Interactions May Contribute to Drinking in Female Same-Sex Couples (ORWH-Co-funded) (Objectives 3.9 and 5.2). This study proposes to examine a model of alcohol misuse and IPV among lesbians. By employing a daily diary approach, it will be possible to examine relationships among alcohol

use, relationship experiences, sexual minority stressors, and affect, as well as person-level factors (e.g., baseline characteristics, such as legally recognized relationship status, positive sexual identity, and connection to the LGBT community), which may serve as protective factors that attenuate the association between stressors and hazardous alcohol use. Participants will be 150 female same-sex couples recruited from an online panel. This research will contribute to our understanding of the mechanisms by which SMW romantic relationships and experiences of minority stress contribute to alcohol use. In turn, this information can inform efforts to reduce SMW health disparities and improve SMWs' health and well-being (R15 AA020424).

Factors Responsible for Racial-Gender Disparities in Alcohol Services Use (Objective 1.8). Alcohol abuse and dependence are responsible for considerable public health harms, yet many people with an AUD do not receive treatment, and some social groups are less likely than others to receive alcohol services. Specifically, racial/ethnic minorities appear less likely than whites to obtain any help for problem drinking, receive specialty alcohol treatment, or attend 12-step programs. This study seeks to explain racial/ethnic and gender disparities in alcohol services use. Using longitudinal data obtained in the National Epidemiological Survey of Alcohol and Related Conditions, a representative sample of the U.S. population that included oversamples of racial/ethnic minorities and young adults, the investigators are examining use of specialty treatment and 12-step groups among white, black, and Latino participants who met *Diagnostic and Statistical Manual of Mental Disorders* criteria for alcohol abuse or dependence at Wave 1 (2001–2002) and who completed a Wave 2 follow-up interview (2004–2005). This study will provide further information about subgroups for whom the risk of unmet alcohol treatment need is greatest, including racial/ethnic minorities and women, by focusing on the combined effects of race/ethnicity and gender. In addition, findings will extend current knowledge about the mechanisms responsible for disparities

and may identify leverage points for interventions to increase alcohol services use (R21 AA023878).

Science, Technology, Engineering, and Mathematics Efforts

NIAAA-Supported Research: A Grantsmanship Workshop at the Research Society on Alcoholism (RSA) (Objective 4.5). This workshop, organized by the RSA Education Committee, provides young investigators with up-to-date information about NIAAA grant funding opportunities and provides the opportunity to participate in breakout sessions on select topics with NIAAA program staff and experienced investigators. The main goal of the workshop is to provide the attendees with the tools and resources necessary to become successful alcohol researchers. In 2015 and 2016, more than 50 percent of the attendees were women.

NIAAA Summer Research Internship Program. This program provides research internships for high school and undergraduate students with a goal of recruiting underrepresented racial/ethnic students into research. This 8-week paid program exposes students to alcohol abuse research and encourages them to pursue careers in biomedical and behavioral research. Students' activities include, but are not limited to, laboratory experiments, data collection activities, data analysis, patient recruitment, manuscript preparation, literature reviews, and library research. In 2015, NIAAA awarded 18 internships, 12 of which were to women (67 percent). In 2016, 22 internships were awarded, 14 of which were to women (64 percent).

Diversity Administrative Supplements. This diversity supplement program to active NIAAA research grants was established to improve diversity in the scientific research workforce by supporting and recruiting undergraduate students, predoctoral and postdoctoral fellows, and investigators from groups that have been shown to be underrepresented in the sciences, including disabled individuals. In 2015, NIAAA funded

11 diversity supplements, seven of which were awarded to women (64 percent; 5 African-American, 2 Hispanic). In 2016, nine diversity supplements were funded, five of which were awarded to women (56 percent; 3 Hispanic, 1 African-American, 1 American Indian).

Funding Initiatives

Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations (PA-17-098). This Program Announcement solicits applications to expand existing research to focus on sexual and gender minority (SGM) health. This trans-NIH effort is intended to encourage investigation in this underrepresented field of research. To increase our collective understanding of the broad range of the health needs of SGM populations, the supplement will focus on areas of specific research interest, including studies on increased disease risk, mental, behavioral and social health, approaches to personalized medicine, access to care, reproductive and sexual development, neurological and cognitive development, and resilience.

Effects of *In Utero* Alcohol Exposure on Adult Health and Disease (PA-12-291 and PA-12-292). The purpose of this effort is to support novel research on how prenatal alcohol exposure may contribute to the etiology of chronic diseases and health conditions later in life. Central to this theme is the concept of the developmental origins of health and disease, which suggests that fetal adaptations in response to adverse intrauterine conditions may increase the risk for childhood and adulthood disease (e.g., cardiovascular disease, type 2 diabetes, obesity, select cancers, asthma, behavioral disorders). Studies supported by this activity will provide fundamental insights into a possible fetal basis to adult disease that may be influenced by maternal alcohol use.

Genetic Susceptibility & Variability of Human Structural Birth Defects (R01) (PA-14-056). NIAAA participates with NICHD in this research designed to study fundamental developmental

processes using animal models in conjunction with translational/clinical approaches with the goal of advancing understanding of the etiology of structural birth defects. Alcohol is a known teratogen capable of causing FASD, a collection of birth defects and developmental disabilities that occur in individuals whose mothers drank alcohol during pregnancy.

Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (PA-14-036, PA-14-037, and PA-14-038). NIAAA continues to participate with the National Institute on Drug Abuse (NIDA) in an initiative to promote research on women and sex/gender differences in drug/alcohol abuse and dependence. This initiative, which was recently reissued, encourages research from basic studies of molecular genetics and neurotransmitters to studies of epidemiology, etiology, and prevention/treatment interventions that focus on sex/gender differences. Studies on sex/gender-based interventions related to HIV/AIDS and cross-cutting issues related to stages of the life cycle, health disparities, methodological approaches, and gender-specific recruitment issues also are encouraged.

Model Continuums of Care Initiative for Women and Girls at Risk and Living with HIV/AIDS and Harmful Alcohol and Associated Comorbidities Planning Cooperative Agreement (U34) (RFA AA-17-013). NIAAA participates with ORWH and NIDA on this initiative, which promotes the development and evaluation of integrated multilevel interventions to reduce alcohol consumption as a key approach to preventing new HIV infections and enhancing treatment adherence in communities in the United States where racial and ethnic minority women bear a disproportionate share of the HIV/AIDS disease burden. Results of this research will provide the evidence base for the development of more effective systems of care for women and girls at risk for and living with HIV, including pregnant mothers who engage in risky drinking and other substance use.

Workshops and Meetings

Second Occasional Meeting of the NIAAA Working Group on Intervention Development for Alcohol-Related Sexual and IPV (Objective 1.9). This meeting provided “one-stop shopping” for those students, grant applicants, and IPV prevention practitioners seeking an overview of the full range and depth of the NIAAA sexual and IPV prevention portfolio. The Workshop comprised talks from NIAAA grantees currently engaged in basic behavioral research on the effects of alcohol on IPV, as well as those conducting preventive interventions for alcohol-related sexual assault, IPV, and teen dating violence. Time was allotted for questions after each talk, followed by summary comments from designated discussants illuminating key barriers in moving the field forward. (RSA Satellite Meeting, Annual Meeting of the Research Society on Alcoholism, New Orleans, Louisiana, June 2016.)

NIAAA Workshop on Emerging Trends in Underage, College, and Emerging Adult Drinking and Related Consequences. This meeting was intended to examine in greater depth and detail—and to clarify—recent findings regarding the prevalence, frequency, intensity, pattern, and amounts of underage, college, and emerging young adult drinking. Despite evidence suggesting that current adolescents may be less likely to report past-month drinking than they were 20 years ago, several recent investigations—using a variety of drinking measures and data sets—have indicated upturns in drinking in the United States. At the same time, little remains known about alcohol use at levels that are far beyond the standard binge thresholds. (NIAAA, Bethesda, Maryland, May 2016.)

Conference on Evidence-Based Interventions to Support Women in Biomedical Research Careers (Objective 4.5). NIAAA staff participated in and chaired a session in this workshop led by ORWH and NIGMS through their “Committee on Advancing Women in Independent Positions,” a subcommittee of the NIH Working Group on Women in Biomedical Careers. The goal of this workshop

was to connect with scientific societies and other organizations that have a proven track record of supporting women in science to discuss strategies, best practices, and lessons learned. (NIH, Bethesda, Maryland, June 2016.)

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National Institute of Allergy and Infectious Diseases (NIAID)

Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to understand, diagnose, prevent, treat, and ultimately cure infectious and immune-mediated diseases, including diseases that affect the health of women and girls. NIAID involves women in many of its clinical studies on treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and other infectious diseases. NIAID also collaborates with other organizations on research initiatives that aim to improve women's health within NIAID's mission areas.

This biennial report provides an overview of selected NIAID-sponsored women's health activities. The first section describes scientific accomplishments and activities in research on HIV/AIDS, non-HIV infectious diseases—including sexually transmitted infections (STIs), malaria, influenza, and Zika virus infection—and immunology and immune-mediated diseases, such as asthma and allergy. Accomplishments in the area of HIV/AIDS include supporting ongoing clinical trials that test antiretroviral (ARV) drugs and topical microbicides to prevent the transmission of HIV to women or their partners; a clinical trial that showed the effectiveness of a new drug regimen to minimize the risk of mother-to-child transmission (MTCT) of HIV during pregnancy and breastfeeding; development and testing of intravaginal rings containing ARV drugs, including a large clinical trial showing that a vaginal ring helped protect women against sexually transmitted HIV infection; and a major international clinical trial demonstrating that HIV-infected individuals have a considerably lower risk of developing AIDS or other serious illnesses if they start antiretroviral therapy (ART) as soon as possible upon diagnosis.

Other highlights include studies to treat and prevent malaria in pregnant women; promising results of a small clinical trial showing that stem cell transplants may halt the progression of multiple sclerosis (MS); basic and clinical research that could lead to new treatment approaches to minimize the impact of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and other autoimmune diseases that disproportionately affect women; improved understanding of how the microbiome may contribute to autoimmune disease; and insights into complications of human pregnancy.

An overview of NIAID activities that address the objectives of the NIH Strategic Plan for Women's Health Research includes a description of the NIAID Women's Health Research Working Group. Additional sections provide overviews of NIAID activities to include women in clinical studies, including efforts to increase the enrollment of pregnant women in ethically appropriate clinical research; career development activities; research initiatives; conferences and publications; and research on health disparities in women and special populations.

The research described in this report supports many ORWH Strategic Plan Goals and Objectives, including the following:

Goal 1.2, Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

Goal 1.6, Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases, including HIV/AIDS and urinary tract and sexually transmitted infections.

Goal 1.8, Further understanding of sex/gender differences in fundamental mechanisms and

patterns of behavioral and social functioning relevant to health and well-being.

Goal 3.3, Encourage research on safe and effective interventions for conditions affecting pregnant women.

Goal 3.9, Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.

Accomplishments and Activities

HIV/AIDS

The United Nations Joint Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that about 37 million people, including 18 million women, are infected with HIV worldwide. In the United States, 285,000 women are living with HIV. Women face a greater risk of acquiring HIV than men because of substantial mucosal exposure to semen, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners.

Three decades into the HIV/AIDS epidemic, young women bear the brunt of new HIV infections. Globally, adolescent girls and young women (ages 15–24) are twice as likely to be at risk of HIV infection as boys and young men in the same age group. This higher risk of HIV is associated with unsafe and often unwanted and forced sexual activity. Too many young women still struggle to protect themselves against sexual transmission of HIV and to get the treatment they require. This also leaves them particularly vulnerable to tuberculosis (TB)—one of the leading causes of death of women ages 20–59 in low-income countries.

According to WHO, women accounted for approximately 50 percent of all adults living with HIV worldwide in 2015. The Centers for Disease Control and Prevention (CDC) reported that the rate of new HIV diagnoses in women in the United States declined from 2008 to 2014, and the death rate in U.S. women declined from 2008 to 2013. HIV/AIDS and associated diseases and coinfections, however, continue to cause substantial illness and death in the United States and worldwide. In 2013, WHO reported that HIV/AIDS is the leading cause of death globally for women of reproductive age (15–44 years).

In addition to facing complications associated with HIV/AIDS similar to those that affect men, infected women also suffer gender-specific manifestations of HIV disease, including human papillomavirus (HPV)-related cervical dysplasia (abnormal, precancerous cell growth) and cervical cancer. HIV-infected women have a higher prevalence of HPV infection, a higher risk of progression from infection to disease, and an increased risk of invasive cervical cancer and other HPV-related cancers, including anal cancer. Anal cancer is emerging as an important clinical entity in HIV-infected women, as well as in men. Combination ART for HIV has not significantly decreased the incidence of HPV-related cancers. (Note: For more information on HPV infection, see “Infectious Diseases Other than HIV/AIDS.”)

Other complications of HIV infection in women—such as recurrent vaginal yeast infections, pelvic inflammatory disease, genital ulcer disease, and severe herpes infections—are reduced by successful combination ART. Drug metabolism differs between women and men, potentially resulting in differential responses to ART and an increased incidence of drug toxicities in women.

In many parts of the world, death and illness due to pregnancy and childbirth occur frequently. Thus, use of contraceptives is the most successful intervention to prevent maternal illness and death, and, by preventing pregnancy, to prevent MTCT of HIV. Hormonal methods of birth control are

most effective but may interact with antiretroviral drugs, which could lead to additional toxicities or treatment failures. Also, several recent studies have shown an increased risk of HIV transmission to an uninfected male partner if the woman is using hormonal contraceptives. Forms of contraception that are effective, safe, and do not increase the risk of transmitting HIV to an uninfected partner are urgently needed, as are safe and effective methods to prevent MTCT of the virus.

Achieving effective treatment of HIV infection may be more problematic for women than for men because women may have difficulty accessing health care and carry a large burden of caring for children and other family members, including those who also may be HIV-infected. Women often lack social and financial resources to cope with HIV and other challenges.

NIAID is supporting investigations of the course of HIV/AIDS in women through multiple initiatives, including intramural studies, investigator-initiated research, the Women's Interagency HIV Study (WIHS) long-term cohort study, and clinical trials to investigate gender-specific differences in HIV disease progression, complications, and/or treatment. Clinical trials are being conducted by the Microbicides Trials Network (MTN), AIDS Clinical Trials Group (ACTG), International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), HIV Prevention Trials Network (HPTN), HIV Vaccine Trials Network (HVTN), and International Network for Strategic Initiatives in Global HIV Trials (INSIGHT).

Epidemiologic Research

NIAID supports epidemiologic research in the following areas:

- The long-term natural history of HIV infection in women—in particular, research that evaluates the impact of ART on the clinical course of HIV disease throughout a woman's lifespan.

- The effect of hormonal, endocrine, bacterial, and local factors on the levels of HIV in the plasma and genital tract and on sexual transmission of the virus.
- Studies of older populations of HIV-infected women to investigate what pathogenic processes are related to HIV, ART, and/or the aging process.
- Characterization of acute clinical events and coinfections and their impact on HIV disease progression.
- Studies of the female genital tract, including the microenvironment, HIV virology, and immunology of the female genital tract compared with blood.

Women's Interagency HIV Study

WIHS is the largest observational study of HIV-infected women and includes participants living in 10 U.S. metropolitan areas. The majority of the more than 3,500 women enrolled in the study are African-American and Latina women living in urban areas. The size of the study, the number of recently diagnosed patients, and the availability of stored biospecimens allow the evaluation of clinical outcomes in the era of highly active ART. Researchers are investigating such factors as the development of AIDS, drug resistance, coinfections, therapy use and treatment effects, metabolic abnormalities and toxicities, hormonal factors, aging, neurocognitive functioning, and physical impairment. This study has led to a better understanding of how HIV is spread, how HIV disease progresses, and how it can best be treated. More information is available at www.statepi.jhsph.edu/wihs/wordpress.

International Epidemiology Databases to Evaluate AIDS (IeDEA)

The IeDEA consortium brings together clinical data collected as part of research initiatives and diverse care programs. Seven global regions enroll nearly 1 million patients who are representative of the HIV epidemic within their region. The North American AIDS Collaboration of Observational Research

Databases includes data from more than 21,000 women living in the United States or Canada. The consortium's size allows for in-depth assessment of clinical outcomes, including rare events and their predictors. Globally, IeDEA represents the severity of the epidemic among women, with more than half of the data coming from women. More information is available at www.iedea.org.

Science Advances

Lung Cancer Incidence and Survival Among HIV-Infected and Uninfected Women and Men.

Lung cancer incidence is significantly higher among HIV-infected individuals than in the general population, yet the precise role of HIV and immune suppression in this phenomenon remains somewhat elusive. Researchers determined the lung cancer incidence and survival time among HIV-infected and uninfected women and men in the cohorts of the WIHS and the Multicenter AIDS Cohort Study (MACS). Overall, the lung cancer incidence rate was significantly higher among women than men, and higher among HIV-infected participants than among uninfected participants. The study found that HIV infection alone was not an independent risk factor for lung cancer, but that the amount of cigarette smoking over time and prior AIDS pneumonia among HIV-infected adults were major contributors for the development of lung cancer. (Hessol et al., 2015.)

Prevention Research—Topical Microbicides

There is an urgent need to develop a safe, effective, and acceptable topically applied chemical and/or biologic barrier to prevent sexually transmitted HIV infection. NIAID-sponsored research focuses on the development of topical microbicides that (1) prevent HIV infection and/or viral replication, (2) are safe and do not irritate vaginal, cervical, urethral, or rectal tissues, and (3) reduce HIV transmission and acquisition, even in the presence of other STIs, which increase the risk of acquiring HIV.

Microbicide Trials Network (MTN)

In 2006, the MTN was formed to develop and evaluate microbicide products aimed at reducing the sexual transmission of HIV. MTN consists of a robust network of expert scientists and investigators, with U.S. and international clinical research sites. The network uses a focused research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission. More information is available at www.mtnstopshiv.org.

Clinical Trials

Vaginal Ring Infused with Antiretroviral Drug Confers Partial Protection from HIV Infection.

The MTN-020/ASPIRE study (A Study to Prevent Infection with a Ring for Extended Use) examined whether a vaginal ring that continuously releases dapivirine, an experimental antiretroviral drug, could protect against HIV infection among women. This study—funded by NIAID, the National Institute of Mental Health (NIMH), and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)—enrolled 2,629 women ages 18–45 in Malawi, South Africa, Uganda, and Zimbabwe. Study participants received a vaginal ring that was replaced every 4 weeks and contained either dapivirine or placebo. All participants also received HIV prevention services, including counseling about how to protect against HIV infection, and free condoms. Two study sites reported such low adherence to the ring protocol—missing follow-up appointments and using the ring inconsistently—that the data gathered from these sites were removed. Without these sites, the dapivirine vaginal ring (DPV VR) reduced the risk of HIV infection by 37 percent among all women. The effect was markedly different according to the age of participants. In women ages 25 and older, the ring lowered the risk of HIV by 61 percent, but the ring provided no protection for 18- to 21-year-olds. This disparity between age groups could be related to lower adherence to ring use or age-related biological differences in susceptibility

to HIV infection. Overall, the results indicate that a DPV VR could offer many women an option, in addition to oral pre-exposure prophylaxis (PrEP), to protect against HIV infection. (Baeten et al., 2016.)

Adherence to Use of Rectal Microbicide Gel.

MTN-017, a Phase II multicountry study, examined the safety and acceptability of the reduced glycerin tenofovir (1%) gel in men who have sex with men and transgender women. As reported in February 2016, this study demonstrated for the first time that the rectal microbicide was safe for extended use. Further analysis showed that participants were just as likely to follow through with use of an anti-HIV gel with anal sex as they were to use daily oral PrEP. (Cranston et al., 2016; [Conference on Retroviruses and Opportunistic Infections \(CROI\)](#); Carballo-Diéguez et al., 2016; [2016 HIV Research for Prevention Conference](#))

Open Label Study of Vaginal Ring for HIV Prevention. The HIV Open-label Prevention Extension (HOPE) or MTN-025 study will build on the results of the ASPIRE study by gathering additional information on the safety of the DPV VR, how women use the ring knowing that it can help reduce their risk of HIV, and the relationship between adherence and HIV protection. The study also seeks to understand why the ring may work well as an HIV prevention strategy for some women but not for others. The DPV VR is meant to be used for 1 month at a time; women can insert and remove it themselves.

Assessment of ASPIRE and HOPE Adherence.

The first phase of the [MTN-032](#) study will assess 224 participants with varying levels of adherence to the DPV VR in the ASPIRE study. ASPIRE participants will be preselected and approached for study participation based on their plasma dapivirine levels and residual drug levels from returned vaginal rings. Participants will be asked to complete a single in-depth interview or a focus group discussion to examine factors influencing adherence. The second phase of the study will examine the motivation for participation in the

study and for use of the DPV VR in HOPE study participants with various levels of adherence.

The DPV VR is being evaluated in other populations of potential users, if it becomes a licensed product, in collaboration with the International Partnership for Microbicides (www.ipmglobal.org):

- [MTN-024/IPM 031](#), a Phase IIa multisite trial that enrolled and randomized 96 postmenopausal U.S. women, demonstrated that the DPV VR was safe and well tolerated when inserted monthly for a 12-week period.
- [MTN-023/IPM 030](#), a Phase IIa study to evaluate the safety, acceptability of, and adherence to the DPV VR among adolescent girls in the United States, was recently completed. The study enrolled and randomized 96 healthy, HIV-uninfected adolescent girls (ages 15–17) to receive either a DPV VR or a placebo vaginal ring, which was inserted once every 4 weeks over a 24-week period. Data analysis is ongoing.
- [MTN-029/IPM 039](#), a Phase I, open-label, multisite study designed to assess the presence of dapivirine in breast milk when lactating women use the DPV VR for 14 days, is ongoing. The trial also will evaluate safety, tolerability, and adherence to the ring among these 16 U.S. women.

Programs to Support the HIV Topical Microbicide Preclinical Pipeline

The development of new topical microbicide products continued in 2015–2016 and was supported by programs designed to create a sustainable pipeline of topical microbicide products, strategies, and technologies supporting microbicide safety and efficacy testing. The first program, the Prevention Innovation Program (PIP), supports innovative, high-risk research to develop microbicide products and delivery systems. Three new PIP awards use nanotechnology-based approaches to develop new drug delivery system strategies for sustained release of topical microbicides.

The second program, the Integrated Preclinical Clinical Program (IPCP) for Microbicides and Biomedical Prevention, supports preclinical and first-in-human clinical trials to advance candidate microbicides to clinical testing. A new IPCP award is supporting the development of sustained-release vaginal films containing the HIV integrase inhibitor MK-2048, an ARV drug. In addition, two safety and pharmacokinetic studies of combination intravaginal rings containing two ARV drugs—MK-2048 and vicriviroc, a CCR5 receptor antagonist—were initiated.

Finally, NIAID issued a Funding Opportunity Announcement (FOA) to support innovative biomedical and proof-of-concept research to understand how reproductive maturation or injury alters the mucosal environments at HIV-susceptible sites. This information is essential to providing the safest and most efficacious biomedical prevention strategies, including topical microbicides.

Science Advance

Rectal Safety, Acceptability, Pharmacokinetic and Pharmacodynamic Study of Tenofovir (1%) Gel. The CHARM-01 study characterized three tenofovir gels for rectal application: a new rectal-specific formulation, a vaginal formulation (used in the CAPRISA 004 and VOICE vaginal phase IIb trials and RMP-02/MTN-006 phase I rectal safety study), and a reduced-glycerin vaginal formulation gel (used in the MTN-007 phase I and MTN-017 phase II rectal microbicide trials). All three formulations were found to be safe and acceptable. Use of all gels was associated with significant inhibition of HIV infection of biopsied tissue (McGowan et al., 2015.)

Prevention of Mother-to-Child Transmission of HIV

According to WHO, the vast majority of all HIV-infected infants and children acquire the virus from their mothers before or during birth or through breastfeeding. Most of this MTCT occurs late in pregnancy or during birth. Currently, the United

Nations Children's Fund (UNICEF) and WHO recommend that infants born to HIV-infected mothers be exclusively breast-fed for at least 12 months. NIAID is conducting studies for prevention of mother-to-child transmission (PMTCT) in HIV-infected pregnant women. NIAID-sponsored PMTCT research focuses on the following goals:

- Define the mechanisms and risk factors for HIV transmission to children and adolescents and from mother to infant, as well as risks for disease progression within the framework of clinical studies and trials.
- Develop and test strategies for PMTCT of HIV infection through clinical trials in the United States and international settings.
- Develop interventions for PMTCT of HIV via breast milk.

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), sponsored by NIAID and NICHD, is a network dedicated to significantly decreasing the mortality and illness associated with HIV disease in children, adolescents, and pregnant women. IMPAACT develops and evaluates safe, cost-effective approaches for interrupting mother-to-infant HIV transmission; evaluates treatments for HIV-infected children, adolescents, and pregnant women; investigates strategies for treating and preventing coinfections and illnesses associated with HIV; and evaluates vaccines for preventing HIV sexual transmission among adolescents. More information is available at impaactnetwork.org.

Science Advance

Postpartum HIV Superinfection Is Not Associated with Mother-to-Child Transmission Through Breastfeeding. HIV superinfection occurs when a person with HIV is infected with a new strain of HIV. This can increase viral load (blood levels of HIV) and the risk of HIV transmission to other people. To examine whether

maternal HIV superinfection affects the risk of MTCT of HIV through breastfeeding, NIAID intramural researchers further analyzed data from the Post-Exposure Prophylaxis of Infants trial in Malawi. Maternal HIV superinfection did not increase the odds of MTCT of HIV via breastfeeding when the researchers considered maternal age, baseline CD4+ cell count, and baseline viral load. Longer breastfeeding duration was associated with a lower risk of HIV superinfection. The high rates of superinfection observed in this study support the use of ART during pregnancy and for a lifetime thereafter, as it is likely to reduce the risk of MTCT and potential adverse effects of HIV superinfection (Redd et al., 2015b).

Clinical Trial

Promoting Maternal-Infant Survival Everywhere (PROMISE) Study. This large, multinational clinical trial, initiated in 2010, was designed to determine how best to reduce MTCT during pregnancy and breastfeeding and preserve maternal health during and after pregnancy and breastfeeding. Study participants were recruited from 12 countries with levels of resources ranging from high to low. The study concluded that there was a significantly lower rate of MTCT during the period before childbirth among those women who received a three-drug combination, and treatment with a combination containing the drug lamivudine resulted in fewer infant deaths in the first 2 weeks of life and fewer very premature deliveries than treatment with another triple-drug combination. The study also found that for HIV-infected women in good immune health, taking a three-drug regimen during pregnancy prevents MTCT more effectively than taking one drug during pregnancy, another during labor, and two more after giving birth. The findings were reported during a scheduled interim review and support the recommendation by WHO and most countries to provide a three-drug regimen to all pregnant women with HIV infection.

Vaccine Research

Vaccines are the foundation of preventive measures to curtail infectious disease epidemics. NIAID is committed to supporting basic, translational, and clinical research to develop a safe and effective vaccine to prevent HIV/AIDS, including ongoing clinical trials of promising vaccine strategies. NIAID is part of a public-private collaboration that aims to build on the landmark NIAID-funded RV144 vaccine trial, which showed for the first time that an investigational vaccine could confer a modest degree of protection against HIV infection in humans. In addition, NIAID is working to develop novel methods, such as broadly neutralizing antibodies, to prevent HIV infection.

HIV Vaccine Trials Network (HVTN)

The HVTN is an international collaboration of scientists searching for an effective and safe HIV vaccine. HVTN's mission is to facilitate the process of testing preventive vaccines against HIV/AIDS, conducting all phases of clinical trials from evaluating experimental vaccines for safety and the ability to stimulate immune responses to testing vaccine efficacy. Studies conducted by HVTN enroll both men and women, and data are analyzed for gender differences with regard to safety, tolerability, and immune responses. In a number of studies, the HVTN collects and analyzes mucosal secretions and tissue samples from the vagina and rectum to evaluate immune responses induced by a vaccine or broadly neutralizing monoclonal antibody. More information is available at www.hvtn.org.

Clinical Trials

Early-Phase Clinical Trial Shows Investigational HIV Vaccine Is Safe and Immunogenic. A recent Phase I/II clinical trial (HVTN 100) in South Africa evaluated an investigational HIV vaccine regimen designed to improve upon the RV144 regimen. Early data from this trial show that the improved vaccine is safe and induces an immune response against the

virus. NIAID has initiated a Phase IIb/III clinical trial to further evaluate the vaccine's efficacy. Even a partially effective HIV vaccine could have a significant positive impact on the health of women, particularly in resource-limited settings.

Other Prevention Research—HIV Prevention Trials Network (HPTN)

Established in 2000, HPTN is a worldwide collaborative clinical trials network that develops and tests the safety and efficacy of primarily nonvaccine prevention strategies. The HPTN research agenda focuses on the use of ART; treatment and prevention of STIs; treatment of substance abuse, particularly injection drug use; behavioral risk reduction interventions; and integrated combination strategies to reduce HIV transmission and acquisition. HPTN studies are conducted in various populations, including women, and in geographical regions that bear a disproportionate burden of HIV infection. More information on HPTN is available at www.hptn.org.

Clinical Trials

Young South African Women Can Adhere to Daily PrEP Regimen. The ADAPT Study (HPTN 067) found that young, single black women in South Africa adhered to a daily pill regimen to prevent HIV infection—an HIV prevention strategy known as pre-exposure prophylaxis, or PrEP. The study involved 179 women with a median age of 26 in Cape Town, South Africa; 179 black men who have sex with men (MSM) and transgender women (TGW) in Harlem, New York; and 178 MSM and TGW in Bangkok, Thailand. Those enrolled in this open-label study were educated about the efficacy of daily PrEP and knew that they were taking active drugs rather than placebo. Although some previous placebo-controlled PrEP clinical trials in women in sub-Saharan Africa had found challenges with adherence, 76 percent of women assigned to take PrEP on a daily basis in the study adhered to the prescribed regimen. (The MSM and TGW from Harlem and Bangkok who participated in the study

adhered to the daily regimen 65 percent and 85 percent of the time, respectively.)

Following completion of the study, a subset of the South African women participated in a qualitative substudy including focus groups and in-depth interviews. Among these women, PrEP use was heavily influenced by underlying beliefs about the safety of PrEP, a desire to contribute something positive to one's community, and trust in transparency and integrity of the research. The researchers propose a framework that could inform future intervention trials and implementation of PrEP programs. (Amico et al., 2017.)

Maraviroc-Containing Regimen Found Safe for HIV Prevention. HPTN 069/ACTG 5305, a Phase II study, evaluated the safety and tolerability of adding the ARV drug maraviroc to drug combinations taken daily as PrEP by MSM and women at increased risk for acquiring HIV. The study findings indicate that maraviroc-containing regimens were as safe and well-tolerated as the U.S. Food and Drug Administration (FDA)-approved form of PrEP, a combination of tenofovir and emtricitabine also known as Truvada (Gulick et al., 2016; CROI).

Study Finds PrEP Use Feasible Among High-Risk Groups in U.S. Community Settings.

A study called the PrEP Demonstration Project found that a majority of MSM and TGW at high risk for HIV infection took anti-HIV medications most of the time. The study findings lend support to the feasibility and potential clinical benefit of this strategy for HIV prevention in community settings (Liu et al., 2015, [International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention](#)).

Long-Acting Injectable Agent for HIV Prevention. Researchers conducted a Phase IIa study to evaluate the safety, tolerability, pharmacokinetics, and acceptability of a long-acting injectable agent, GSK1265744 (cabotegravir), in healthy, HIV-uninfected men and women (HPTN 077).

Antibody-Mediated Prevention Studies. Two Phase IIb studies currently are examining whether intravenous infusions of the broadly neutralizing anti-HIV antibody VRC01 are safe and effective at preventing HIV infection. The first study, [HVTN 703/HPTN 081](#), will enroll 1,500 sexually active women in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe. The antibody will be delivered as an intravenous infusion every 8 weeks. The study also will examine the levels of antibody in the blood of study participants who receive different amounts or doses of the antibody. The second study, [HVTN 704/HPTN 085](#), will evaluate antibody-mediated prevention among men and transgender men and women who have sex with men. More information is available at: www.ampstudy.org.

Oral PrEP in Young African Women. [HPTN 082](#) is a sub-Saharan-based research study designed to assess the number and characteristics of young women who accept versus decline PrEP at enrollment. The study also will compare adherence to PrEP between women who are randomized to receive standard adherence support and those receiving enhanced adherence support.

Population Effects of ART to Reduce HIV Transmission (PopART). The [PopART/HPTN 071](#) study is exploring whether providing a package of HIV prevention strategies can reduce HIV transmission at a population level. These prevention interventions include universal household voluntary HIV counseling and testing, linkage of HIV-infected individuals to care, and early initiation of ART for all those testing HIV positive. The study is being conducted in 21 communities in the Western Cape of South Africa and in Zambia.

Detecting HIV Using Self-Administered Vaginal Swabs. The [HVTN 915](#) study, which completed follow-up visits in 2015, was an observational study that followed 50 South African women to evaluate whether HIV exposure can be detected in daily vaginal swabs after episodes of unprotected sex. Using a mobile phone-based application, the study investigators sought to correlate data on sexual

behavior with vaginal swab samples collected by the clinicians and participants. The study found that mobile phone surveys appear to be a viable method to collect risk behavior information.

Therapeutics Research

AIDS Clinical Trials Group (ACTG)

Established in 1987, ACTG is a multicenter clinical trials network that conducts translational and therapeutics research in the United States and internationally. Research priorities include translational research and optimization of the clinical management of HIV/AIDS, including HIV-related coinfections and diseases. In collaboration with other clinical trials networks, ACTG also pursues research and development of therapeutic vaccines and research on HIV treatment in pregnant women. More information is available at www.actgnetwork.org.

Centers for AIDS Research (CFAR)

CFAR is a unique trans-NIH program that provides infrastructure to support interdisciplinary, peer-reviewed HIV/AIDS research in an environment that coordinates studies, promotes communication, provides shared services/expertise, and funds short-term feasibility studies that cannot easily be funded by other mechanisms. There are currently 18 CFARs at academic and research institutions throughout the United States. Several of them are actively supporting research activities in women. In 2015–2016, 12 CFARs supported more than 20 women's health pilot projects through the CFAR Developmental Cores. In addition, the Inter-CFAR Collaboration on HIV Research in Women is a network of CFAR investigators dedicated to promoting cutting-edge HIV research in women. The collaboration develops new strategies for future research to address HIV-related issues unique to women and promotes career development and professional growth among junior investigators interested in this field. Finally, the Harvard CFAR has a scientific working group that focuses on safer conception and contraception for HIV-

infected persons in resource-limited settings. More information on CFAR is available at www.niaid.nih.gov/research/centers-aids-research.

Science Advances

Initiation of Antiretroviral Therapy in

Early Asymptomatic HIV Infection. A major international randomized clinical trial known as the Strategic Timing of AntiRetroviral Treatment (START) study found that HIV-infected individuals have a considerably lower risk of developing AIDS or other serious illnesses if they start taking antiretroviral drugs sooner, when their CD4+ T-cell count is higher, instead of waiting until the CD4+ cell count drops to lower levels. The START study was conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) at 215 sites in 35 countries. The trial enrolled 4,685 HIV-infected men and women who had never taken ART and had CD4+ cell counts in the normal range—more than 500 cells per cubic millimeter (cells/mm³). Approximately half of the study participants were randomized to initiate ART immediately (early treatment), and the other half were randomized to defer treatment until their CD4+ cell count declined to 350 cells/mm³. Previous evidence to support early treatment among HIV-positive people with CD4+ cell counts less than 350 cells/mm³ was limited to data from non-randomized or observational studies and expert opinion. The START study is the first large-scale randomized clinical trial to establish that earlier ART benefits all HIV-infected individuals. The 2015 results were rapidly reflected in the updated WHO guidelines, which recommend immediate treatment of anyone infected with HIV. (The INSIGHT START Study Group, et al., 2015.)

Understanding Sex-Specific Differences in HIV Disease. HIV-infected women tend to have lower levels of the virus in their blood than men, both before and after starting ART. Yet, HIV disease progresses at the same rate or faster in women than in men. To investigate possible reasons for these sex-specific differences, researchers looked at markers of immune activation and inflammation in

215 HIV-infected, treatment-naïve men and women who participated in the NIAID-funded multinational Prospective Evaluation of Antiretrovirals in Resource-Limited Settings trial. The investigators found that, with treatment, women had greater increases in their CD4+ T-cell counts, and either greater increases or less reduction in various key markers of inflammation and immune activation compared with men. These findings suggest that women experience less reduction in immune activation and inflammation than men in response to ART. Further studies are needed to investigate how this relates to the worse HIV-related outcomes in women. (Mathad et al., 2016.)

Virus Reactivation, Immune Activation, and ART in HIV-Positive Women. NIAID intramural investigators examined the expression of vaginal inflammation-promoting factors called cytokines in HIV-infected women before and after initiation of ART. Initiation of ART can lead to a short-term increase of herpes virus-related illnesses, including varicella-zoster virus infection; increased cytomegalovirus (CMV) retinitis; herpetic genital ulcers; and rare occurrences of herpes simplex virus (HSV)-associated encephalitis. The association of viral shedding with higher levels of the cytokine interleukin-6 suggests that HSV reactivation may play a role in immune activation after ART initiation. (Nason et al., 2016.)

Sex Differences in Response to the First-Line HIV Drug Atazanavir. The first-line HIV therapy atazanavir is commonly used in combination ART regimens because it is a potent, once-daily drug that patients tolerate well. Prior studies have shown sex-related variability in blood concentrations of atazanavir. How the body processes the drug over time and the resulting clinical implications had not been determined. NIAID-funded researchers studied atazanavir concentration in the blood of 131 women and 655 men infected with HIV. They found that women cleared atazanavir from their blood 14 percent more slowly than men, after accounting for differences in body weight. In addition, women with fast clearance of atazanavir and men with slow clearance had worse clinical

outcomes, including an inability to tolerate atazanavir and failure to suppress HIV. These outcomes occurred despite patients' adherence to atazanavir treatment. This study showed that a patient's sex is an important factor in atazanavir clearance and treatment outcomes. (Venuto et al., 2014.)

HIV Infection Has a Small but Negative Effect on Cognitive Function in Women. Although several studies have reported cognitive impairment in women infected with HIV, previous studies were too small to understand the factors that may affect cognitive function in these women. As part of the NIAID-funded WIHS, the largest and longest running study to investigate the impact of HIV on U.S. women, researchers studied cognitive function in American, urban-dwelling women. To distinguish the effects of HIV from other factors that could affect cognitive function, the researchers studied socially and demographically similar women who were either HIV-infected or uninfected. The results showed that HIV infection had a very small but significant effect on cognition. HIV-infected women performed worse than uninfected women on tests of verbal learning, delayed recall and recognition, attention, and psychomotor speed (coordinating thinking and physical movement). The factor most strongly associated with cognitive deficit in HIV-infected women was low reading level. HIV-infected women with low education or compromised immune functions were most vulnerable to cognitive deficits. Results of this study will help define how best to treat HIV-infected women in the United States and globally. (Maki et al., 2015.)

Analysis Reflects HIV Treatment Practices and Behaviors in Washington, D.C. To identify factors that could help HIV-positive women achieve long-term suppression of the virus and reduce HIV transmission, scientists funded by NIAID analyzed data from 329 HIV-positive women living in Washington, D.C., who participated in four or more visits as part of the D.C. WIHS between 1994 and 2012. The researchers characterized three distinct patient populations: approximately 40 percent of women had a high probability of

being non-suppressed and viremic (having virus in the bloodstream) at each visit, a second group (35.6 percent) had a moderate risk of intermittent viremia, and a third group (27.3 percent) had a low risk of viremia during study follow-up. The women in the group with a high risk of viremia were most likely to succumb to HIV/AIDS, with a 31 percent mortality rate. Women in the groups at moderate or low risk of viremia on follow-up did not have significantly different mortality rates, at 6.9 and 4.7 percent, respectively. Despite the availability of ART, only one-third of the women in the study maintained consistently low virus levels. D.C. WIHS is a community-based study and the findings likely reflect the characteristics and behaviors of participants in the Washington, D.C., area and thus regional treatment successes and failures. The study highlights gaps in the success of treatment programs to fully suppress HIV and suggests that more tailored interventions may be needed to reduce HIV transmission, prevent the emergence of drug resistance, and improve outcomes of community HIV treatment programs. (Ocampo et al., 2015.)

Untreated HIV Infection Has No Association with Low Bone Mineral Density (BMD). HIV infection is associated with osteoporosis, a reduction of BMD that leaves bones vulnerable to breaking under mild stress, such as coughing or bending over. In people older than age 50, women are four times more likely than men to have osteoporosis. The contribution of untreated HIV infection to BMD loss is unclear. NIAID-funded investigators examined the association of traditional osteoporosis risk factors and HIV parameters with BMD at the hip and spine in HIV-infected adults who had normal CD4+ cell counts and had not undergone ART. The START Bone Mineral Density Substudy involved 424 ethnically diverse participants in 11 countries. Although osteoporosis among the participants was rare (1.9 percent), low BMD was common (35.1 percent). A longer duration of HIV infection (time since HIV diagnosis) was associated with lower BMD at the hip, but not the spine. The scientists found that low BMD was associated with traditional risk factors, such as

female sex and older age, but not with CD4+ cell count or viral load, which are markers of HIV/AIDS severity. This is the first study to evaluate BMD in untreated HIV-infected adults across more than one region. (Carr et al., 2015.)

Antiherpes Drug's Role in Decreased Viral Load and Disease Progression in HIV-Positive Women. NIAID intramural investigators published results from a clinical trial ([ClinicalTrials.gov NCT00405821](https://clinicaltrials.gov/ct2/show/study/NCT00405821)) of the antiherpes drug acyclovir in HIV-positive women, which sought to determine changes in immune activation due to the drug. Study data suggest that decreased monocyte activation may play a minor role in the ability of daily acyclovir use to slow HIV disease progression (Redd et al., 2015a.).

Clinical Trials

Promoting Maternal-Infant Survival Everywhere (PROMISE) Study. Some of the maternal health components of this study (described previously) are being conducted in settings where highly active ART is the standard of care during pregnancy and women do not typically breastfeed. This maternal health component is seeking to determine the best strategy for treating infected new mothers who have not progressed to AIDS.

The Effect of Vitamin D Repletion on Postmenopausal Women with HIV. This study ([ClinicalTrials.gov NCT01375010](https://clinicaltrials.gov/ct2/show/study/NCT01375010)) examined the effects of vitamin D supplementation on bone turnover, rates of bone loss, and indices of immune function in HIV-infected postmenopausal African-American and Hispanic women. Previous research revealed that low vitamin D levels are common in this population. The study followed 83 women to determine the change in BMD over 1 year. As other research has suggested that HIV-positive women have higher rates of bone loss than HIV-negative women, vitamin D therapy may help prevent complications of bone loss, particularly bone fractures. Data are currently being analyzed.

Evaluating Pharmacokinetic Interactions with Vaginal Ring Contraceptives and ART. This study is evaluating whether the ARV drugs efavirenz and atazanavir/ritonavir affect the hormones released by the birth control method NuvaRing®. Some studies have shown that ARV drugs interact with the hormones released by some birth control drugs. These interactions may cause the birth control drug to be less effective at preventing pregnancy and may increase the spread of HIV to others. The results of this study will ultimately inform whether NuvaRing® is safe and effective for women with HIV infection who are taking ARV drugs. The study also will examine the hormone levels in HIV-infected women who will use the NuvaRing® but not ARV drugs. (A5316, Enrolling)

Infectious Diseases Other than HIV/AIDS

Many infectious diseases, including malaria and such STIs as HPV, are critical global and national health priorities. These diseases can have a devastating impact on women, with the potential for causing long-term health problems. For example, many diseases can cause pregnancy loss at any stage, problems with the development of the fetus, or complications for the newborn.

Malaria

The parasite *Plasmodium falciparum* is the deadliest and most common malaria-causing species in Africa. Malaria infection during pregnancy has substantial risks for the pregnant woman, her fetus, and the newborn child.

Science Advances

New Vaccine Targets for Pregnancy-Associated Malaria. The *P. falciparum* protein VAR2CSA is a promising target for vaccine development against pregnancy-related malaria. This protein is expressed on the surface of infected red blood cells and binds to the placenta. NIAID-funded researchers studied fragments of VAR2CSA to

determine which part of the protein is targeted in women who have acquired natural immunity after pregnancy and thus identify new targets for a vaccine against pregnancy-associated malaria. In a trial conducted in Mali, researchers measured the reactivity of serum collected from men, women, and children to five different fragments of VAR2CSA. They found that serum from malaria-exposed women with a history of at least one pregnancy reacted more strongly to two of the five VAR2CSA fragments than did serum from men, children, and women who had never been pregnant. In addition, a greater number of pregnancies was associated with stronger reactivity to the two fragments. This finding is consistent with previous observations that with each pregnancy, women exposed to *P. falciparum* develop more antibodies that protect against the parasite and are associated with better birth outcomes. This study provides insight into how natural immunity to pregnancy-associated malaria is acquired and could inform the development of a vaccine. (Travassos et al., 2015.)

Additional Insights into Pregnancy-Associated Malaria Vaccine Development. Pregnant women are highly susceptible to malaria, particularly during their first pregnancy. Red blood cells that are infected by the malaria parasite *P. falciparum* concentrate in the placenta, leading to such serious consequences as severe anemia in the pregnant woman, stillbirth, low birth weight, or death of the newborn. Immunity from infection may be mediated in part by antibodies against VAR2CSA that block adhesion of the infected blood cells to the placenta. Studies suggest that women who have been pregnant multiple times acquire a repertoire of naturally occurring antibodies against VAR2CSA, and VAR2CSA is considered a prime vaccine candidate against placental malaria. NIAID intramural researchers used a new approach to assess domains, or regions, of VAR2CSA that are recognized by naturally acquired antibodies. They found that the broadly neutralizing antibodies in women who have had multiple pregnancies did not strictly recognize the type of VAR2CSA domains used in the study, suggesting that development

of vaccines based on isolated VAR2CSA domains might induce antibodies with only limited broadly neutralizing activity. (Doritchamou et al., 2016.)

Mouse Model Mimics Human Malaria Infection During Pregnancy. To better understand malaria infection during pregnancy, NIAID scientists established a new malaria pregnancy model in mice that mimics two processes common to humans during pregnancy: (1) re-emergence of a prior malaria infection and (2) infection with a new strain of malaria parasite following a prepregnancy infection with another strain. These infections resulted in a variety of symptoms, including anemia and elevated levels of inflammation-causing factors called cytokines in the pregnant mouse, stillbirths and deaths of newborn mice, and lower weight and altered susceptibility to future infection in the offspring. Many of these symptoms mimic the human condition, suggesting that this mouse model will be useful for studying the mechanisms underlying malaria infection during pregnancy. (Sharma et al., 2016.)

Clinical Study

NIAID intramural scientists have established the Pregnancy Malaria Immunology, Pathogenesis, and Vaccine Development initiative. Clinical and laboratory investigations for this project aim to determine factors associated with malaria in pregnant women and young children. These studies are informing intramural scientists' efforts to develop a pregnancy-associated malaria vaccine.

Clinical Trial

Host and Parasite Factors That Influence Susceptibility to Malaria Infection and Disease During Pregnancy and Early Childhood in Ouelessebouyou and Bamako, Mali (NCT01168271). Researchers are conducting a longitudinal cohort study in Ouelessebouyou, Mali, an area of intense seasonal malaria transmission. As many as 2,000 pregnant women and their infants and 2,000 children ages 0–3 years will be enrolled.

Infants and children will be followed to age 5, with clinical evaluation and periodic blood samples obtained. In addition, 2,000 children up to age 10 who have fevers will be enrolled at district health centers or a pediatric hospital, and samples will be obtained and evaluated. Finally, 500 pregnant women will be enrolled for a case-control study on pregnancy malaria and preeclampsia (hypertension occurring in pregnancy). Researchers will analyze various endpoints to determine parasite and host (human) factors that are associated with infection and disease in pregnant women and young children.

Zika Virus

Zika virus is a mosquito-borne virus that can be sexually transmitted and causes serious birth defects, including microcephaly, in babies born to mothers infected with the virus during pregnancy. Microcephaly is a condition marked by an unusually small head, brain damage, and developmental delays. Zika virus infection has been associated with other fetal development problems, including eye defects, hearing loss, and impaired growth. Most people who are infected with Zika virus do not become sick. The Zika virus, however, can persist in the body for several weeks after infection, even in a person without symptoms. There is no medicine or vaccine to treat or prevent Zika virus infection.

Science Advance

Nonhuman Primate Model Shows Effects of Zika Infection on Developing Brain. Studies to test the relationship between fetal brain injury and Zika virus infection during pregnancy were previously hampered due to the lack of an animal model that closely mirrors Zika infection and fetal brain development in humans. To address this issue, researchers studied Zika infection in nonhuman primates that have a placental structure and timing of fetal brain development similar to that of humans. They infected pregnant pigtail macaque

monkeys with Zika virus at a time equivalent to the third trimester of human pregnancy, tracked fetal development after infection via sonograms and magnetic resonance imaging, and performed autopsies at a time equivalent to 38 weeks of human pregnancy to evaluate brain development and invasion of the Zika virus into the fetal brain. The researchers found a pattern of virus invasion of the brain and associated brain developmental abnormalities similar to that observed in humans. The results provided the first direct evidence that Zika virus can cross the placental barrier late in pregnancy and impair fetal brain development. The findings underscore the need for rapid treatment or preventive measures after a mosquito bite. Researchers hope that this animal model may serve as a valuable tool to test possible vaccines and treatments against the potentially serious effects of Zika infection on the developing fetus. (Adams Waldorf et al., 2016.)

Clinical Study

Zika in Infancy and Pregnancy (ZIP) (NCT02856984). In June 2016, NIAID and other NIH Institutes launched the Zika in Infants and Pregnancy (ZIP) trial. The study aims to enroll as many as 10,000 pregnant women at up to 15 sites where Zika virus is prevalent. Participants will enroll in their first trimester of pregnancy and will be followed throughout their pregnancies to determine if they become infected with Zika virus and, if so, the outcomes for both mother and child. The participants' infants will be carefully followed for at least 1 year after birth.

Influenza

Influenza virus causes an acute respiratory infection in humans by entering and replicating in lung cells. Each year, seasonal influenza kills between 3,000 and 49,000 Americans and hospitalizes as many as 200,000. Pandemic influenza can produce even greater devastation.

Science Advances

Estrogen Provides Women, but Not Men, Enhanced Protection Against Influenza. Young women with influenza virus infections have more severe outcomes than men of the same age. Since the severity of infection in females changes with respect to age and during pregnancy, it is thought that hormones are responsible for sex-specific differences in response to influenza. To investigate these differences, researchers infected human nasal epithelial cell cultures with a seasonal influenza strain and studied how the infected cells responded to the female hormone estrogen or to chemicals that mimic estrogen, termed estrogenic compounds. Treatment of nasal cells with estrogen or estrogenic compounds reduced influenza virus replication, lowered virus levels, and dampened cell metabolic processes in cells isolated from female, but not male, donors. Together, these results demonstrate that estrogen and estrogenic compounds have antiviral properties and can control cellular function in tissues outside the reproductive tract, suggesting that FDA-approved estrogenic drugs could be used to help treat influenza virus infections in women. (Peretz et al., 2016.)

Progesterone Protects Female Mice Against Influenza Infection. Progesterone is a female hormone present in contraceptives used by more than 100 million women worldwide and is known to have anti-inflammatory effects in the reproductive tract. The role of progesterone in viral infections outside the reproductive tract is an open question. To investigate this question, scientists asked whether progesterone has any effect on influenza A virus (IAV) infection in mice. Mice that had had their ovaries removed to deplete progesterone received either progesterone or placebo and were subsequently infected with IAV. The progesterone-treated mice had less inflammation and tissue damage in the lungs, better lung function, and more rapid repair of inflammatory damage to the lung cells than mice that received placebo. Progesterone treatment elevated the number of immune cells known as T-helper cells and increased the levels of a growth factor called amphiregulin (AREG).

Progesterone treatment of mechanically damaged lung tissue also increased expression of AREG and enhanced wound repair. These findings suggest that progesterone stimulates tissue repair in the respiratory tract following influenza infection and show that sex hormones have notable health effects beyond the reproductive tract. (Hall et al., 2016.)

Human Papillomavirus (HPV)

HPV is the most common STI. Persistent infection with certain strains of HPV can lead to cervical cancer, which is the third most common cancer in women worldwide. The greatest burden occurs in resource-limited settings, particularly among those who are younger, female, and infected with HIV. Other strains of HPV cause genital warts, other skin warts, and benign tumors of the respiratory tract. These lesions can be especially problematic in individuals whose immune systems are compromised by HIV infection or by drugs given after organ transplantation. Two vaccines, Gardasil® and Cervarix®, are FDA-approved for the prevention of genital warts and cervical cancer due to HPV.

Science Advance

Repeated Evolutionary Loss of a Papillomavirus Gene. Infection with certain papillomavirus types can lead to the development of carcinomas, particularly in women. NIAID intramural investigators analyzed the sequences of more than 300 genetically distinct papillomaviruses, discovering evolutionary gene loss in certain papillomavirus genomes. Understanding the genetic evolution of these viruses helps researchers better understand their function and pathogenesis. (Van Doorslaer and McBride, 2016.)

Clinical Trials

Evaluating the Effectiveness of the Quadrivalent HPV Vaccine at Preventing Anal HPV Infection in HIV-Infected Men and Women (ACTG A5298). In this study, researchers are evaluating the safety and efficacy of the HPV vaccine Gardasil® to prevent anal HPV infection in HIV-infected women. In addition, the study is comparing two different

strategies to prevent advanced cervical cancer in women infected with HIV.

HPV Test-and-Treat Strategy Versus Cytology-Based Strategy for Prevention of CIN2+ in HIV-Infected Women (ACTG A5282). This study is comparing two different methods to prevent cervical cancer in women who have HIV. One experimental group will receive cervical cryotherapy (test-and-treat) and another group will be assigned to a cytology-based management plan involving multiple steps, including cytology, colposcopy with directed biopsies, and a surgical procedure as needed. This study will test if these methods are safe and tolerable in women who have HIV.

Bacterial Vaginosis (BV)

BV is the most common infection of the female reproductive tract and occurs when the natural balance between strains of bacteria, or flora, in the vaginal tract is altered. Previous studies have shown that BV increases the risk of STIs, including HIV.

Science Advance

Impact of BV on Levels of Cervical Gamma Delta T Cells May Increase HIV Risk. To better understand how BV can increase the risk of STI, a study explored the relationship between BV and the levels of two types of immune cells found in the female reproductive tract—gamma delta (GD) T cells 1 and 2—in some of the women enrolled in the Miami WIHS. The researchers found that HIV-uninfected women with abnormal vaginal flora had lower levels of GD1 cells and higher levels of GD2 cells than HIV-uninfected women with normal vaginal flora. The lower GD1 cells could indicate a decreased early immune response to infection. Furthermore, higher levels of GD2 cells could increase the number of cells that can be targeted by HIV, because these cells have the CD4 and CCR5 cell-surface receptors necessary for HIV to enter cells and establish infection. (Alcaide et al., 2016)

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV)

Viral hepatitis—in particular, HCV infection—is common among persons with HIV/AIDS. As a result of prolonged survival, greater numbers of HIV-infected people are experiencing the long-term complications of HCV and HBV infections, namely cirrhosis, liver failure, and hepatocellular carcinoma (liver cancer). Liver inflammation related to HCV and HBV infection may interfere with the ability to take highly active ART or medications used to treat other HIV-associated conditions.

Science Advance

Exploring Racial/Ethnic Differences in Liver-Related Mortality in HIV/HCV-Coinfected Women. In the United States, 10 to 30 percent of HIV-positive individuals also are infected with HCV, and liver-related disease and death from chronic HCV infection remain a significant problem in people coinfecting with HIV. Previous studies show that African-American women coinfecting with HIV and HCV are 60 percent less likely to die from liver-related disease than are coinfecting Hispanic or Caucasian women. However, the basis for these disparities is not known. To examine the genetic factors that might explain these racial/ethnic differences, scientists studied participants in the WIHS. They investigated whether the differences in liver-related mortality were linked with common genetic variants in and around the *IFNL3* and *IFNL4* genes—two related genes that are associated with HCV and the response to antiviral drugs. The analysis showed that two genetic variants were associated with increased mortality due to HCV. These differences, however, did not explain the lower risk of death among African-American HIV/HCV-coinfecting women, suggesting that other genetic, behavioral, and/or environmental factors may contribute to racial/ethnic differences in liver-related mortality. (Sarkar et al., 2015.)

Clinical Trials

Viral Hepatitis C Infection Long-Term Cohort Study (V-HICS) (ACTG 5320). This is a long-term follow-up study for people who have HCV infection alone or who have both HCV and HIV infection. The study will elucidate the impact of successful or unsuccessful HCV treatment on a person's long-term health. It also will help to understand how long resistance to new hepatitis C medications lasts and whether it affects future hepatitis C treatments. The study will analyze each person's HCV and underlying genetic differences to determine how these influence the success or failure of the HCV treatments and how treatment affects a person's quality of life.

Sofosbuvir-Containing Regimens Without Interferon for Treatment of Acute Hepatitis C Virus (HCV) Infection (SWIFT-C) (ACTG A5327). People with HCV have a greater chance of being cured of the infection when they are treated with a combination of two drugs within the first 6 months of being infected. This study is being conducted to see if a combination of two new drugs, ledipasvir and sofosbuvir, in one pill, can replace pegylated-interferon alfa, a drug given as a weekly injection under the skin, and provide a safer, more effective, and better tolerated treatment for new HCV infection. The fixed-dose combination of ledipasvir and sofosbuvir has been approved by FDA.

Tuberculosis

Tuberculosis (TB) is a major cause of disability and death worldwide. More than 95 percent of TB deaths occur in low- and middle-income countries, according to WHO. In 2014, 9.6 million people became ill with TB, and 1.5 million people died from the disease. TB is the leading cause of death for people infected with HIV. In 2015, one in three HIV deaths was due to TB. Globally in 2014, an estimated 480,000 people developed multidrug-resistant TB. TB is a major cause of illness and death in women of reproductive age. Pregnant and postpartum women with latent TB are at higher risk of developing active TB.

Clinical Trials

Pharmacokinetic Interactions of DMPA, Rifampicin and Efavirenz in HIV/TB Coinfected Women (PRIDE-HT) (ACTG A5338). The purpose of this study is to evaluate the effect of HIV and TB treatment on a commonly used birth control method called depot medroxyprogesterone acetate (DMPA), which is given as an injection every 3 months. The study will establish the best schedule to provide DMPA in women with HIV and TB who are taking efavirenz (EFV; Sustiva; an anti-HIV medication), rifampicin (RIF; an anti-TB medication) and isoniazid (INH; an anti-TB medication) and will ascertain if it is safe to take RIF, EFV, and DMPA simultaneously.

Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-Infected and HIV-1-Uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection (IMPACT 2001). The purpose of this study is to evaluate the treatment of HIV-infected and uninfected pregnant and postpartum women with rifapentine (RPT) and INH for a latent TB infection. This study will enroll HIV-infected and HIV-uninfected pregnant women with latent TB and their infants into two cohorts: Cohort 1 participants will be enrolled in their second trimester of pregnancy, and Cohort 2 participants will be enrolled in their third trimester. All participants will receive 12 directly observed once-weekly doses of RPT, INH, and pyridoxine (vitamin B6).

Fungal Infections

Fungal diseases often are caused by fungi that are common in the environment. Most fungi are not dangerous, but some types can be harmful to health, causing a wide range of issues, from mild, rash-like skin diseases to lung infections, meningitis, and bloodstream infections that can be deadly.

Science Advance

Gender Differences in Murine Models of Fungal Infections. Fungal infections frequently occur in people with weakened immune systems who have inhaled fungal spores, but they also can occur in healthy individuals. Aspergillosis, which is caused by infection with *Aspergillus fumigatus*, can result in an allergic reaction that affects the airways and lungs, or it can manifest in a more invasive form that damages organs. Mucormycosis is caused by infection of any member of the fungal group *Mucorales*. Mucormycosis can be a pulmonary infection, or it can be a skin infection when the fungus enters the skin through a cut or wound. Research in an upcoming study (HHSN27220100038I) will examine the effect of sex on fungal infection disease progression and treatment in mice. The major activity to be supported is the evaluation and modification of standardized small animal models of fungal infections caused by *A. fumigatus* or members of the *Mucorales*, respectively, to determine sex differences, if any, in the natural history of disease, immunosuppression, dosing, and response to therapy.

Immunology and Immune-Mediated Diseases

NIAID supports investigations of immunology and immune-mediated diseases and their effects on women's health. The goal of this research is to increase the health and well-being of women by developing new methods to prevent and treat autoimmune and other immune-mediated diseases.

Immune Response to Vaccinations

NIAID is committed to developing new and improved vaccines. Research to bring about new, more broadly protective vaccines is balanced with efforts to ensure the safety and efficacy of vaccines in various populations. Recent research has shown that immune responses to vaccines

can vary between different populations and sexes. Heterogeneous post-vaccination immune responses in men and women have been widely documented for many different vaccines. The underlying causes of these sex differences are an area of active investigation.

Science Advance

Sex Difference in Immune Response to Smallpox Vaccination. IMVAMUNE® is a smallpox vaccine based on the modified *vaccinia Ankara* (MVA) virus. It was developed as a way to prepare for the possibility of a bioterrorist attack using smallpox. Recently, it has been shown that immune responses to vaccines can vary among different populations. To test whether there are sex-based differences in the immune response to IMVAMUNE®, researchers compared responses from 275 individuals (136 men, 139 women) in a meta-analysis of data from three randomized trials of IMVAMUNE®. In comparing healthy men and women who had not been previously exposed to the smallpox vaccine, the results demonstrated that men showed higher levels of antibody against smallpox. These findings suggest that sex-based differences in immune response could affect the efficacy of IMVAMUNE® and other MVA-based vaccines. (Troy et al., 2015.)

Immune Changes in Pregnancy

Pregnancy alters immune function. It has been suggested that pregnancy causes an immunosuppressive state that prevents the mother's immune system from attacking the fetus and results in an increased susceptibility to infection. During pregnancy, the placenta performs many critical functions, including protecting the fetus from infection. Researchers are trying to develop new technologies to understand how the placenta functions and how to better protect the fetus against infection.

Clinical Trial

Pregnancy Immune Function. Progress in treating and managing infections during pregnancy will require further understanding of the changes to the immune system that occur during pregnancy. NIAID intramural scientists recently completed a clinical trial that evaluated blood samples drawn from pregnant women during early, mid-, and late pregnancy and postpartum for changes in the innate immune system and compared them to those of healthy, nonpregnant women. Changes in the cytokine profile and in the lymphocyte and natural killer cell populations are being identified. (NCT01200979)

Science Advance

A Novel 3-D Culture System to Study the Development and Microbial Resistance of the Human Placenta. The human placenta is covered with a protective layer of multinucleated cells (cells with many nuclei) that serves as a barrier to prevent the transfer of toxins, bacteria, and viruses from mother to fetus. The molecular mechanisms that control the formation of these specialized cells, called syncytiotrophoblasts, are not well understood. To study these mechanisms, scientists devised a three-dimensional (3-D) system for culturing cells that models placental development and function. This 3-D cell culture model could provide a means to study the process by which trophoblasts fuse together to become syncytiotrophoblasts and develop resistance to microbial infection that protects the developing fetus. In addition, this culture system may be very useful in elucidating how some viruses, such as Zika virus, are able to penetrate the placental barrier and harm the developing fetus. (McConkey et al., 2016.)

Asthma

Asthma is a severe and chronic disease that causes wheezing, breathlessness, chest tightness, and coughing. It affects more than 230 million

people worldwide, including more than 18 million adults and 7 million children in the United States. The prevalence of asthma in girls increases after puberty. Early prevention of asthma is essential to reducing the burden of this high-impact disease in adolescent girls.

Urban Environment and Childhood Asthma (URECA)

Asthma severity increases in girls during and after puberty, whereas it tends to improve in boys. Subjects in the URECA birth cohort, funded by NIAID, are reaching puberty. NIAID plans to support research to understand the immunologic mechanisms through which this sex-based difference occurs in association with pubertal changes. This plan will be in place by mid-2017.

Role of Epigenetics in Sex-Specific Changes in Asthma Severity and Incidence. The effect of puberty on asthma may have its basis in epigenetic modifications, or changes in gene expression caused by environmental factors such as hormones, rather than in alteration of the genetic code itself. Some studies have suggested that sex hormones lead to modifications of the gene *GATA3*, which regulates the immune response associated with asthma. In fiscal year (FY) 2016, NIAID awarded a new research grant (Zhang and Holloway, 2016. 1R01 AI121226-01) to study the gender switch in adolescent asthma. In this project, researchers are examining asthma and associated risk factors during adolescence at the genome level, and collecting epigenomic, genomic, and transcriptomic data from two well-characterized groups of individuals whom researchers have followed since birth. The overall goals are to record the extent of genome-wide DNA methylation, a type of epigenetic modification, and its change in adolescence and to identify sex-specific effects in association with changes in asthma severity and incidence. Findings from this project could potentially lower incidence and promote remission of asthma during adolescence.

Allergy

Allergic diseases are very prevalent in the United States and around the world. The development, history, genetics, diagnosis, management, and prevention of these conditions are important scientific research areas for NIAID. Severe allergic reactions and anaphylaxis—a rapid-onset, potentially life-threatening allergic reaction—are more common in adult women than in adult men, and the mechanism underlying this disparity is not well understood.

Science Advance

Estrogen Worsens Allergic Reactions in Mice. To study sex differences in severe allergic reactions, NIAID intramural researchers used a mouse model of anaphylaxis. They used two methods to investigate estrogen involvement in severe allergic reactions—pretreatment of the mice with a drug to block estrogen activity or surgical removal of the ovaries. Both of these methods eliminated the enhanced severity of anaphylactic responses in female animals. Severity was restored following administration of estradiol (a form of estrogen) in mice that had their ovaries removed. The study further showed that estradiol increased tissue expression of endothelial nitric oxide synthase (eNOS), the enzyme responsible for producing nitric oxide (NO). NO is known to regulate many processes involved in anaphylactic shock, such as vasodilation and vascular leakage. Blockage of eNOS activity with an inhibitor, or genetic eNOS deficiency, abolished the sex-related differences. This study establishes estrogen's contribution to anaphylaxis severity and delineates the mechanisms of its action through regulation of eNOS expression and NO production. (Hox et al., 2015.)

Autoimmune Diseases

Autoimmune diseases are a group of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues, and cells. Some of the more common autoimmune diseases

include rheumatoid arthritis (RA), type 1 diabetes, multiple sclerosis (MS), celiac disease, systemic lupus erythematosus (SLE), and inflammatory bowel disease. Many autoimmune diseases disproportionately affect women, and this group of diseases is among the leading causes of death for young and middle-aged women. NIAID supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs.

Systemic Lupus Erythematosus (SLE)

SLE, more commonly known as lupus, is a relapsing autoimmune disease that causes inflammation that can affect many body systems, including the central nervous system, joints, skin, kidneys, blood cells, heart, and lungs. Approximately 322,000 Americans are diagnosed with, or suspected of having, SLE. Ninety percent of people with lupus are women, and the age of onset generally is between 15 and 45 years. Lupus is more common in black, Hispanic, Native American, and Asian women than in white women.

Science Advance

New Insights into Disease Flares in SLE.

People with SLE have high serum levels of autoantibodies—antibodies that react against the body's own cells and tissues. These autoantibodies are continuously present in SLE, but the levels of some autoantibodies and of antibody-secreting immune cells, called B cells, increase in patients suffering a relapse, or “flare,” of the disease. NIAID-supported researchers used state-of-the-art techniques to create a detailed picture of the interrelationships, diversity, and origins of autoantibody-producing cells from people with SLE during disease flares. They then compared them to the conventional antibody response that occurs in healthy people after immunization (vaccination). Their analysis indicates that autoantibody-producing B cells in people with SLE arise via several distinct pathways, including pathways that differ from those of a conventional immune response. Unlike antibody-producing cells that form

in response to vaccines, a substantial number of these autoreactive cells persist in the circulation of people with SLE for several months. These findings shed light on the disease process in SLE, help explain the benefit of existing therapies that target B cells, and could facilitate the design of new therapies. (Tipton et al., 2015.)

Ten Genes Newly Associated with the Heritability of Lupus Among Asians. SLE is approximately 10 times more common in women than in men. In addition, Asians have a higher SLE incidence, more severe disease, and greater risk of organ damage than people of European ancestry. Although SLE is known to have a strong genetic component, only about 10 percent of disease heritability is explained by previously identified genetic variations. To identify genetic variants associated with SLE in individuals of Asian ancestry, NIAID-funded researchers studied the DNA of thousands of individuals, either with SLE or unaffected, from six East Asian populations, focusing on immune-related regions, or loci, of the genome. By combining their data with those of previous studies to narrow these regions, they identified 10 genes newly associated with a predisposition for SLE and confirmed 20 genetic regions previously suspected to be associated with SLE. Six of the 10 newly identified genes also are associated with other autoimmune diseases. Together with previous studies, these results increase the explained heritability of SLE to 24 percent among individuals of Asian descent. These findings provide valuable insight into the pathogenesis and manifestations of lupus and point to new targets for treatment of SLE. (Sun et al., 2016.)

Systems-Level Analysis Identifies a Potential Biochemical Signature of Lupus. Toll-like receptors (TLR) are cell-surface proteins involved in the initial recognition of microbes, and activation of TLRs leads to an inflammatory immune response. When TLRs inappropriately recognize “self” molecules, the inflammatory immune response can lead to autoimmune diseases, such as SLE. To investigate how the response to TLR activation can

vary across cells of the immune system, NIAID-supported scientists initially analyzed blood samples from healthy volunteers. Using different types of stimuli, the researchers activated the TLR proteins and measured changes in the expression patterns of different immune signaling proteins and factors called cytokines that affect immune function. Systems-wide analyses revealed that in newly diagnosed SLE volunteers, white blood cells called monocytes produced increased levels of particular cytokines compared with monocytes from healthy donors, defining a potential biochemical signature for SLE. These findings provide a systems-level framework that can be applied to study immune perturbations in people with inflammatory diseases, such as SLE, and might be used to help diagnose and treat these diseases. (O’Gorman et al., 2015.)

Cell Type Identified as Key Player in Lupus Initiation and Aggravation. NIAID intramural researchers recently proved that a rare type of immune cell, with immature phenotype and quick turnover in healthy individuals, plays a key role in lupus initiation and aggravation. These atypical natural killer (NK) cells were shown to be expanded in number during chronic innate immune stimulation, such as in lupus and other conditions that involve chronic inflammation. The researchers’ work also suggests that NK cell types can affect the priming and progression of diseases like lupus. This type of mechanistic information on pathways and cell populations provides valuable insights on how lupus progresses, might be used as a specific biomarker of disease, and, ultimately, identifies points in the disease process that could be disrupted through targeted therapies. (Voynova et al., 2015.)

Personalized Immunomonitoring Uncovers Molecular Networks That Stratify SLE Patients. Scientists have previously identified several sets of genes, termed modules or signatures, that can be dysregulated in a coordinated manner in individuals with SLE. The first and most widely investigated of these is the interferon response signature. Researchers compared these modules

among 158 pediatric participants with SLE over a 4-year period and found seven distinct genetic patterns, one correlating with disease progression to kidney inflammation (nephritis). These genetic patterns will help physicians diagnose SLE more accurately and prescribe more effective therapy for the individual patient. (Banchereau et al., 2016.)

Multiple Sclerosis (MS)

MS, an inflammatory disease of the central nervous system, is the leading cause of neurologic disability among young adults, causing visual disturbances, muscle weakness, and loss of coordination. Severe, progressive cases can result in partial or complete paralysis. MS affects about 400,000 Americans, and women are affected about twice more frequently than men.

Science Advance

Functional Differences in Immune Cells

Provide Clues to Disease Process in MS. MS is thought to result from immune cells called autoreactive (self-reactive) T cells that target myelin, the sheath that surrounds and insulates nerve fibers. Because individuals with MS have similar numbers of myelin-reactive T cells as healthy people, researchers looked for possible functional differences between the myelin-reactive T cells. They compared the production of cytokines (small proteins that regulate the immune system) by these cells and found that the T cells from people with MS produced more inflammation-causing cytokines, such as IL-17, compared with T cells from healthy people, whereas T cells from healthy people produced more of an anti-inflammatory cytokine called IL-10. The researchers also identified some striking differences between the genetic profiles of myelin-reactive T cells in people with MS and healthy individuals. These findings suggest that functional differences between myelin-specific T cells from people with MS and healthy individuals play a role in disease development. (Cao et al., 2015.)

Clinical Trial

Stem Cell Transplants May Halt Progression of MS.

A treatment that may be promising for achieving long-term remission of MS involves resetting the immune system through a combination of high-dose chemotherapy and hematopoietic stem-cell transplantation (HSCT). To test this approach in MS patients with active relapsing-remitting disease unresponsive to conventional treatment, researchers designed a clinical trial called High Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS). The HALT-MS study enrolled 25 participants experiencing active relapsing-remitting MS with worsening neurological disability, despite taking standard medications. Researchers harvested stem cells from the participants' own bone marrow. Participants next received high-dose chemotherapy to destroy their immune cells, and then received their previously harvested stem cells to reset and then rebuild their immune systems. After 3 years, 78 percent of participants remained in remission. The HALT-MS study researchers plan to follow participants for a total of 5 years. Final results from this and similar studies will help inform the design of larger clinical trials to further evaluate this treatment approach for people with MS. (Nash et al., 2015.)

Rheumatoid Arthritis (RA)

Rheumatoid arthritis is an autoimmune inflammatory disease that causes pain, swelling, and stiffness in the joints and can result in serious joint damage. About 1.5 million Americans have RA, and two to three times as many women as men are affected.

Science Advance

RA-Associated Antibodies May Arise from Mucosal Immune Responses.

RA is associated with the production of autoantibodies—antibodies that can bind to and attack normal tissues within the body and appear to play a major role in disease development. Determining the source of these

autoantibodies is thus key to better understanding of how RA develops. Scientists isolated antibody-producing cells called plasmablasts from individuals known to be at risk of developing RA and compared them to plasmablasts from subjects with established RA and from healthy controls not at risk for RA. Individuals at risk for RA exhibited a higher frequency of plasmablasts producing antibodies of the IgA type, which is associated with immune responses from mucosal membranes—thin layers of tissue that line body cavities and surround internal organs. Those at risk for RA also showed increased serum levels of disease-associated IgA autoantibodies. These results suggest that some autoantibodies that drive the development of RA may arise from immune responses at mucosal surfaces and may also provide a means of identifying individuals at the greatest risk of progressing from at-risk status to clinical disease. (Kinslow et al., 2016.)

The Microbiome and Autoimmunity

Microbes inhabit just about every part of the human body. Sometimes they cause sickness, but most of the time microorganisms live in harmony with their human hosts, providing vital functions essential for human survival. NIAID participates in the NIH Human Microbiome Project, which is mapping the microbial makeup, or microbiome, of humans to better understand the role of microbes in health and disease. Some NIAID projects study how the microbiome influences immune responses.

Science Advance

Gut Microbiota Promote Autoimmune Arthritis by Triggering Migration of Gut T Cells to Systemic Sites. Gut microbiota are known to influence the development and function of the immune system and to play a role in such immune-mediated diseases as autoimmunity. The question remains of how microbiota colonizing the gut can influence development of disease at sites distant from the gut. Researchers addressed this

question using a mouse model of autoimmune arthritis that was shown to be dependent on a type of bacteria present in the gut microbiota, segmented filamentous bacteria (SFB). Their results demonstrate that SFB in the gut trigger expansion of immune cells called follicular helper T cells in the gut and induce migration of these cells from the gut to the lymphatic system, where antibody production occurs. This expansion and migration of follicular helper T cells led to increased autoantibody production and disease exacerbation. (Teng et al., 2016.)

Systemic Sclerosis (Scleroderma)

Scleroderma is a group of autoimmune diseases in which the immune system is thought to stimulate cells called fibroblasts, which then produce too much of the fibrous protein collagen. Systemic sclerosis is the form of the disease that not only includes the skin but also involves the tissues beneath the skin, the blood vessels, and the major organs. The excess collagen forms thick connective tissue that can interfere with the function of affected organs. An estimated 40,000 to 165,000 people in the United States have this disease, and women—especially middle-aged women and African-American women—are affected more than men.

Clinical Trial

The Scleroderma Cyclophosphamide or Transplantation (SCOT) study is comparing the safety and potential usefulness for scleroderma of high doses of drugs to suppress the immune system followed by transplantation of immune system stem cells versus monthly high doses of the immunosuppressive drug cyclophosphamide. The hypothesis is that high-dose immunosuppressive therapy will destroy the malfunctioning immune system, and replacement with immature immune cells will permit the development of a healthy immune system, inducing a long-term remission or even eradicating the disease. High doses of

cyclophosphamide may reduce symptoms more effectively than the standard low-dose therapy. The follow-up phase of the study is complete and the data are being analyzed. More information is available at www.sclerodermatrtrial.org. (NCT00114530).

NIH Strategic Plan for Women's Health Research

The Trans-NIAID Women's Health Research Work Group focuses on women's health and gender-based research activities that advance the mission and research priorities of NIAID and provides recommendations for future women's health research opportunities. The work group performs the following functions:

- Heightens awareness across NIAID of the importance and substance of women's health and gender-based research.
- Develops a common framework for identifying and assessing gender-based and women's health research.
- Encourages trans-NIAID and trans-NIH collaborations on women's health and gender-based research activities.
- Coordinates various NIAID-wide presentations on such topics as the effects of antibiotics on the vaginal microbiome and health and sex as a biological variable.

Inclusion

NIAID supports many research studies that focus on better understanding gender differences in disease outcomes, as reflected in the previous section.

Over the last two decades, researchers and clinicians have acknowledged that there are critical scientific gaps in the evidence base for clinical care of pregnant women. The PHASES project, funded by NIAID, seeks to increase enrollment of pregnant women in ethically appropriate clinical research

through development of a carefully vetted ethical framework and guidance document for researchers, institutional review boards, and regulators. The research effort focuses on HIV prevention methods and novel HIV treatment regimens, including treatment for women with comorbidities, such as HIV/TB coinfection. This large multi-institution project, initiated in 2014, includes a project team of bioethics experts, legal and regulatory scholars, clinical researchers, and community stakeholders who will address the challenges and barriers of inclusion of pregnant women in research (Krubiner et al., 2016). More information is available at www.bioethics.unc.edu/phases.

Finally, NIAID has structured several longitudinal HIV/AIDS studies and programs, described above, to enable the study of sex and gender differences, including the following:

- The WIHS is closely linked to the MACS, a study of MSM, to ensure that data collected in the two studies can be combined and compared whenever appropriate. Studies that compare outcomes for men and women in pharmacology, cardiovascular disease, aging, sleep patterns, metabolic disorders, mental health, and neurologic diseases are ongoing. These projects have demonstrated differences in the pharmacology of ARV drugs and differences in the clinical outcomes between men and women with HIV in the United States.
- The International Epidemiology Databases to Evaluate AIDS (IeDEA) program combines data from nearly 1 million people with HIV globally. With these data, researchers can evaluate gender differences in disease outcomes and therapy response.

STEM Career Development Efforts

NIAID continues to co-sponsor the Building Interdisciplinary Research Careers in Women's Health mentored career development awards, which support the development of women's health

researchers. This activity supports NIH ORWH strategic goal 6.2, *Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs*. NIAID also continues to co-sponsor the Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers, which aims to encourage individuals to re-enter an active research career after an interruption for family responsibilities.

The Inter-CFAR Collaboration on HIV Research in Women develops new strategies for future research to address HIV-related issues unique to women and promotes career development among junior investigators in this field.

NIAID actively supports NIH efforts to increase diversity in the scientific workforce by contributing to internal working groups, publicizing ongoing opportunities, and participating in NIH-wide efforts, such as the Building Infrastructure Leading to Diversity initiative.

NIAID's outreach program to populations underrepresented in biomedical research, the Intramural NIAID Research Opportunities (INRO) program, has been successful in recruiting women (undergraduate seniors and graduate students) to its annual 4-day program. Of the 202 applications submitted for INRO between 2015 and 2016, 133 were female. Of the 44 selected students, 24 were female. In addition, in 2015 and 2016, NIAID accepted three young women (high school students) from the Bnos Yisroel Scientific Bridge Program into NIAID's Summer Intern Program, for laboratory work, mentoring, and attending guest lectures.

Research Initiatives

NIAID supports a number of initiatives on research related to women's health, including the following:

Increased Knowledge and Innovative Strategies to Reduce HIV Incidence—iKnow Projects.

The purpose of this FOA is to (1) devise optimal strategies to improve the identification of persons

unaware of their HIV infection and successfully link them to HIV testing, treatment, and prevention interventions and (2) develop and examine the feasibility and acceptability of novel integrated interventions of biomedical and behavioral strategies that substantially reduce the likelihood of onward HIV transmission in these populations. (PAR-16-117)

Methods for Prevention Packages Program IV (MP3 IV). The purpose of this FOA is to promote multidisciplinary research programs that (1) devise optimal HIV prevention packages (combination interventions) for specific populations and (2) perform feasibility and acceptability studies to demonstrate that the proposed prevention package is acceptable to the intended population and the study design is appropriate and feasible. This FOA is intended to encourage collaborations between behavioral and biomedical clinical specialists, epidemiologists, mathematical modelers, and clinical research specialists. (PAR-16-124)

Harnessing Big Data to Halt HIV. The purpose of this FOA is to promote innovative research using Big Data Science (BDS) to understand the complex and substantially interrelated factors that place persons at risk of HIV infection and that influence their HIV treatment course. BDS approaches have the potential to bring together data on populations so that the epidemiology of risk and care can take into account the complexity of contextual factors in individual's lives. (PA-15-273)

Administrative Supplements for Research on Sex/Gender Differences. This FOA was reissued in 2015 and 2016 to provide administrative supplements to support research highlighting the impact of sex/gender in human health and illness. The research will address at least one of following objectives: (1) increasing sex differences research in basic science studies; (2) incorporating findings of sex/gender in the design and development of new technologies, medical devices, or therapeutic drugs; or (3) actualizing personalized prevention, diagnostics, and therapeutics for girls and women (PA-16-066 and PA-15-034).

Administrative Supplements for Research on Sexual and Gender Minority (SGM)

Populations. This FOA was issued in FY 16 to provide administrative supplements to support research focused on health issues affecting SGM populations, such as lesbian, gay, bisexual, and transgender people, and individuals with differences or disorders of sexual development (sometimes referred to as “intersex” or as specific diagnoses). The research will address areas beyond HIV/AIDS, including, but not limited to, studies on increased disease risk, behavioral and social health, approaches to personalized medicine, access to care, reproductive and sexual development, and resilience (PA-15-329).

Conferences and Publications

The Inter-CFAR Joint Symposium on HIV Research in Women was held December 8–9, 2014, to (1) identify gaps in knowledge in research related to HIV and women and develop strategies that will move the field forward, (2) generate collaborative activity between the different CFARs and with other research networks highlighting cutting-edge science, and (3) promote and emphasize opportunities for young investigators. The most recent meeting was hosted by the University of Washington CFAR on November 4–6, 2015, focusing on (1) HIV research in women and children, (2) HIV malignancies, (3) progress in HIV/AIDS combination prevention research and implementation, and (4) cohort research on HIV and comorbidities.

Guest editors and authors from NIH and the Bill & Melinda Gates Foundation facilitated the publication of a special issue of the journal *Vaccine* (Volume 33, Issue 47) in 2015 titled “Advancing Maternal Immunization Programs Through Research in Low- and Medium-Income Countries.” Articles addressed current and future prospects through specific examples and literature reviews. The article “Maternal Immunization Efforts of the National Institutes of Health” described NIAID-sponsored

studies of licensed vaccines during pregnancy. (Rubin et al., 2015.)

NIH collaborated with the International Alliance for Biological Standardization to organize the Harmonized Safety Monitoring of Immunization in Pregnancy International Consensus Conference in Bethesda, Maryland, on March 29–30, 2016. Experts highlighted a need for harmonized study protocols, case definitions, and a globally concerted effort to move toward enhanced surveillance. The report from this conference will be published in the journal *Biologicals*.

Staff from NIAID, NICHD, and the National Cancer Institute are participants in Global Alignment of Immunization Safety Assessment in Pregnancy, a 2-year global project coordinated by the Brighton Collaboration Foundation. The project’s objective is to develop standards, guidance, and tools toward harmonized assessments of maternal, fetal, and neonatal health outcomes. Multiple working groups are preparing manuscripts to be published in 2017.

The Assistant Secretary for Health charged the National Vaccine Advisory Committee (NVAC) with reviewing the state of maternal immunizations and proposing recommendations. NVAC established the Maternal Immunization Working Group (MIWG) in August 2012. NIAID representatives served as members of the MIWG and attended conferences during the following 4 years. The MIWG identified four main areas of discussion: (1) ethical issues, (2) policy issues, (3) preclinical and clinical research issues, and (4) provider education and support issues. In 2013 and in 2016, MIWG provided NVAC with documents that addressed these areas.

Health Disparities

NIAID supports research to understand and eliminate health disparities among women and special populations, including minorities, rural women, lesbians, women of lower socioeconomic status, and women with disabilities. The following

ongoing and planned activities and scientific advances are highlighted in this report:

Ongoing and Planned Activities

- WIHS
- IeDEA
- ASPIRE and several MTN studies
- ADAPT and other PrEP studies
- PROMISE Study and other studies to evaluate approaches for PMTCT
- Host and parasite factors that influence susceptibility to malaria infection and disease during pregnancy and early childhood in Mali
- Zika in Infants and Pregnancy (ZIP)
- Exploring racial/ethnic differences in liver-related mortality in HIV/HCV-coinfected women
- Viral Hepatitis C Infection Long-Term Cohort Study (V-HICS)

Scientific Advances

- HIV infection has a small but negative effect on cognitive function in women.
- Untreated HIV infection has no association with low bone mineral density.
- Ten genes have been newly associated with the heritability of lupus among Asians.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Executive Summary

Overview

NIAMS supports a broad range of research, research training and career development activities, and health information programs for many debilitating diseases affecting Americans. NIAMS funds studies on a number of diseases that affect women disproportionately, including osteoporosis, osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus (lupus), scleroderma, and fibromyalgia.

Program Highlights

The anticipated increase in the United States' elderly population will be accompanied by an increased number of women who are at risk of fragility fractures. Effective osteoporosis medications are available, but the rates of treatment and adherence are excessively low. Most of the data regarding the benefits and risks of pharmacologic fracture prevention interventions come from the clinical trials that led to the drugs' regulatory approval. These trials generally looked at a treatment duration of 3–5 years. Thus, health care providers lack clear guidance regarding which patients will benefit or may be harmed from continued drug intervention beyond the original trial period. These and other issues related to bone-preserving medications have prompted NIAMS, the National Institute on Aging (NIA), the NIH Office of Disease Prevention, and several other NIH components, such as the Office of Research on Women's Health (ORWH) to launch a Pathways to Prevention effort on Appropriate Use of Pharmacologic Therapies for Osteoporotic Fracture Prevention.

NIAMS also manages the Accelerating Medicines Partnership in Rheumatoid Arthritis and Systemic

Lupus Erythematosus (AMP RA/SLE) Program for the National Institutes of Health (NIH). Begun in Fiscal Year (FY) 14, this 5-year, \$41 million effort will generate a comprehensive understanding of the mechanisms of tissue damage in RA and lupus. Partnering organizations include AbbVie Inc., Bristol-Myers Squibb, Merck and Co., Pfizer Inc., Sanofi, Takeda Pharmaceuticals, the Arthritis Foundation, the Lupus Foundation of America, the Lupus Research Alliance, the Rheumatology Research Foundation, and the Foundation for the National Institutes of Health. In March 2016, the AMP RA/SLE Network finished developing and validating their standard operating procedures and began comparing samples collected from people with and without RA or lupus.

With support from ORWH and other NIH components, NIAMS provides a robust information dissemination and outreach program to distribute research-based information to patients, health care providers, and other members of the public. For example, NIAMS oversees the NIH Osteoporosis and Related Bone Diseases National Resource Center (ORBD~NRC), which is co-funded by the NIA, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, ORWH, and the U.S. Department of Health and Human Services Office on Women's Health.

NIAMS also disseminates results from funded studies by providing lay-language summaries on the Institute's website and contributing to NIH-supported information resources (e.g., the consumer-oriented *News in Health*, *NIH Research Matters*, and *MedlinePlus Magazine*). Additionally, NIAMS staff members contributed background to or were quoted in many print and online articles in the mainstream and in trade press about diseases

within the Institute's mission. Perhaps the most widely read of these is from FY 16—a front-page *New York Times* story about osteoporosis medications (Kolata, 2016).

Accomplishments and Activities

Fibromyalgia

Fibromyalgia syndrome is a common and chronic disorder characterized by widespread pain, diffuse tenderness, and a number of other symptoms. Scientists estimate that fibromyalgia affects 5 million Americans ages 18 and older. For unknown reasons, between 80 and 90 percent of those diagnosed with fibromyalgia are women; however, men and children also can be affected. Most people are diagnosed during middle age, although the symptoms often present earlier in life.

Pregabalin Induces Changes of Brain Structure and Connectivity in Fibromyalgia Patients.

Researchers demonstrated that a short-term, 2-week treatment with the U.S. Food and Drug Administration (FDA)-approved fibromyalgia medication pregabalin alters the neural connections responsive to pain. Of note, these changes in neuroanatomy and function were associated with a reduction of “clinical” pain, as measured by a standard pain questionnaire, although the correlation between the reduced pain sensation and the neural changes was small enough that it could have occurred by chance. However, the findings of this small, 16-woman study reinforced the concept of brain “plasticity” and could provide the foundation for the development of targeted analgesics for patients with fibromyalgia or other chronic pain conditions (Puiu et al., 2016).

Osteoarthritis

Osteoarthritis is the most common form of arthritis. Nearly 27 million Americans ages 25 and older have OA. Before the age of 45, more men than women have OA; after age 45, it is more common

in women. Although OA can develop without any obvious trauma to a joint, people who have torn their anterior cruciate ligament (ACL) are at high risk of developing knee OA. The ACL is a flexible, stretchable tissue that tunnels through the knee, connecting the femur, or thigh bone, with the tibia, or shin bone. According to the American Academy of Orthopaedic Surgeons, female athletes who participate in jumping and pivoting sports, such as basketball and soccer, are between 2 and 10 times more likely to injure the ACL than male athletes who participate in the same sports. These types of injuries also increase the likelihood that a person will develop knee OA within one or two decades after the injury. Total joint replacement is the only treatment for end-stage OA. Data from the National Hospital Discharge Survey and the Healthcare Cost and Utilization Project State Inpatient Databases revealed that 7 million Americans, 4.4 million of whom were women, were living with a hip or knee replacement in 2010.

Testosterone Levels May Explain Sex Difference in Knee Injury Rates Leading to OA.

New data show that male rats without testosterone have weaker ACLs than those that have normal testosterone levels. Because researchers generally accept that a stronger ACL is less prone to injury, these results support a link between testosterone and ACL injuries. Additional work is needed to determine how testosterone and estrogen act to influence ligament strength and whether these hormones have the same impact on other ligaments. Eventually, the research could lead to techniques that use circulating sex hormone levels to identify athletes at higher risk for ACL injury who may benefit from training strategies to strengthen the ligament (Romani et al., 2016).

Re-Repairing ACLs with a Patient's Own Tissue Is Associated with Better Outcomes 2 Years Following Surgery.

When active people injure their ACL, surgery is often required to restore joint stability and function. ACL reconstruction surgery is generally successful and many athletes are able to return to competitive sport activities. However, reinjury could require a second ACL

reconstruction. As with initial repairs, surgeons can choose the source of the replacement tissue. In a study conducted by 83 sports medicine orthopaedic specialists at 52 academic sites or private practices around the United States, researchers demonstrated that autografts (i.e., the patient's own tissue) appear to be superior to allograft (cadaver donor tissue) in ACL revision surgery as well as for the initial repair. However, the impact of ACL revision surgery approaches on the development of OA will require many more years of follow-up (MARS Group, 2014).

Imaging Predicts the Onset of Knee OA.

Investigators recently demonstrated that changes in bone marrow detected by magnetic resonance imaging (MRI) are early warning signs of knee OA. This provides insight into the bone and joint changes that precede the cartilage degeneration traditionally thought to cause OA. The findings also open a window of opportunity for prevention before irreversible destruction of cartilage occurs. Although there are no disease-modifying OA drugs to slow or stop the progression of structural changes once they begin, aggressive behavior-based prevention strategies such as weight control and avoidance of potentially harmful activities could be implemented to delay or alter the course of OA development. The data and images used for this study came from the Osteoarthritis Initiative (OAI), a multicenter, longitudinal, prospective, observational study of knee OA that was launched by NIH in 2002 to develop a public-domain research resource to facilitate the scientific evaluation of biomarkers for OA as potential surrogate endpoints for disease onset and progression (Sharma et al., 2016).

OA Biomarkers Emerge from the OAI. The OAI also provided the data on which the Foundation for the National Institutes of Health Biomarkers Consortium based a privately funded study to determine which blood and imaging biomarkers should be used in future studies of OA. Unlike the structural changes seen on X-rays that have been used as markers in countless OA clinical studies, these newly identified markers seen only through MRI also correlated with the amount of

pain that patients experience. Ultimately, these and other markers that are emerging from the study could allow researchers to identify the molecular pathways that successful treatments could target and to improve the design of trials of disease-modifying agents (Eckstein et al., 2015; Hunter et al., 2016).

Readily Available Pain Medication, a Cost-Effective Choice for Many Older Adults with Knee OA.

Managing knee OA pain in older adults with coexisting health concerns, such as diabetes and heart disease, requires a delicate balance between pain relief and toxicity. Researchers now know that over-the-counter or prescription naproxen—with or without a proton pump inhibitor drug to ease gastrointestinal upset—is more cost-effective for this group than the opioid tramadol and the prescription-only nonsteroidal anti-inflammatory drug celecoxib. In addition, naproxen use was associated with lower rates of cardiac risks compared with celecoxib. Naproxen users also were more likely to continue to use the drug, compared with those who used tramadol. Ibuprofen-based treatments showed similar outcomes as naproxen-based treatments (Katz et al., 2016).

Small Molecules Improve Lubrication in Joints and Other Moving Surfaces.

Efficient strategies to improve lubrication and minimize friction in joints are expected to reduce tissue dysfunction, such as the progression of cartilage degeneration in OA. Hyaluronic acid (HA) is one of the major lubricating molecules found in the synovial fluid that surrounds the knee joint, and sometimes patients will have HA injected directly into their knees to provide better lubrication. To increase HA retention in the joints, researchers developed a short amino acid sequence (a peptide) that could bind collagen in joint tissues on one end and HA on another. Experiments using rat knees showed that the peptide captured HA and retained it in the joint for at least 12 times longer than unmodified HA. Additional experiments demonstrated that HA-binding via this peptide increased joint lubrication. Although improved lubrication was seen in healthy

and damaged tissue, the benefits were greater for the diseased cartilage (Singh et al., 2014).

Complication Rates Decrease as More Patients Choose High-Volume Hospitals for Hip and Knee Replacement Surgeries. Hospitals that perform large numbers of knee and hip replacement surgeries report lower complication rates and better patient outcomes from these procedures. From 2000 to 2012, an increasing number of patients chose to have their procedures at hospitals that performed more than 400 total hip and knee replacement surgeries per year (i.e., “high volume” hospitals). Although more than 80 percent of the U.S. population lives within 50 miles of a high-volume hospital, approximately 6 percent of people still elect to have these surgeries at lower volume hospitals—an observation that raises questions about factors that influence patient decisions about where they receive care (Laucis et al., 2016).

Osteoporosis and Fracture Risk

Osteoporosis, or porous bone, is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures of the hip, spine, and wrist. In the United States, more than 53 million people either already have osteoporosis, or are at high risk of developing the condition due to low bone mass. Osteoporosis can occur in both men and women and at any age, but it is most common in older women. Hip fracture is the most devastating consequence of osteoporosis; it leads to short- and long-term functional impairment, loss of ability to live independently, and even death. According to the Healthcare Cost and Utilization Project, there were more than 300,000 hospital admissions for hip fractures among people ages 65 and older in 2012; three-quarters of these fractures occurred in women (Agency for Healthcare Research and Quality, 2012). The incidence of hip fracture increases with age. Therefore, hip fracture is expected to become an even larger public health problem as the U.S. population ages.

Abnormal Bone Microarchitecture in the Extremities May Predict Increased Susceptibility to Vertebral Fractures in Postmenopausal Women. Osteoporosis is characterized by low bone mass and the deterioration of trabecular and cortical bone at common fracture sites such as the hip and spine. However, because the measurement of bone at these central sites requires greater radiation, measurement of the extremities as a surrogate for vertebral bone is an appealing alternative technique. Researchers used noninvasive powerful imaging tools to demonstrate marked differences in trabecular microarchitecture, cortical thickness, and stiffness at the radius and tibia between postmenopausal women with vertebral fractures and nonfractured controls. These newer tools to assess trabecular and cortical microarchitecture may prove helpful in predicting which vertebral fracture patients are most susceptible to hip and other fractures in the future (Wang et al., 2016).

Probiotics Prevent Menopause-Like Bone Loss in Female Mice. By studying mice raised in germ-free conditions (lacking a microbiome), mice raised in conventional conditions (having a normal microbiome), and mice raised in a germ-free environment that were later given a normal mixture of gut-colonizing microbes, scientists showed that gut microbiota play a critical role in sex steroid deficiency-induced bone loss. Importantly, when the diet of sex steroid-depleted mice with normal microbiota was supplemented with the probiotic *Lactobacillus rhamnosus* GG (found in some yogurt and cheese products), or the commercially available probiotic supplement VSL#3, the mice showed significantly strengthened intestinal barrier integrity, reduced signs of inflammation, decreased levels of proteins that stimulated bone destruction, and less bone loss than the control animals. The beneficial effects of the probiotics depended on the types of bacteria used: a strain of *Escherichia coli* bacteria (DH5-alpha), commonly used in the laboratory showed no beneficial effect, and a mutated strain of *L. rhamnosus* GG that does not adhere to the intestinal surface was less protective than the normal strain. These results demonstrate

the importance of gut microbiota to maintain bone health in mice and suggest that specific types of probiotics could be a potential therapeutic option for preventing postmenopausal bone loss (Li et al., 2016).

Rheumatoid Arthritis (RA)

Rheumatoid arthritis affects an estimated 1.5 million Americans. It is a debilitating autoimmune disease, characterized by chronic joint inflammation, in which the body's natural defense system attacks its own tissues. RA occurs in all races and ethnic groups. Although the disease often begins in middle age and occurs with increased frequency in older people, children and young adults also develop it. Like many other autoimmune diseases, RA occurs much more frequently in women than in men. About two to three times as many women as men have the disease.

A Link Between Powerful Gene Regulatory Elements and RA Revealed. Researchers combed the genome of a type of immune cells, called T cells, for DNA segments that can control gene activity. Several hundred of these segments were identified, and further analysis showed that they largely control the activities of genes that encode proteins known as cytokines and cytokine receptors. These types of molecules are important because they enable T cells to communicate with other cells to mount an immune response. The most striking observation was that many genetic alterations known to be associated with RA and other autoimmune diseases were located in the same regions identified by the study, suggesting that these areas contain DNA sequences involved in autoimmunity (Vahedi et al., 2015).

Genetic Variants May Protect Against RA and Other Autoimmune Diseases. International leaders of RA genetic research, including some supported by NIH, identified three variants of the gene encoding the protein tyrosine kinase 2 (TYK2) that protect against RA. Subsequent analysis showed that the variants also protect against lupus, and two of the three variants may protect against

irritable bowel disease (IBD). These results support a likely role for TYK2 in the pathogenesis of RA, lupus, and IBD and also highlight it as a potential drug target for autoimmune diseases (Diogo et al., 2015).

Rheumatoid Arthritis Disease Mechanisms May Differ Among Joints. Research conducted by NIAMS-funded scientists suggests that the behavior of cells in the joints of RA patients differs with the cells' location. The researchers examined the DNA methylation patterns of fibroblast-like synoviocytes (a type of cell that lines joints and contributes to joint destruction in RA) and found differences between cells obtained from the knees versus the hips of RA patients. Because methylation controls gene expression, these joint-specific patterns may help to explain why some joints improve, while others do not in response to a treatment (Ai et al., 2016).

Potential Drug Target Identified for RA Treatment. Although an errant immune system is thought to be the primary culprit in RA, fibroblast-like synoviocytes also contribute to the disease progression by invading joint cartilage and secreting damaging enzymes and inflammatory molecules. Researchers determined that a receptor called receptor protein tyrosine phosphatase sigma (RPTP-sigma), which is present at high concentrations in the cell membranes of fibroblast-like synoviocytes of RA patients, regulates the cells' invasiveness. Exposing cells to a decoy fragment of RPTP-sigma interrupted their interactions with molecules that activate RPTP-sigma, impaired their ability to infiltrate human cartilage, and reduced the severity of disease in a mouse model of RA. These findings suggest that fibroblast-like synoviocytes are regulated by a RPTP-sigma-dependent molecular mechanism, which could be targeted for RA therapy (Doody et al., 2015).

Metabolic Interventions Correct Dysfunctional Immune Cells in RA. NIAMS-supported researchers studying the role of the immune system in RA found that enzymes involved in how cells use energy are present at different levels in T

cells from RA patients compared with T cells from healthy controls. The researchers identified several energy metabolism components that play a role in the proliferative, as well as the proinflammatory and arthritis-promoting behaviors of RA T cells. Furthermore, small molecules were able to revert the metabolic abnormalities in RA T cells and reduce their proliferation and proinflammatory and arthritogenic functions. These results suggest that the metabolic abnormalities in RA T cells may be reversible and could be a potential target to correct abnormal cell behaviors that contribute to RA (Yang et al., 2016).

Imaging Studies Suggest Ongoing Inflammation Occurs in RA Patients While in Remission. A NIAMS-funded study using MRI to evaluate RA patients' responses to various treatments uncovered lingering signs of inflammation even when patients reported that their symptoms had improved. This suggests that joint destruction might continue even when patients appear to be in remission. Until this clinically important issue is clarified, physicians who want to withdraw or temporarily stop therapy for patients should carefully consider the possibility that the disease may continue to progress undetected (Ranganath et al., 2015).

Scleroderma/Systemic Sclerosis (SSc)

Scleroderma is a rare, severe, and heterogeneous autoimmune disease that involves progressive hardening of the skin and internal organs due to fibrosis. Systemic sclerosis (SSc) is one form of scleroderma and involves many parts of the body, such as skin, internal organs, and blood vessels. Women are approximately four times more likely than men to develop systemic SSc.

Experimental Compound Shows Promise in Reversing Skin Disease Associated with SSc.

Previous research in animals has implicated a protein called transforming growth factor beta (TGF- β) and two of the genes it regulates—thrombospondin-1 (*THBS1*) and cartilage oligomeric protein (*COMP*)—in the development of fibrosis,

but no clinical data have been found to directly support the role of TGF- β in humans who have scleroderma. To test whether TGF- β is involved in human disease, researchers examined the inhibitory effect of a not-yet-approved compound, called fresolimumab, in 15 patients (11 women) with early stage scleroderma. *THBS1* and *COMP* expression significantly declined 3–7 weeks after patients received the drug. In addition, skin condition improved clinically, further implicating these genes in skin fibrosis. The researchers report that this rate of fibrosis reversal had not been seen in any previous clinical trials. By week 24, however, patients began to experience disease recurrence as the effects of the drug diminished, indicating that future studies involving treatment with fresolimumab will need to be longer in duration. Also, a larger, placebo-controlled clinical trial is needed to confirm the findings (Rice et al., 2015).

Novel Antibodies May Contribute to Gangrene in SSc Patients. Although the percentage of patients with SSc who develop ulcers and gangrene in their fingers is small, this complication has a major impact on the patients' quality of life. Earlier studies demonstrated that antibodies to gamma-interferon-inducible protein 16 (IFI-16) are more prevalent in scleroderma patients who are at high risk of developing digital gangrene. Data from a recent paper suggest that anti-IFI-16 antibody levels change over time, peaking around the time of the digital gangrene event. These findings suggest that anti-IFI-16 antibodies may represent a longitudinal biomarker of ongoing and potentially severe vascular injury in patients with SSc and may offer insight into future therapeutic targets in patients with scleroderma (McMahan et al., 2016).

Systemic Lupus Erythematosus (SLE, Also Known as Lupus)

Lupus is a chronic autoimmune disease that, for unknown reasons, causes the immune system to mistakenly attack the body's own healthy cells and tissues. An estimated 90 percent of people diagnosed with lupus are women. Lupus is more prevalent in African-Americans, Hispanics, and

Asians. African-American women are three times more likely to develop lupus than Caucasian women. African-Americans and Hispanics/Latinas tend to develop lupus at a younger age and have more symptoms (including kidney problems) at diagnosis compared to other groups.

Bacterial Biofilms May Trigger Lupus. NIAMS-funded investigators have found that bacterial communities known as biofilms may play a role in the development of lupus. The researchers studied a protein, called curli, produced by certain gut bacteria. They found that curli-DNA complexes that are present in many commonly occurring bacterial biofilms can accelerate lupus pathology in mice that are prone to developing the disease, and can elicit autoimmunity even in normal control mice. The findings shed light on the role of microorganisms in lupus, and suggest that treating underlying infections may benefit people with the disease (Gallo et al., 2015).

IgE Autoantibodies Are Linked to Immune Responses in Lupus. Immunoglobulin E (IgE) antibodies are released by the immune system in response to allergens. Researchers found significantly increased autoreactive IgE levels in mice that spontaneously develop lupus-like disease, suggesting that IgE is involved in the development of lupus. When researchers impaired antibody production in the predisposed mice, the animals had fewer autoantibody-producing plasma cells, prolonged survival, and less severe disease. In addition, accumulation of immune cells in the spleen and lymph nodes was reduced, and activation of white blood cells called basophils was impaired. Importantly, data from the mouse model of lupus correlated with data from people with lupus. Compared with healthy controls, patients with elevated levels of autoreactive IgE displayed increased basophil activation and disease activity. Taken together, the data from this study demonstrate that elevated autoreactive IgE levels promote heightened autoimmune responses and suggest a critical role for IgE in the immune response to lupus (Dema et al., 2014).

IgE Autoantibodies Against DNA Are Associated with Worsening Lupus Inflammation. Building on findings that IgE autoantibodies against circulating fragments of double-stranded DNA are associated with increased lupus activity and kidney damage, investigators explored the mechanisms by which they might contribute to inflammation. The researchers determined that the autoantibodies provoked the generation of interferon (IFN)-alpha (a molecule that is thought to play a role in lupus pathogenesis) by a class of immune cells called plasmacytoid dendritic cells. This previously unrecognized link between IgE autoantibodies and the IFN pathway provides additional insight into the pathological mechanisms underlying autoimmunity, and might be useful in the rational design of therapies for treatment (Henault et al., 2016).

Risk of Kidney Failure in Lupus Patients Has Plateaued Since the Mid-1990s. More than one-half of patients with systemic lupus erythematosus develop nephritis, and this common complication increases the mortality risk more than 25-fold. Researchers in the NIAMS Intramural Research Program found that the risk of kidney failure decreased during the 1970s and 1980s, and plateaued in the mid-1990s. These results suggest that, while treatment advances have improved kidney outcomes for patients with lupus, the reason for the lack of further risk reduction in end-stage renal disease in the 1990s and 2000s is not known. These data may indicate that the effectiveness of current treatments has reached its limit and new treatments are required for additional improvement. Alternatively, the data may indicate a lack of progress in the delivery systems for existing treatments, either due to limited access to the treatments, or reduced patient adherence (Tektonidou et al., 2016).

Researchers Discover a Protein Associated with Lupus Nephritis. Kidney inflammation, or nephritis, continues to be a substantial source of both morbidity and early mortality in patients with lupus. Results using kidney biopsies from eight lupus patients showed that an autoimmune response to a protein called vimentin drove

tubulointerstitial inflammation (TII), a type of nephritis that can be a precursor to kidney failure. The findings suggest that circulating anti-*vimentin* autoantibodies could potentially serve as biomarkers of severe TII and predict which patients will develop kidney failure. Furthermore, this research also demonstrates the feasibility of an alternative approach for exploring the pathogenic mechanisms of lupus nephritis. Investigators traditionally answer questions about the molecular mechanisms of lupus by looking at antibodies and other molecules in the blood; in this case, they looked directly at the immune cells that had invaded the inflamed kidney tissue before examining whether the antibodies produced by these immune cells were in the blood (Kinloch et al., 2014).

Vitamin D Deficiency May Contribute to Cardiovascular Disease in Lupus Patients.

Systemic lupus erythematosus is associated with increased risk for cardiovascular disease (CVD), but the reason is not fully understood. Researchers from the NIAMS Intramural Systemic Autoimmunity Branch used lupus-prone mice to study the effects of vitamin D deficiency on CVD risk. Mice were fed a vitamin D deficient diet and analyzed for factors associated with CVD. Researchers observed that blood vessel relaxation and the formation of new blood vessels were decreased in vitamin D deficient lupus-prone mice, compared to vitamin D sufficient mice. Maturation of cells in the blood vessel walls was comparable between lupus-prone mice on either control or vitamin D deficient diets, suggesting the observed effects on blood vessels were not due to differences in cell viability. Expression of certain genes that responded to signaling molecules called type I interferons was increased in vitamin D deficient mice compared to control mice. Similarly, vitamin D deficient lupus patients showed similar gene expression changes compared with lupus patients who were vitamin D sufficient. This study provides evidence that vitamin D deficiency and the resulting increase in type I interferon gene signatures, contributes to a risk of CVD in lupus patients (Reynolds et al., 2016).

Many Women with Mild to Moderate Lupus Can Expect to Have Healthy Pregnancies. A large, long-term study among women with lupus has yielded important insights into how to predict who may develop pregnancy complications associated with the disease, and who are most likely to have healthy pregnancies. A related study identified key factors that may put a woman at risk for problems, allowing for early detection and monitoring. These findings should assure many women with mild or moderate lupus that they can pursue pregnancy provided they have appropriate medical care. The results also should reduce the need for lupus patients who are at low risk of complications to undergo frequent and costly prenatal monitoring (Buyon et al., 2015; Kim et al., 2015).

An FDA-Approved RA Drug Holds Promise as a Lupus Treatment.

Researchers from the NIAMS Intramural Research Program partnered with colleagues at NIH to investigate if inhibition of the Janus kinase (JAK) signaling pathway affects lupus onset and progression in a mouse model of the disease. Mice that received the JAK inhibitor tofacitinib prior to disease onset did not develop any signs of lupus. In addition, administration of tofacitinib after disease onset and symptom development resulted in a reversal of symptoms. These results demonstrate that tofacitinib is both a preventative and therapeutic strategy for the control of lupus in a mouse model. A study to test the safety of tofacitinib in lupus patients began in 2015 and is ongoing at the NIH Clinical Center (ClinicalTrials.gov, 2015).

NIH Strategic Plan for Women's Health Research

Although all of the accomplishments and activities described in this document relate to the goals and objectives outlined in the NIH Strategic Plan for Women's Health Research, the following efforts are particularly noteworthy. Both are examples of NIAMS-led strategic alliances and partnerships to maximize the domestic and global impact of women's health research (Goal 4).

NIH Develops a New Action Plan for Lupus Research. In response to a request from the Congressional Lupus Caucus, the NIH released its Action Plan for Lupus Research in January 2016. NIAMS led the development of this collaborative effort on behalf of NIH. The report, which represents a synthesis of internal and external input on promising future research directions to improve the lives of people with lupus, highlights many opportunities to better understand lupus at the molecular, individual, and population levels. Topics include research needs related to disease etiology, mechanisms, treatments, diagnostic approaches, and health services, as well as workforce issues and opportunities for partnerships (NIAMS, 2015).

NIAMS and the National Institute on Aging Lead a Pathways to Prevention Effort on the Appropriate Use of Pharmacologic Therapies for Osteoporotic Fracture Prevention. Despite short-term efficacy of osteoporosis therapies, data are limited to provide evidence for their safe and long-term use. The Pathways to Prevention effort on Appropriate Use of Pharmacologic Therapies for Osteoporotic Fracture Prevention will clarify major questions related to the safe, long-term use of pharmacologic osteoporosis therapies. Topics under consideration include the benefits and risks of long-term osteoporosis therapies; how these risks and benefits vary among populations; the prevalence of serious complications associated with pharmacologic fracture prevention strategies; the persistence of elevated risks of adverse events after discontinuation of therapy following long-term use; patient and clinician factors that impact the uptake of and adherence to osteoporotic therapies; and the utility of a risk/benefit modeling tool in facilitating informed/shared decision making between clinicians and patients about osteoporotic therapies.

Information Dissemination

Publications

Disseminating information about research progress continues to be an essential component of the NIAMS mission. ORWH has a long history of supporting the NIAMS-led NIH ORBD~NRC, which provides health professionals, patients, and the public with bone health resources. In FY 15 and FY 16, NIAMS updated almost 200 of its publications, many of which are focused on diseases or conditions that disproportionately affect women.

Social Media

NIAMS Hosts Osteoporosis Facebook Question and Answer Session. In partnership with the [National Osteoporosis Foundation](#) and the [National Bone Health Alliance](#), NIAMS hosted a bilingual Facebook discussion about osteoporosis on May 26, 2016. The partners solicited questions from Facebook followers for 2 weeks before the event and addressed those and other questions received during the session. The chat reached nearly 5,000 Facebook users. An archive of the chat is available at www.facebook.com/events/1585703731742560.

NIAMS Videos Feature Patients and Researchers

In FY 15, NIAMS launched a series of videos featuring patients who have participated in studies at the NIH Clinical Center and the study investigators. Four patient videos feature women who describe their experiences with clinical research after being diagnosed with lupus or giant cell arteritis (a type of vasculitis that disproportionately affects women). Others, such as a video of Dr. Mariana Kaplan discussing the role of mitochondria in autoimmune disease, highlight NIAMS investigators and their work. All of the videos are available through NIAMS' website and YouTube channel.

Funding Initiatives, Workshops, and Conferences

NIAMS Funding Opportunity Announcements

Rheumatic Diseases Research Resource-Based Centers (P30): In FY 15, NIAMS issued a funding opportunity announcement ([RFA-AR-16-002](#)) to invite applications for NIAMS Resource-Based Centers Program (P30) for rheumatic diseases research areas within its mission. The awarded Centers listed below will provide critical research infrastructure, shared facilities, services, and/or resources to groups of investigators conducting research on rheumatic diseases.

- Resource-Based Center for the Advancement of Precision Medicine in Rheumatology (Dr. Lindsey Criswell, University of California at San Francisco, Grant No. P30 AR070155)
- Joint Biology Consortium Resource-Based Center (Dr. Peter Nigrovic, Brigham and Women's Hospital, Grant No. P30 AR070253)
- Johns Hopkins Rheumatic Diseases Resource-Based Core Center (Dr. Antony Rosen, Johns Hopkins University, Grant No. P30 AR070254)
- Cincinnati Rheumatic Diseases Resource Center (Dr. Susan Thompson, Cincinnati Children's Hospital Medical Center, Grant No. P30 AR070549)

Centers of Research Translation (P50): In FY 15, NIAMS issued a funding opportunity announcement ([RFA-AR-16-001](#)) to invite applications for the Centers of Research Translation (CORT) (P50) program. Research topics could cover any area in NIAMS' mission. Two selected for funding (listed below) are related to diseases that disproportionately affect women. A second round of applications submitted under [RFA-AR-17-001](#) will be funded in FY 17.

- Center for Lupus Research (Dr. Maria Pascual, Baylor Research Institute, Grant No. P50 AR070594)

- University of Michigan Fibromyalgia Center of Research Translation (Dr. Daniel Clauw, University of Michigan, Grant No. P50 AR070600)

Participation in ORWH Funding Opportunity Announcements

NIAMS participated in the ORWH-led Administrative Supplements for Research on Sex/Gender Differences funding opportunity announcements ([PA-15-034](#) and [PA-16-066](#)) and Building Interdisciplinary Research Careers in Women's Health (BIRCWH) ([RFA-OD-15-001](#)).

Health Disparities

Several of the diseases mentioned above disproportionately affect women from underserved or underrepresented minority groups. NIAMS is committed to exploring genetic, biological, and environmental risk factors among different populations; conducting behavioral research into cultural issues that can influence disease management and outcomes (e.g., risk behaviors and medical compliance); investigating problems concerning access to care, including the impact of language barriers and cultural health literacy on health care delivery; and incorporating findings from these efforts into patient education strategies to promote healthy behaviors and improve lives. To meet an increasing demand for Spanish-language resources, NIAMS launched a Spanish-language portal on NIAMS' website in FY 15.

Publications

Over the past 2 years, NIAMS created approximately two dozen culturally and linguistically appropriate health information resources for African-Americans, Chinese, Hispanics/Latinas, Koreans, and Vietnamese, and distributed these resources through communication channels used by these groups. Many of the topics focus on diseases or conditions that disproportionately affect women. Examples of new and updated materials are listed on the next page.

Bone Health

- Osteoporosis and African-American Women
- 骨質疏鬆症與亞裔美國婦女 (Osteoporosis and Asian-American Women, Chinese)
- ¿Cómo se pueden prevenir las caídas y evitar posibles fracturas? Esenciales: hojas informativas de fácil lectura (How to Prevent Falls and Fractures. Fast Facts: An Easy-to-Read Series of Publications for the Public, Spanish)
- Lo que las personas con diabetes deben saber sobre la osteoporosis (What People With Diabetes Need to Know About Osteoporosis, Spanish)

Osteoarthritis and Total Joint Replacement

- 什麼是骨性關節炎？簡明讀物 為大眾準備的簡單易懂的讀物系列 (What Is Osteoarthritis? Fast Facts: An Easy-to-Read Series of Publications for the Public, Chinese)
- 골관절염이란 무엇인가? 빠른 참조: 일반 대중을 위한 읽기 쉬운 간행물 시리즈 (What Is Osteoarthritis? Fast Facts: An Easy-to-Read Series of Publications for the Public, Korean)
- ¿Qué es el reemplazo de cadera? Esenciales: hojas informativas de fácil lectura (What Is a Hip Replacement? Fast Facts: An Easy-to-Read Series of Publications for the Public, Spanish)
- Cirugía de reemplazo articular: Información básica de salud para usted y su familia (Joint Replacement Surgery: Health Information Basics for You and Your Family, Spanish)
- Viêm Xương Khớp Là Gì? Thông Tin Nhanh: Chuỗi Ấn Phẩm Dễ Đọc cho Công Chúng (What Is Osteoarthritis? Fast Facts: An Easy-to-Read Series of Publications for the Public, Vietnamese)

Scoliosis

¿Qué es la escoliosis? Esenciales: hojas informativas de fácil lectura (What Is Scoliosis? Fast Facts: An Easy-to-Read Series of Publications for the Public, Spanish)

Autoimmune and Rheumatic Diseases

- 何謂狼瘡？簡明資料：為大眾準備的簡單易懂的讀物系列 (What Is Lupus? Fast Facts: An Easy-to-Read Series of Publications for the Public, Chinese)
- 류마티스 관절염이란 무엇인가? 빠른 참조: 일반 대중을 위한 읽기 쉬운 간행물 시리즈 (What Is Rheumatoid Arthritis? Fast Facts: An Easy-to-Read Series of Publications for the Public, Korean)
- ¿Qué es la fibromialgia? Esenciales: hojas informativas de fácil lectura (What Is Fibromyalgia? Fast Facts: An Easy-to-Read Series of Publications for the Public, Spanish)
- ¿Qué es el fenómeno de Raynaud? Esenciales: hojas informativas de fácil lectura (What Is Raynaud's Phenomenon? Fast Facts: An Easy-to-Read Series of Publications for the Public, Spanish)
- ¿Qué es la esclerodermia? Esenciales: hojas informativas de fácil lectura (What Is Scleroderma? Fast Facts: An Easy-to-Read Series of Publications for the Public, Spanish)
- Bệnh Thấp Khớp Là Gì? Thông Tin Nhanh: Chuỗi Ấn Phẩm Dễ Đọc cho Công Chúng (What Is Rheumatoid Arthritis? Fast Facts: An Easy-to-Read Series of Publications for the Public, Vietnamese)

Social Media

NIAMS Participates in FDA Twitter Chat on Minority Women's Health. NIAMS participated in FDA's bilingual (English and Spanish) Twitter chat on minority women's health on April 19, 2016. NIAMS tweeted about its Spanish and Asian language publications and health issues of special concern to minority women, including lupus, fibromyalgia, and osteoporosis. Tweets from the chat can be viewed by searching for #FDAHealthChat on Twitter and scrolling down to the tweets for April 19, 2016.

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National Institute of Biomedical Imaging and Bioengineering (NIBIB)

Executive Summary

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) was established by law on December 29, 2000, and received its first appropriation and grant funding authority in fiscal year (FY) 2002. As NIBIB continues to mature and establish programs, funding opportunities have been developed to support a variety of scientific areas, including programs aimed at fostering women's health research.

NIBIB serves as the hub within the National Institutes of Health (NIH) for the coordination of biomedical imaging and bioengineering efforts. NIBIB fosters, conducts, supports, and administers research and research training programs in biomedical imaging and bioengineering by means of grants, contracts, and cooperative agreements; provides coordination, integration, and review of progress and planning of biomedical imaging and bioengineering research; formulates research goals and long-range plans with the guidance of the National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB); and sponsors scientific meetings and symposia, collaborates with industry and academia, and fosters international cooperation regarding biomedical imaging and bioengineering.

NIBIB continues to develop and support a research portfolio that pursues cutting-edge science in the area of women's health research and recognizes the significant potential of improved technologies in early disease detection. During FY 15 and FY 16, NIBIB funded grants that were focused on women's health research or technologies aimed at improving health care for women. These projects range from advanced imaging methodologies to tissue engineering activities designed specifically for women's diseases, such as breast cancer, and

diseases with profound consequences for women, such as sexually transmitted diseases.

The NIBIB Office of Program Evaluation and Strategic Partnerships (OPESP) serves as the primary link to the Office of Research on Women's Health (ORWH) through participation with the Coordinating Committee on Research on Women's Health and through informal interactions with ORWH colleagues. OPESP staff collaborate with NIBIB Program Directors to facilitate support of NIBIB-funded research and research training related to women's health and sex or gender influences, as well as career development for women in biomedical engineering. In one example of the collaboration, the Director of ORWH spoke at NACBIB about sex as a biological variable; members of her staff made a presentation to NIBIB Program Directors about how NIH-funded investigators must comply with policies related to sex as a biological variable. In addition, OPESP staff members work with NIBIB Program Directors to monitor grant compliance with inclusion policies for women and other groups.

Highlighted below are a few examples of new research and significant NIBIB research accomplishments related to women's health.

Accomplishments and Activities in Women's Health Research

Breast Cancer

A High-Resolution and High DQE Detector Optimized for Mammography Using Single-Shot Bidirectional Tricontrast Imaging (EB021125). This Small Business Innovation Research (SBIR) project is developing a high detective quantum efficiency (DQE) detector that is optimized to

enable clinical imaging with tricontrast imaging to provide three different modes of X-ray contrast: absorption imaging (currently used in medical X-ray imaging equipment), phase contrast (provides up to 1,000 times more contrast than current X-ray imaging techniques for soft tissue), and scatter contrast (provides information of features at dimensions smaller than the resolution of absorption and phase contrast). Bringing tricontrast capabilities to hospitals and clinics could have a dramatic effect on the diagnosis and treatment of breast cancer and osteoarthritis, because it has the potential to detect and monitor very subtle changes in soft tissue.

Node-Pore Sensing for Cellular Screening

(EB019181). The aim of this project is to develop node-pore sensing (NPS), a variation on flow cytometry cell screening to enable the differentiation of more than 10 cellular markers, surpassing the limit on current flow cytometry technology. NPS technology will assess differences in the mechanical properties of the cells, sorting them into subpopulations for downstream analysis and culture. NPS will first be developed and tested using breast-cancer cell lines, and the project will create an integrated platform for screening specific markers on cells. The goal is to be able to screen simultaneously, directly and without loss of sensitivity, for more than 10 specific cell-surface markers that indicate metastatic potential and sort cells into sub-populations of breast-cancer cell lines that have different malignancy and metastatic status. A better understanding of breast cancer cell characteristics and the heterogeneity of a patient's disease would likely lead to more personalized treatment.

An Activatable PET Tracer for Imaging PARP-1 Activity in Breast Cancer (EB018477). When cancer radiation therapy and chemotherapeutic agents damage a tumor cell's DNA, the enzyme poly (ADP-ribose) polymerase-1 (PARP-1), which is involved in DNA damage sensing and repair, is activated. Imaging cancer cells with probes that detect active PARP-1 could help monitor for early responsiveness to therapy and facilitate a

more personalized approach to cancer treatment. This research proposes to develop a novel PARP-1 responsive positron emission tomography (PET) tracer for live imaging of PARP-1 activity. This imaging approach is relevant to breast cancer because of its heterogeneity and range of sensitivities to different therapies.

Biomaterial-Based Breast Cancer Vaccine

(EB015498). Cancer cells are generally ignored by the immune system, because—for the most part—they more closely resemble cells that belong in the body than pathogens, such as bacterial cells or viruses. The goal of developing cancer vaccines is to provoke the immune system to recognize cancer cells as being foreign and attack them. This grant proposes a new approach to cancer vaccines, in which biomaterials that can be introduced into the body in a minimally invasive manner (via injection) are used to program, *in situ*, host dendritic cells to generate a potent cytotoxic T lymphocyte response. Biomaterial scaffold-based vaccines show significant potential in generating potent antigen-specific immunity. A recent finding from this award suggests that modifying the surface chemistry of the biomaterial scaffold can alter immune cell infiltration, which would have significant implications for the design of new biomaterial-based cancer vaccines.

MR Signal Amplification for Receptor Imaging

(EB000858). The magnetic resonance (MR) signal amplification (MRamp) strategy is designed to improve the molecular sensitivity of MR imaging by modulating the MR signal output. Better specificity and sensitivity are gained by using a pair of receptor-targeted enzymes that colocalize in the specific tissue compartment, resulting in rapid accumulation of paramagnetic substrates that lead to an amplified MR signal. This project capitalizes on the use of the MRamp technique for imaging of the epidermal growth factor receptor (EGFR) and other potential markers for metastatic breast cancer. EGFR is overexpressed in 15–20 percent of all breast carcinomas, and its expression level correlates with the ability of breast cancer to metastasize. A goal of this research is the

development of a new imaging capability for breast cancer treatment monitoring.

Ovarian Cancer

CTC Screening Assay to Address Health Disparities in Women with Ovarian Cancer (EB021212). This SBIR project is focused on developing an assay of circulating tumor cells (CTCs) to detect epithelial ovarian cancer (EOC) at an early stage. EOC has been called a “silent killer” because most women (> 70%) are diagnosed at a late stage of the disease due to a lack of a clinically sensitive and specific screening test and a lack of observed symptoms until late-stage disease onset. This project proposes to increase the sensitivity of current CTC technologies to detect disease at earlier stages. The CTC detection technology proposed will utilize a low-cost, disposable, plastic CTC fluidic cartridge possessing the ability to select and count CTCs directly from whole blood with high recovery (> 90%) and purity (> 85%). In addition, it is envisioned that the technology will provide a simple workflow with full process automation, ideal for a screening test that can be used in resource-limited settings.

Vascular Disease

Preclinical Investigation of a Bioengineered Vascular Graft (EB017129). Blockage of blood vessels due to atherosclerosis is a significant cause of disease often requiring graft vessel replacement or revascularization. Unfortunately, harvesting a patient’s own nondiseased vessel as a graft is often not an option, and synthetic grafts used to replace small-diameter blood vessels have high rates of failure. The goal of this preclinical award is to evaluate whether endothelial progenitor cell–derived bioengineered grafts are safe and efficacious in a preclinical model. The long-term goal of the work is the development of protocols that could be adapted for use in routine hospital settings. Because of the reported differences in the epidemiology and manifestations of vascular

disease in men and women, supplemental funding provided by ORWH is being used to investigate sex differences, such as cellular, clotting, and hormonal variations that can be used to optimize endothelial progenitor cell–derived bioengineered grafts.

Obstetrics

Low-Cost Handheld Medical Device for Neuroaxial Anesthesia Guidance in the Obese (EB015232). Epidural and spinal anesthesia often is performed by utilizing manual palpation of spinal bone landmarks to guide a needle. In overweight individuals, however, spinal bone landmarks may not be detectable by palpation. X-ray fluoroscopy can be performed to guide needle placement, but it lacks portability, has a higher cost, and exposes patients to ionizing radiation. An SBIR award recipient developed a handheld ultrasound device that uses a bone visualization algorithm and automatic detection of spinal bone landmarks to identify the needle injection site for epidural or spinal anesthesia. Potentially, this device may be used for challenging obstetric epidural or spinal anesthesia administrations. The company has received U.S. Food and Drug Administration 510(k) clearance for this handheld ultrasound device.

Sexually Transmitted Diseases

Center for Point-of-Care Technologies Research for Sexually Transmitted Diseases (EB07958). This center develops Point-of-Care (POC) tests to rapidly and accurately diagnose sexually transmitted diseases (STDs), with the goals of improving the sexual health of individuals and preventing the spread of these infectious diseases, both in the United States and in resource-poor settings throughout the world. This center will address the diagnosis of several STDs, including chlamydia, which is far more prevalent in women than in men, and trichomonas, a sexually transmitted parasitic vaginal infection. This center will conduct needs and health impact assessments and will collaborate with experimental and

computational scientists, clinicians, and patients to develop STD-diagnosing POC technologies for use in emergency departments, clinics, and at home.

NIH Strategic Plan for Women's Health Research

Most NIBIB-funded projects in women's health align strongly with Goal 2 of the ORWH Strategic Plan: "Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs." In particular, many projects align with Objective 2.6: "Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas, such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery."

An example of such a project is developing a mammography system that incorporates phase and scatter contrast with conventional absorption imaging. Many other projects funded by NIBIB align with Objective 2.7: "Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls." An example project aligning with this objective is the development of a novel biomaterial-based breast cancer vaccine.

Inclusion

The NIBIB Inclusion Policy Officer works closely with Program Directors and Investigators to ensure compliance with inclusion policies and to promote opportunities related to women's health research. NIBIB staff work with grantees to assure compliance with the policies on sex as a biological variable and on how developing technologies may be applied to support women's health.

Science, Technology, Engineering, and Mathematics (STEM) Training Efforts

NIBIB is committed to increasing the participation and success of STEM undergraduates. In 2015 and 2016, NIBIB supported contracts with the University of Maryland, Baltimore County and Savannah State University to enhance the training of minorities and underrepresented populations in science and engineering. These contracts are enabling the institutions to test the effectiveness of a concerted program that combines intensive recruitment and outreach efforts; strong faculty and peer-to-peer mentoring; exposure to academic and industrial research experiences; professional development counseling; and social networking to increase the number of underrepresented populations in STEM fields. We envision that outcomes and best practices developed by these institutions will inform the design of future programs to further increase the STEM diversity pipeline.

As part of its STEM training efforts, NIBIB continues to host an undergraduate prize competition for biomedical design projects. This annual competition, Design by Biomedical Undergraduate Teams (DEBUT) Challenge, receives numerous entries from across the country. The 2016 third-place DEBUT winner was an entry that integrates a speculum-fitted custom camera system with cancer-detection algorithms to create a handheld cervical cancer detection device that can be used with a smartphone. The cerVIA system seamlessly integrates into the visual inspection with acetic acid (VIA) workflow and fits within standard speculums. The custom camera system contains a light-emitting diode ring and diffusion filters to standardize input images for precancerous lesion detection, capturing images with similar brightness, hue, and saturation values. The algorithm then outputs heat maps to highlight problem areas that clinicians can use to make more informed diagnoses.

Funding Initiatives

In FY 15–16, NIBIB led and participated in several initiatives that addressed areas relevant to women's health.

NIBIB-Led Initiatives

PA-14-161 Translational Research to Help Older Adults Maintain Their Health and Independence in the Community (R01) and

PA-14-159 Translational Research to Help Older Adults Maintain Their Health and Independence in the Community (R21)

The National Institute on Aging and NIBIB published these R01 and R21 announcements for translational research that moves evidence-based research findings toward the development of new interventions, programs, policies, practices, and tools that organizations can use to help older adults in the community remain healthy, productively engaged, and living independently in their own homes. Approximately twice as many older women as older men live alone.

PAR-13-390 Indo-U.S. Collaborative Program on Low-Cost Medical Devices (R03)

This announcement encourages collaborative research and technology development between scientists and engineers in the United States and India to develop new, low-cost, and appropriate diagnostic and therapeutic medical technologies for low-resource settings and underserved populations in the two countries. The announcement supports a wide range of research, including maternal, neonatal, and infant health; cardiovascular diseases; cancer screening; and translational research.

RFA-EB-14-002 Blood Pressure Measurement Technologies for Low-Resource Settings in the United States and India (U01)

NIBIB initiated a new partnership with India's Department of Science and Technology to develop

new methods of measuring blood pressure. Technologies developed under this initiative should be mobile and usable at the point of care, and they should be affordable and appropriate for use in low-resource settings. The technologies developed under this announcement have wide applicability, including use in management of hypertension, a condition more prevalent in women than men ages 65 and older.

Joint Initiatives

PA-15-321 Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (Admin Supp)

This announcement is for administrative supplements for research grants to support individuals with a high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances. The purpose of these supplements is to encourage such individuals to re-enter research careers within the missions of all the program areas of NIH. This program will provide administrative supplements to existing NIH research grants for the purpose of supporting full-time or part-time research conducted by awardees to update their existing research skills and knowledge.

PAR-16-106 and PA-17-085 Rapid Assessment of Zika Virus (ZIKV) Complications (R21)

A possible association between ZIKV infection in pregnant women and severe microcephaly in their babies has been very concerning and prompted the World Health Organization to declare this potential association a public health emergency. Additionally, the virus detected in the blood has fueled growing concerns about the risk of transmission from transfusions, particularly for pregnant women. The purpose of this announcement is to provide support for research on ZIKV and its complications.

PA-14-358 Biology of the Temporomandibular Joint in Health and Disease (R01) and

PA-14-359 Biology of the Temporomandibular Joint in Health and Disease (R21)

The National Institute of Dental and Craniofacial Research and NIBIB released these announcements to encourage research advancing our understanding of the temporomandibular joint (TMJ) in health and disease and to stimulate research that complements previous efforts in this area. TMJ disorders are at least twice as prevalent in women as in men.

Health Disparities

RFA-EB-15-001 and RFA-EB-16-001 Development and Translation of Medical Technologies to Reduce Health Disparities (SBIR) (R43/R44)

The National Institute on Minority Health and Health Disparities and NIBIB sponsored an announcement focused on reducing health

disparities through the development and translation of appropriate medical technologies, new or existing, that can have a significant impact on health care access and health outcomes alleviating health disparities. An example project funded from this initiative is a low-cost handheld medical device for neuroaxial anesthesia guidance that could be used in obstetrics (EB015232).

PA-16-288 Research Supplements to Promote Diversity in Health-Related Research (Admin Supp)

NIBIB participates in this announcement for research supplements to promote diversity in health-related research by funding underrepresented minorities and women. As this funding opportunity announcement points out, women from disadvantaged backgrounds face particular challenges at the academic graduate level and beyond. Supplements are available to a broad range of grant mechanisms.

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Executive Summary of Women's Health and Sex/Gender Influences on Health and Disease

The mission of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is to ensure that every child is born healthy and wanted; that women suffer no harmful effects from the reproductive processes; that all children can achieve their full potential for healthy and productive lives, free from disease or disability; and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation. NICHD supports essential research that plays a unique role in women's health, aiming to overcome many of the complex challenges that women encounter over their lifetime. NICHD is home to much of the Nation's leading science related to women's overall health, gynecological health, pregnancy, and childbirth, as well as studies of sex/gender influences on diseases and conditions related to pediatric and adolescent health, and medical rehabilitation.

NICHD supports a wide-ranging research portfolio in women's health. Among the Institute's major research areas are: preconception care; pregnancy; maternal health; gynecological conditions (including vulvodynia, pelvic floor disorders, impaired fertility, uterine fibroids, and endometriosis); HIV and its associated coinfections as they affect women; and other critical aspects of women's health. NICHD incorporates analysis of sex as a biological variable throughout its extensive portfolio, including areas such as pediatrics, medical rehabilitation, and population health. A strong Institute priority is training the next generation of researchers in women's health, with a special emphasis on career-

building for women scientists. Furthermore, the Institute maintains multiple, diverse outreach and dissemination activities to share research results and health information with the general public. NICHD research and research training are conducted primarily in the following seven major Institute programs, although interest in women's health extends across the Institute.

The Gynecologic Health and Disease Branch (GHDB). GHDB focuses on basic science, translational and clinical research, and research training programs related to gynecologic health in women and adolescent girls. The Branch portfolio emphasizes studies of the menstrual cycle, uterine fibroids, endometriosis, polycystic ovary syndrome, pelvic floor disorders, and menopause transition/perimenopause, as well as mechanistic studies of underlying chronic pelvic pain, vulvodynia, and dysmenorrhea. The Branch also supports research training and career development programs of investigators interested in women's reproductive health (www.nichd.nih.gov/about/org/der/branches/ghdb/Pages/overview.aspx).

The Contraceptive Research Branch (CRB). CRB develops and supports research and research training programs in contraceptive development. Major research areas include studies of: new contraceptive methods (female and male); mechanisms of action and effects of contraceptive and reproductive hormones, drugs, and devices; and procedures, as well as optimal formulation and dosage of contraceptive agents and spermicidal microbicides (www.nichd.nih.gov/about/org/der/branches/crb/Pages/overview.aspx).

The Fertility and Infertility Branch (FI). FI supports scientific research aimed at alleviating human infertility, uncovering new possible pathways to control fertility, and expanding fundamental

knowledge of processes that underlie human reproduction. FI emphasizes basic, clinical, and translational studies to enhance understanding of normal reproduction and reproductive pathophysiology, as well as enable the development of more effective strategies for the diagnosis, management, and prevention of conditions that compromise fertility, with the ultimate goal of promoting a better quality of life for all individuals (www.nichd.nih.gov/about/org/der/branches/fi/Pages/overview.aspx).

The Maternal and Pediatric Infectious Disease Branch (MPIDB). MPIDB develops and supports a wide range of domestic and international research related to the epidemiology, diagnosis, clinical manifestations, pathogenesis, transmission, treatment, and prevention of HIV infection and associated coinfections (such as tuberculosis [TB], malaria, and hepatitis), as well as noninfectious complications of HIV in pregnant and non-pregnant women, infants, children, adolescents, and the entire family unit (www.nichd.nih.gov/about/org/der/branches/mpidb/Pages/overview.aspx).

The Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB). OPPTB promotes basic, translational, and clinical research to improve the safety and efficacy of pharmaceuticals, and to ensure centralization and coordination of research, clinical trials, and drug development activities for obstetric and pediatric populations. The Branch is responsible for developing and supporting a comprehensive national effort to increase the knowledge base for understanding how to treat disease appropriately during pregnancy as well as infancy and childhood, using pharmaceuticals carefully tested for safety and efficacy in their target populations (www.nichd.nih.gov/about/org/der/branches/opptb/Pages/overview.aspx).

The Pregnancy and Perinatology Branch (PPB). PPB seeks to improve the health of mothers and children by supporting research in maternal health, pregnancy, fetal well-being and labor and delivery, as well as neonatal and infant health and well-being, and the long-term health outcomes

associated with pregnancy and maternal health across the lifespan (www.nichd.nih.gov/about/org/der/branches/ppb/Pages/overview.aspx).

Additionally, the *NICHD Division of Intramural Research (DIR)* conducts interdisciplinary research in both basic and translational science to enhance the understanding of the biology of development and reproduction. The Division strives to understand the basics of science through research in cell biology and metabolism, molecular medicine, genomics, and developmental endocrinology. The intramural Program in Perinatal Research and Obstetrics studies pregnancy and pregnancy complications, including the long-term effects of preeclampsia on maternal health (www.nichd.nih.gov/about/org/dir/Pages/index.aspx). The NICHD Division of Intramural Population Health Research designs and conducts innovative etiologic and interventional research from preconception through adulthood, focusing on successful reproduction, the health and well-being of pregnant women and their infants, and related areas across the lifespan (www.nichd.nih.gov/about/org/diphtr/Pages/default.aspx).

Accomplishments and Activities

NIH Strategic Plan for Women's Health Research Priority Programmatic Activities

NICHD Highlights: Research on Women's Health

PregSource[™]. This innovative NICHD project is based on the method of crowdsourcing by collecting a wide range of data from pregnant women to enhance the understanding of what normal pregnancy is like versus what can cause adverse complications during pregnancy. The project's methodology and unique new data resources are expected to support the Strategic Plan Objective 2.3, "Develop the information systems needed for collecting, sharing, and comparing clinical data for diseases and conditions of women

and girls,” and Objective 3.4, “Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.” The initiative design leverages social media to create a unique national registry allowing researchers with appropriate confidentiality and consent policies to hear directly from women about their experiences during pregnancy, including preterm and term births. Throughout their pregnancy, participants will enter information into online surveys and trackers via a website and/or mobile applications (“apps”). As a result, participants can track their pregnancy data over time, print out reports to share with their health care providers, and compare their data to that of other women in the initiative’s database. In addition, the project will provide participants with links to trusted, evidence-based information from partner organizations about healthy pregnancy and pregnancy-related complications. After a critical mass of data is collected, de-identified data will be available to researchers for analysis. The project will become available to the public in FY 17 (www.clinicaltrials.gov/ct2/show/NCT02577536).

NICHD National Child and Maternal Health Education Program (NCMHEP). NICHD activities in this area are responsive to Strategic Plan Objective 5.1, “Serve as a key informational resource for Federal and state agencies, elected representatives, the media, health and advocacy organizations, and the public on women’s health research issues,” and Objective 4.4, “Create solid partnerships by engaging in scientific briefings and *ad hoc* meetings with policymakers, elected officials, and advocacy groups.” NICHD brought together more than 30 of the Nation’s most prominent maternal and child health care provider associations, Federal agencies, and other organizations to create the NCMHEP partnership. Program objectives are to identify key challenges in maternal and child health, review relevant research gaps, initiate activities, and propose solutions. NCMHEP’s most recent initiative, “Mom’s Mental Health Matters,” aims to help women recognize signs of depression and anxiety during or following pregnancy, and to know how to

get the help they need. The program also continued its focus on the preterm period of birth, with online public information about the importance of waiting to deliver until at least 39 weeks of pregnancy for most pregnancies, to protect the health of the mother and the baby (www.nichd.nih.gov/ncmhep/Pages/index.aspx).

Outreach to Stakeholders. Also responsive to Objective 5.1 is NICHD’s ongoing information updating of policymakers, elected officials, and constituency groups, and responding to their queries about ongoing research and emerging issues and priorities. For example, in June 2016, NICHD worked with the Friends of NICHD to hold a Congressional briefing called *Research from A to Zika*. With the American Physical Therapy Association and other groups representing people with disabilities, NICHD rolled out the NIH Research Plan on Medical Rehabilitation on Capitol Hill. The plan specifically recommends including more women (and other specific populations) in rehabilitation research.

The Human Placenta Project is responsive to Strategic Plan Objective 2.5, “Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis and treatment of diseases and conditions in women and girls.” The placenta is the least understood human organ because up until now, scientists have lacked the technology and techniques to study the placenta throughout pregnancy and detect the earliest signs of risk for the pregnant woman and/or the fetus. The initial goals of NICHD’s Human Placenta Project include developing new non or minimally invasive technologies for the real-time *in vivo* assessment of placental development, and evaluating markers for the prediction of adverse pregnancy outcomes. Moreover, the project aims to improve understanding of the contributions of placental development to long-term health and disease of women and their offspring (www.nichd.nih.gov/research/HPP/Pages/default.aspx). NICHD issued multiple funding opportunity announcements (FOAs) for this project in FY 15–16 (see the next page).

NICHD Highlights: Research on Sex/Gender Influences on Health and Disease

Research on the Health of Sex and Gender Minority (formerly LGBTI) Populations. Research in this area is responsive in part to Strategic Plan Objective 1.8, “Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being.” The research focuses on behavioral, social, biological, and clinical processes that affect the health and development among lesbian, bisexual, and transgender women as well as other sexual and gender minority populations. This research will be essential to developing effective supportive, preventive, and treatment interventions and health service delivery methods that will enhance health and mitigate or prevent health risk factors for these populations (see also Funding Opportunity Announcements below).

Sex/Gender Influences on Health and Disease.

Activities in this area include research on disorders or differences of sex development (DSD), sometimes referred to as “intersexuality.” Research in this area is responsive in part to Strategic Plan Objective 1.1, “Encourage genetic and epigenetic studies to identify sex differences in gene expression” and also in part to Objective 1.7, “Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues and organs...” In focusing on atypical developmental processes from the earliest sex determination and differentiation to the phenotypic level in the approximately 40 congenital conditions known collectively as DSD, this research also can inform the understanding of typical developmental processes that may underlie sex and gender influences on human health and disease. Examples of individual grants in this area include the following:

- *Neuroendocrinology, Sex Differences, and Reproduction.* This pre- and postdoctoral training program provides the next generation of investigators with intensive training and mentoring in how, among other things, hormones and sex chromosome genes produce

sex differences that influence the basic function of organs and the susceptibility to disease (T32HD007228). This program also is responsive to Strategic Plan Objective 1.5, “Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders.”

- Grants that were responsive to Strategic Plan Objective 1.9, “Incorporate sex/gender considerations into discussions in scientific conferences and meetings” included:
 - *Organization for the Study of Sex Differences Annual Meeting*, supported by NICHD, the National Institute on Aging, the National Institute on Drug Abuse, and the Office of the Director (R13HD080243).
 - *TRN Symposium 2016: Consensus Study Group Meeting for the Care of Girls and Women with Turner Syndrome*, supported by NICHD and the National Center for Advancing Translational Sciences. Turner syndrome is a complex, multisymptom condition, affecting only girls and women who lack or have a missing part of their X chromosome (R13HD089663).
 - *7th International Symposium on the Biology of Vertebrate Sex Determination*, supported by NICHD, brings together senior and junior researchers to advance understanding of the processes of sex determination and sex differentiation, which establish characteristics that differentiate female and male phenotypes at the earliest stages of development (R13HD085723).

NICHD Accomplishments: Scientific Research Advances in Women’s Health

Contraception

Prior Use of Oral Contraceptives Is Not Associated with a Risk of Birth Defects. A very large NICHD-supported study from Denmark has indicated that the use of oral contraceptives around the time of

conception does not increase the risk of having a child with a major birth defect. Despite decades of use of these contraceptives, it has not been clear whether their use around the time of contraception increases the risk of such defects (Charlton et al., 2016).

A Change in Texas Women's Health Program Decreased Long-Acting Contraception and Increased Birth Rates. Interviews by NICHD-supported researchers of a large cohort of postpartum women in Austin, Texas, indicated that two-thirds of the women studied were unable to access their preferred method of long-acting or permanent contraception, especially because of financial barriers. The study was designed to determine the effects of the state's decision in 2012 to reduce Federal funding for its family planning program, which it restructured to make organizations that provided abortions, in addition to cancer screening, contraception, and other women's health services, ineligible for state funds. By analyzing medical claims data, the researchers found that the use of the most effective long-active contraceptive products had declined and the birth rate increased (Potter et al., 2016).

Endometriosis^a

Endometriosis Is Linked to an Increased Risk for Heart Disease. A new examination of health and lifestyle data collected from female nurses for more than two decades, until 2009, found that women with endometriosis were at an increased risk of developing coronary heart disease, compared with women without this painful gynecologic condition. A possible explanation of this risk was the increased frequency and earlier age at which the women with endometriosis underwent a hysterectomy, which included removal of the ovaries. Such "surgical menopause," with the loss of endogenous hormones and extended use of hormone replacement therapy, were independently associated with increased cardiovascular disease (CVD) risk. Researchers recommended careful consideration of surgery for endometriosis as well

as choosing a heart-healthy lifestyle and periodic checkups for early stages of heart disease (Mu et al., 2016).

Identifying the Source of Inflammatory Cells in Endometriosis. To understand the origins of endometriosis, researchers worked with an experimental model of endometrial stromal fibroblasts (eSF), which perform a number of tasks during pregnancy, such as helping to create a blood supply for the embryo. In endometriosis, these cells are unable to respond to progesterone and do not function properly, leading to infertility or poor pregnancy outcomes. With the experimental model, using tissue samples from women with or without endometriosis, the researchers found that the eSF develop from a type of cells—mesenchymal stem cells (eMSC), that promote tissue repair and regeneration after menstruation. They also found that in endometriosis, eSF lose the ability to respond to progesterone during the eMSC stage and further; inflammatory behavior associated with endometriosis occurs relatively late in this cellular process. Identifying the origin of abnormal endometrial cells and understanding their response to progesterone may help to identify promising targets for future therapies (Barragan et al., 2016).

Fertility and Infertility

Egg Freezing in a Woman's 30s Is More Cost-Effective than In Vitro Fertilization at Age 40. Although recent data indicate that egg freezing, as a way to extend a woman's capacity to have a child, yields increased pregnancy rates comparable to those of *in vitro* fertilization (IVF) using eggs taken directly from a woman's body. Both methods are expensive; however, data have been lacking on whether one is more cost-effective than the other. Researchers recently reported that their mathematical model predicted that egg freezing up until a woman is age 30, would increase the probability of a woman later having a baby, while decreasing the cost per live birth, compared with trying to conceive naturally or undergoing IVF at age 40 (Devine et al., 2015).

^a See also Osteoporosis and Bone Health below

Incontinence

Bacteria May Be Related to an Overactive Bladder, Even Without Symptoms of Infection. A recent study found that women with the difficult-to-treat condition, “overactive bladder” (urgency urinary incontinence), may have bacteria in their bladders that may cause the condition, even without any signs of infection. Researchers found the bacteria in the urine of about one-half of the women in a recent study. Those with the bacteria had more daily episodes of incontinence, responded better to treatment, and were less likely to develop a urinary tract infection compared to those without the bacteria (Pearce et al., 2015).

Surgical and Injection Treatments Is Equally Effective for Urinary Incontinence in Women. A comparison of two common approaches to treating urinary incontinence in women found advantages and disadvantages for both options. For women for whom initial treatments with muscle training and/or medication had failed, Botox injections were somewhat more effective than surgery in reducing episodes of incontinence, but carried a higher risk of urinary tract infections. There is information that can help women and their physicians make more informed choices regarding urinary incontinence (Amundsen et al., 2016).

International Women’s Health

In Low- and Middle-Income Countries, One in Four Pregnant Women Faces Depression. More than 100 studies, between 1998 and 2005 in Africa, Asia, Latin America, The Middle East, the Caribbean, and Oceania documented relatively high levels of depression among women. As many as 25 percent of women in these low- and middle-income countries reported depression, with about 20 percent of mothers reporting depression in their first year after their child’s birth. Researchers hoped that their findings would draw attention to the need for depression screening tools and prenatal health care programs that diagnose and treat depression

in these countries, where such programs are often the first source of medical care that women receive (Gelaye et al., 2016).

Maternal Mortality

Increase in the United States Maternal Mortality Rate. Two groups of researchers recently reported that in the United States, deaths related to maternal complications have been historically underreported, and appear to have been rising at a time when maternal mortality outside the United States has been falling. The two groups used different methods to interpret complex U.S. vital statistics data on maternal mortality and consequently arrived at somewhat different conclusions. One group attributed the apparent increase more to better maternal death surveillance while the other, acknowledging improvements in such surveillance, still considered that U.S. maternal mortality has been “moving in the wrong direction” from 2000 to 2014. Of note, the second group found that maternal mortality in California had declined, while rising elsewhere in the United States (MacDorman et al., 2016; Joseph et al., 2017).

Mental Health^b

Size of Fragile X Mutations Correlates with Risk for Psychiatric Disorders. Some women who carry a “permutation” version of the gene that causes Fragile X syndrome and its associated conditions are at risk for psychiatric conditions, such as anxiety, depression, and obsessive-compulsive disorder. To assess the relationship between the risk of these disorders and the magnitude of the abnormality in the permutation gene, researchers found that women with a permutation in the midsize range of abnormal “repeats” in the gene were at greatest risk of developing the psychiatric disorders. These findings could help identify women with permutations that place them at risk of the disorders, so that clinicians can ensure that they receive appropriate care (Loesch et al., 2015).

^b See also the aforementioned International Women’s Health, and below, Pregnancy, Health Disparities

Osteoporosis and Bone Health

Osteoporosis Is Linked to High Levels of Homocysteine, an Indicator of Poor B-Vitamin Status. Women with high blood levels of the amino acid homocysteine, which is an indicator of inadequate B-vitamins status, are twice as likely as others to have lumbar spine (lower back) osteoporosis compared to other women. This finding emerged from a large study of bone health in a representative sample of U.S. women, which focused on whether high levels of homocysteine, which is associated with such health risks as renal (kidney) disease, might be implicated in osteoporosis. High levels of the amino acid is used as an indicator of vitamin B12 status, which also is of interest in osteoporosis, but the researchers did not find that low B12 blood levels were associated with the bone disorder (Bailey et al., 2015).

Estrogen Addition Can Prevent Bone Loss in Young Women Treated for Endometriosis. “Add-back” therapy, in which estrogen is added to progesterone therapy for endometriosis treatment in adolescent women, appears to counter the risk of bone loss associated with the use of progesterone alone, according to a relatively small clinical trial. A comparison of the two hormonal therapies indicated that both were effective in reducing the painful symptoms of endometriosis, but the addition of the second hormone to progesterone was more protective against loss of bone mineral density. This combination therapy had been found effective in adult women, but its efficacy in adolescents had not been shown (DiVasta et al., 2015).

Pelvic Organ Prolapse

Surgery for Pelvic Organ Prolapse and Improved Quality of Life. In a follow-up of a large clinical trial that compared two common surgical techniques to repair pelvic organ prolapse, researchers found that 2 years after surgery, women still experienced improved quality of life and sexual functioning, as originally reported (Lukacz et al., 2016).

° See also Health Disparities

Preeclampsia

A Preliminary Study of a Drug for the Prevention of Preeclampsia in High-Risk Pregnant Women. A preliminary trial in a small cohort of women at high risk of preeclampsia has shown that the drug Pravastatin, typically used to reduce the risk of CVD, appeared to prevent preeclampsia. The high-risk women were those who had previously experienced preeclampsia, a dangerous spike in a pregnant woman’s blood pressure and related symptoms. None of the high-risk women taking the Pravastatin developed preeclampsia, while 40 percent of those in the placebo group did experience preeclampsia; this is about the same rate of occurrence as in the general population. Having found no safety risks, as well as first evidence of efficacy, for the drug, researchers plan research to more fully assess the safety and effectiveness of the drug against preeclampsia (Costantine et al., 2016).

Identifying a Biomarker for Preeclampsia. Apart from a prior history of preeclampsia, clinicians and researchers have generally lacked reliable methods to identify pregnant women at risk of this potentially life-threatening condition before it occurs. In a recent study, researchers focused on copeptin, a molecule in the hormone arginine vasopressin, which acts on multiple systems in the body to increase water retention and blood pressure. They found that higher concentrations of the molecule were associated with preeclampsia, and these higher levels were evident before preeclampsia was diagnosed, suggesting that copeptin could be a valuable tool to identify women at risk before they develop clinical symptoms of the condition (Yeung et al., 2014).

Pregnancy^c

The Risk of Persistent Opioid Use Following Cesarean Delivery Is Low. Although opioids are typically prescribed for serious pain from short-term illness, clinicians have generally not been able to identify patients whose short-term use of the painkillers could progress to an addiction. A new study of clinical and prescription records

for more than 80,000 women, insured by a large health plan, found that only one in 300 women who were prescribed opioids after cesarean delivery became persistent opioid users. They found that women with preexisting mental health conditions, certain pain conditions (e.g., migraine) or a history of substance abuse were more likely to become persistent users. These findings should help clinicians consider prescribing opioids after a cesarean delivery (Bateman et al., 2016).

Pregnancy Complications Can Indicate Increased Risk of Heart Disease Later in Life. Certain complications of pregnancy, notably preeclampsia, hemoglobin decline during pregnancy, and preterm birth put women at risk for CVD years or decades after they have given birth. This was the result of analyzing data from pregnancy complications in more than 14,000 who were included in a nearly 10-year pregnancy study, and data from the death certificates of the research participants. The research findings suggest careful monitoring of women for signs of CVD after they have experienced pregnancy complications (Cirillo et al., 2015).

Antipsychotic Use During Pregnancy and the Risk of Congenital Malformations. Studies of antipsychotic drug use during early pregnancy have yielded only limited and conflicting data on whether the drugs increase the risk of birth defects in the developing fetus. Now, an analysis of medical records of more than a million pregnant women and their offspring has provided clearer information on the risks of individual antipsychotic drugs, which are used to control such serious psychotic symptoms as hallucinations and paranoia. For the more than 9,000 women taking the drugs, the risk of congenital malformations in their children was 44.5 per 1,000 live births, compared to 32.7 per live births in women not taking the drugs. The researchers noted that although these drugs should be avoided if possible during pregnancy, avoidance is frequently not possible when serious disorders such as schizophrenia pose a risk to mother and child (Huybrechts et al., 2016).

Pretreatment with Azithromycin Lowers Infection Rate After a C-Section. When a dose of the antibiotic azithromycin was added to the standard preventive dose of the antibiotic cephalosporin before unplanned cesarean deliveries, the two-antibiotic regimen reduced post-cesarean infection rates by about 50 percent, compared with infections in women treated only with cephalosporin. There were no differences in the rates of complications among newborns of women in each group (Tita et al., 2016).

Uterine Fibroids

Biomarkers for Cellular Precursors of Fibroid Cells Identified. Researchers have identified two specific cells among the cells that form uterine fibroids that show characteristics of stem/progenitor cells. These are cells in their formative status—before they become fully “committed” to the type of cell they are genetically programmed to become. The cells, known as CD34 positive/CD49b positive for their genetic identity, are “tumor-initiating” cells. Understanding how to block their function could reveal better ways to treat, or even prevent, uterine fibroids. These benign tumors of the uterus can cause severe pain and infertility, are the leading cause of hysterectomy, and occur in about 77 percent of women in the United States (Yin et al., 2015).

Vulvodynia and Pelvic Pain

Variability in Vulvodynia Symptoms. A 3-year study of vulvodynia symptoms in a group of women in Michigan indicates that the condition—persistent pain without apparent cause in the external genital area in women—is a heterogeneous disorder that varies among affected women. Periodic surveys of the women found that although they commonly experienced remission of vulvodynia symptoms, more than one-half reported a return of symptoms within 6 to 30 months. Those who experienced such relapse were more likely to have additional conditions associated with vulvodynia (e.g., fibromyalgia), and have more severe and

long-lasting pain than those without relapse. The researchers also proposed two empirically identified subgroups of affected women. One group differed from the other in having such comorbid conditions and also spontaneously occurring pain (as opposed to pain that is “provoked” by touch or pressure). This group also had greater morbidity in different types of vulvar pain and general health. The new subgroup characterizations may enable the field of obstetrics to more effectively match vulvodynia therapies to the disease processes that underlie vulvodynia symptoms (Reed et al., 2016; Reed et al., 2016).

Pelvic Pain is Common Among Reproductive-Aged Women. Among women scheduled for surgery or imaging procedures for a variety of gynecological concerns (e.g., infertility, menstrual irregularities, tubal sterilization, or pelvic pain), researchers found that reports of pain were highest among women with endometriosis, but one-third of the women without any pelvic condition also reported a high degree of ongoing pelvic pain or pain during the menstrual cycle. It may be useful, according to the researchers, for clinicians to specifically ask women about pelvic pain, even during routine office visits (Schliep et al., 2015).

NICHD Scientific Research Advances in Sex/Gender Influences on Health and Disease

Exome Sequencing for the Diagnosis of Disorders of Sex Development. Research on the disorders of sex development may increase the understanding of sex/gender influences on health and disease by providing new information on the earliest developmental processes that determine an individual’s biological sex. DSDs comprise of approximately 40 rare congenital conditions in which atypical fetal development may make it difficult to determine if a newborn is male or female; a DSD may not emerge later until an affected girl fails to begin menstruation. A DSD diagnosis can be difficult, time-consuming, and ultimately inconclusive. Recently, researchers

demonstrated that large-scale genetic testing, known as exome sequencing, could identify significantly more genetic mutations associated with a specific DSD than were previously known. The immediate benefits to patients that are participating in the study could, in some cases, support their gender identity with a better understanding of treatment options (e.g., hormone replacement) (Baxter et al., 2015).

Sex Differences in Neurofibromatosis Type I. Researchers recently found that the rare genetic condition, neurofibromatosis 1 (NF1), compromises the vision of affected girls more than that of affected boys. Medical records of a large group of children with NF1 showed that both girls and boys developed tumors (optic gliomas) on the nerve that leads from the eye to the brain (optic gliomas) but only the girls had been treated for visual decline. The researchers also found that in genetically engineered mice that were to have the mouse equivalent of the disorder, only the females had reduced visual acuity. In addition, male but not female mice had learning and memory deficits (Baxter et al., 2015).

Markers for Bone Health in Adults Are Apparent in Children. In a search for genetic variants in children comparable to those known to be associated with low bone density in European adults, U.S. researchers found genetic changes that were associated with increased bone density in children and in adolescent females but not males. The findings provide evidence that genetic variants associated with bone mass in adults also affect childhood bone health, and may be protective against development of osteoporosis in adulthood (Mitchell et al., 2016).

Career Development for Women in the Sciences^d

Building Interdisciplinary Research Careers in Women’s Health (BIRCWH) Program. NICHD participates in the BIRCWH program, which is led by ORWH, along with nearly a dozen other NIH Institutes and Centers. BIRCWH research centers

^d See also the Executive Summary

provide “bridging support” to physician-scientists as they move between completion of clinical or postdoctoral training and an independent research career. BIRCWH research subjects span the spectrum of women’s health topics and the program is open to all types of clinicians and non-clinicians. (orwh.od.nih.gov/career/mentored/bircwh)

Reproductive Scientist Development Program (RSDP). The NICHD FI Branch continued to support a national career development program with the goal of developing a cadre of reproductive physician-scientists based in academic departments who could employ cutting-edge cell and molecular technologies to address important problems in the field of Obstetrics and Gynecology (OB/GYN). The mentored research experiences this program offers seek to assist junior faculty in their transition to productive, independent physician-scientists who are highly competitive for research funding. The program accepts approximately four scholars each year for a 5- to 6-year training period. (www.nichd.nih.gov/research/supported/Pages/rsdp.aspx)

Women’s Reproductive Health Research (WRHR) Career Development Program. NICHD and ORWH support a national program of mentored institutional career development programs for junior faculty who have recently completed postgraduate clinical training in obstetrics and gynecology, and are committed to an independent research career in women’s reproductive health. The supervised research training will assist junior faculty in their transition into productive physician scientists in areas related to obstetrics and gynecology and its subspecialties. (www.nichd.nih.gov/research/supported/Pages/wrhr.aspx)

Inclusion

Within NICHD, responsibility for direct oversight implementation of inclusion policy rests with the Institute’s Office of Extramural Policy, which oversees a range of specific activities involving scientific program, review, contracts management, grants management and support staff, with Institute staff participating as appropriate. Specific activities

range from communication by scientific program staff with potential applicants in the pre-application stage, to ensure outreach and dissemination of inclusion requirements; administrative review of all grant applications and contract proposals by scientific review officers to ensure accurate coding of applications prior to peer review; peer review of applications and proposals with respect to adequacy of investigator plans for meeting inclusion requirements; and scientific program staff interaction with investigators whose applications/proposals were deemed unacceptable regarding inclusion requirements. Activities also include review of annual progress reports (PHS Form 2590) by scientific program staff to ensure appropriate accrual and achievement of inclusion targets and entry and approval of both target and actual enrollment data into the Population Tracking System. In addition, NICHD program, review grants management, and contracts management staff members are encouraged to participate in all NIH training opportunities relevant to inclusion; newly hired staff is required to have such training as soon as possible after assuming their position. The most recent report of the Institute’s inclusion-related policies, strategies, and specific activities is the *2015 Biennial Advisory Council Report Certifying Compliance with Inclusion Guidelines*. (www.report.nih.gov/UploadDocs/NICHD%202015.pdf)

STEM Efforts

Not applicable.

Funding Initiatives, Workshops, and Conferences

Funding Opportunity Announcements

Assessing Human Placental Development and Function Using Existing Data (RFA-17-004, RFA-17-005, published 2/9/2016)

Biomedical and Behavioral Research Innovations to Ensure Equity (BRITE) in Maternal and Child Health (PAR-15-319)

Collaborative Research in Genomics, Epigenomics, and Bioinformatics in Gynecologic Health and Disease (RFA-HD-16-003, RFA-HD-16-004)

Developing Paradigm-shifting Innovations for *in vivo* Human Placental Assessment in Response to Environmental Influences (RFA-HD-15-034,

Eunice Kennedy Shriver *NICHD Maternal-Fetal Medicine Units (MFMU) Network* (RFA-HD-16-019)

Limited Competition: Addressing Health Disparities in Maternal and Child Health through Community-Based Participatory Research (PAR-15-072)

Multidisciplinary Approaches for Developmental Research with Individuals with DSD (RFA-HD-021, RFA-HD-022, RFA-HD-023)

Multidisciplinary Research in Vulvodynia (PA-16-100, PA-16-101, PA-16-102)

National Centers for Translational Research in Reproduction and Infertility (RFA-HD-16-010)

Novel Tools to Assess Human Placental Structure and Function (RFA-HD-15-030, RFA-HD-15-031)

Pelvic Floor Disorders Network Clinical Sites (RFA-HD-012) and Pelvic Floor Disorders Network Data Coordinating Center (RFA-HD-011)

Pregnancy in Women with Disabilities (PAR-14-354, PAR-14-355, published October 1, 2014)

Safety and Outcome Measures of Pain Medications Used in Children and Pregnant Women (PA-16-311, PA-16-312, PA 16-313)

The Health of Sexual and Gender Minority (SGM) Populations (PA-15-260, PA-15-261, PA 15-262, PA 15-263)

The Human Placenta Project: Developing Paradigm-shifting Innovations for *in vivo* Placental Assessment (RFA-HD-15-032)

Using Omics to Define Human Placental Development and Function Across Pregnancy (RFA-HD-16-036, RFA-HD-16-037)

Women's Reproductive Health Research (WRHR) Career Development Program (RFA-HD-15-011)

Workshops and Conferences

(See also examples for grants responsive to Objective 1.9 above)

Determinants of Peak Bone Mass (November 17, 2016, NIH Main Campus)

2nd Annual Meeting: Incorporating Omics and Imaging into the HPP [The Human Placenta Project] (April 27–28, 2015, NIH Main Campus)

Incorporating Novel Technology into the HPP (April 14–15, 2016)

Opioid Use in Pregnancy and Neonatal Abstinence Syndrome (April 4–5, 2016)

Bridging Knowledge Gaps to Understand How Zika Virus (ZIKV) Exposure and Infection Affect Child Development (September 22–23, 2016)

Health Disparities

NICHD's Office of Health Equity (OHE), within the Office of the Institute Director, develops, coordinates, and serves as a catalyst for NICHD's commitment to ensuring the health and well-being of all children, adults, families, and communities. In 2016, a working group of the National Advisory Child Health and Human Development Council (NACHHD) reviewed OHE and provided recommendations on how the Office could better assist the Institute's Extramural and Intramural research programs accomplish their goals as they relate to reducing health inequities among different populations and improving the number of underrepresented individuals in the scientific workforce.

The working group's final report (www.nichd.nih.gov/about/advisory/nachhd/201610/Documents/NICHD_OHE_Handout_508.pdf) and September 2016 presentation of recommendations to the NACHHD (www.nichd.nih.gov/about/advisory/nachhd/201610/Documents/GILLIAM_OHE_NICHD_508.pdf) may be viewed online. To accomplish its mission, the OHE works closely not only within NICHD but also with other NIH components.

Scientific Research Advances

Spiritual and Religious Resources Can Help Protect African-American Women from Postpartum Depression. Repeated interviews of more than 700 predominantly Christian, low- to middle-income

African-Americans, during the year after they had given birth, found that those with strong religious and spiritual lives were significantly less likely to experience postpartum depression, for which racial minority women are at elevated risk. This protective effect was found even after researchers adjusted for such factors as women's socioeconomic status and whether the women were in relationships (Cheadle et al., 2015).

Study Explores Increased Production of Estrogen in African American Women. In general, African-American women have higher levels of estrogen across the menstrual cycle, but scientists have not known where in the body the additional estrogen originated, or what cellular mechanisms account for differing levels of estrogen production. New research has found higher levels of estradiol (the main form of estrogen throughout a woman's reproductive years) in the ovaries of African-American women and has identified differences in gene expression as the likely explanation for the difference. Related research also ruled out other body sites as possible sources of the higher estradiol in the African American women. Better understanding of the influence of racial background of production of female sex hormones may help scientists find ways to address such disparities as higher risk of breast cancer and uterine fibroids in African-American women, compared to white peers, and lower success rates of assisted reproductive technologies to address infertility (Shaw et al., 2015).

Racial and Ethnic Differences in Maternal Morbidity. Severe complications of childbirth, such as postpartum hemorrhage, infection, and unintentional tearing of the soft tissues between the vagina and anus, were more likely to occur in non-Hispanic black and Asian women than non-Hispanic white women, according to data from more than 100,000 births in 25 U.S. hospitals, according to a recent report. Although the researchers reporting these findings observed some differences in the care provided to the different groups of women, it was not clear if the differences

in care were related to differences in outcomes (Grobman et al., 2015).

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National Institute on Deafness and Other Communication Disorders (NIDCD)

Executive Summary

Congress established the National Institute on Deafness and Other Communication Disorders (NIDCD) in October 1988. The Institute's mission is to conduct and support biomedical research, behavioral research, and research training in the normal and disordered processes of hearing, balance, taste, smell, voice, speech, and language. NIDCD conducts and supports research and research training related to disease prevention and health promotion, addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders, supports research evaluating approaches to the identification and treatment of communication disorders and patient outcomes, and supports efforts to create devices that substitute for lost and impaired sensory and communication function. To accomplish these goals, NIDCD manages a broad portfolio of both basic and clinical research. As a whole, the Institute supported approximately 1,300 research grants, training awards, and research and development contracts in Fiscal Year (FY) 16. Through research and education, NIDCD strives to reduce both the direct and indirect economic burdens of communication disorders on individuals, families, and society, thereby improving the quality of life for people living with a communication disorder.

Several diseases, disorders, or conditions within NIDCD's mission disproportionately affect women. Examples of significant research programs on such disorders have been selected for inclusion in this report, with the latest research advances and the future directions of these projects highlighted.

Accomplishments and Activities

Voice Disorders

Voice production and its quality influence communicative exchange throughout the lifespan. Voice disorders affect millions of Americans, influencing their quality of life and impairing their ability to communicate effectively and to function in our society. Voice disorders are not trivial, although they are overwhelmingly under-recognized. Women have a higher prevalence of voice disorders than men (46.3% vs. 36.9%). A number of voice disorders, such as occupational voice disorders and spasmodic dysphonia (SD), appear to affect women more frequently than men.

Occupational voice disorders are estimated to affect 28 million Americans and have a significant impact on the livelihoods of teachers/professors, television and radio journalists, lawyers, and singers. Data in the literature clearly identify voice disorders as teachers' primary occupational risk, not only in the United States, but also internationally. Women constitute the largest proportion of teachers in U.S. classrooms. Moreover, voice problems constitute a global women's health concern. Until recently, few reports had been available on the treatment of these problems in teachers, and even fewer had addressed the equally important question of prevention.

NIDCD supports basic, clinical, and translational research studies that focus on normal voice production and the prevention and treatment of voice disorders. NIDCD-supported investigators are observing the cycle-to-cycle variation of the laryngeal tissue vibratory pattern or the potential impact of upper airway temperature changes on laryngeal tissue function throughout the menstrual cycle (*R03 DC013664*). Another multidisciplinary

research team is investigating specific gender-based speech production differences that may underlie women's elevated incidence of vocal health problems, especially in high-voice-use professions (*R01 DC012315*).

SD is a voice disorder that predominantly affects women, with estimates as high as 80 percent of affected individuals being female. SD is a neurological disorder (dystonia) affecting the voice muscles in the larynx. In SD, the muscles inside the vocal folds experience sudden involuntary movements—called spasms—which interfere with the ability of the folds to vibrate and produce voice. SD causes voice breaks and can give the voice a tight, strained quality. People with SD may have occasional breaks in their voice that occur once every few sentences. Usually, however, the disorder is more severe and spasms may occur on every other word, making a person's speech very difficult for others to understand. At first, symptoms may be mild and occur only occasionally, but they may worsen and become more frequent over time. SD is a chronic condition that continues throughout a person's life. It is a rare disorder, occurring in roughly one to four per 100,000 people and estimated to affect 50,000 people in North America. The first signs of this disorder are found most often in individuals between the ages of 30–50. There is no cure for SD, and the most common treatment is the injection of very small amounts of botulinum toxin directly into the affected muscles of the larynx. Repeat injections are necessary as the effects last only a few months.

NIDCD currently funds research aimed at determining the causes and pathophysiology of SD to develop new diagnostic and better treatment options. NIDCD-supported scientists are using multimodal assessment functional magnetic resonance imaging and transcranial magnetic stimulation to examine focal hand dystonia and SD (*R01 DC015216*). Others are using multimodal imaging and next-generation DNA sequencing to identify brain abnormalities and genetic risk factors for SD (*R01 DC008567* and *R01 DC012545*). The identification of genes responsible for this voice

disorder may lead to better and more accurate detection and diagnosis in this clinical population. Locating specific brain areas involved in regulating laryngeal muscles and understanding the neural mechanisms by which they exert their control may open avenues for new pharmacological therapies and surgical interventions.

NIDCD will continue to support voice disorders research based on recommendations from a 2013 NIDCD-sponsored workshop on voice sciences and disorders. The consensus of leading experts in the field was that it is essential to strengthen the pipeline of future voice scientists from various academic backgrounds to encourage collaborative efforts to address lingering research questions. As a result of the workshop, NIDCD issued two Funding Opportunity Announcements (FOAs) on advancing research in voice disorders. These FOAs call for cutting-edge research proposals, such as the development of biomaterials for engineering vocal fold tissue and development of ambulatory biofeedback approaches for management of patients with voice disorders. Additionally, patient outcomes research, health services research, and community-based research with special attention to the needs of low socioeconomic status, disparities, rural, second language populations, and women's health have been highlighted and are especially encouraged.

Cytomegalovirus

Cytomegalovirus (CMV) is the leading cause of nonhereditary deafness. Maternal transmission of CMV is well recognized as a common cause of sensorineural hearing loss (SNHL). CMV also is recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. It is estimated that the sequelae of congenital CMV infection may account for as many as 40,000 new cases of SNHL per year. NIDCD-sponsored scientists continue to make significant progress to fully characterize the effects of CMV on SNHL, as well as the mechanisms and epidemiology of CMV maternal transmission. CMV infection has a highly significant effect on the development of

late-onset SNHL. Recent results indicate that a targeted CMV testing approach that tests newborns who fail their newborn hearing screening (NHS) identified the majority of infants with CMV-related SNHL at birth. However, 43 percent of the infants with CMV-related SNHL in the neonatal period and congenital CMV infants who are at risk for late-onset SNHL were not identified by NHS. There is a potential role for targeted CMV screening, which would minimize the diagnostic etiology odyssey for some of the infants with suspected hearing loss, because congenital CMV can only be reliably diagnosed within the first few weeks after birth. These infants would have the opportunity for more focused audiologic monitoring, early intervention, and antiviral treatment (*HHSN263201200010C*).

Otosclerosis

Otosclerosis is caused by abnormal bone remodeling in the middle ear. Bone remodeling is a lifelong process in which bone tissue renews itself by replacing old tissue with new. In otosclerosis, abnormal remodeling disrupts the ability of sound to travel from the middle ear to the inner ear. Otosclerosis affects more than 3 million Americans. Many cases of otosclerosis are thought to be inherited. White, middle-aged women are most at risk.

The complicated architecture of the ear makes it difficult to study. Because researchers cannot remove and analyze a sample of the inner ear from a living person who has otosclerosis or other hearing disorders, they must study ear bone samples from cadavers donated for research. These samples, called temporal bones, are in short supply. To encourage more research on otosclerosis, NIDCD supports the National Temporal Bone, Hearing and Balance Pathology Registry at the Massachusetts Eye and Ear Infirmary (*U24 DC013983*).

The Registry is an information center that coordinates and archives data about recruited temporal bone donors and the location of specimens nationwide and maintains a network of contacts for timely procurement of tissue. In

addition, during the reporting period, the NIDCD Otopathology Research Collaboration Network has encouraged scientists to combine modern biology, imaging, and computer technologies with information from patient history and pathology reports to look for new clues and solutions to ear disorders caused by bone abnormalities (*U24 DC013983*, *U24DC011962*, *U24 DC119430*, and *U24 DC011968*).

In 2016, the National Human Ear Tissue Laboratory Resource was established to serve the auditory and vestibular research communities by improving the quantity, quality, and availability of human specimens by developing and sharing advances in methods for human ear tissue processing, developing technologies for noninvasive imaging, and providing technical instruction, all to enhance opportunities for needed research on human ear tissues (*U24 DC015910*).

Balance Disorders

NIDCD supports research on balance and the vestibular system, which is housed in the inner ear and helps us maintain balance and navigate through our world. Normal balance is maintained by interactions among the visual, vestibular, proprioceptive (position sensation), and musculoskeletal systems. All of these systems can deteriorate with trauma, disease, and/or age, and the number of Americans older than age 65 is rising rapidly. Vestibular dysfunction and disorders, some of which are more common in women, can lead to dizziness, vertigo, migraines, blurred vision, nausea, and various forms of balance disturbances, including postural instability. More than 4 in 10 Americans, especially the elderly, will experience an episode of dizziness sometime during their lives that is significant enough to send them to a doctor.

Balance disorders are associated with falling, which is the leading cause of severe trauma and deaths among older adults. Each year, more than 4 million older U.S. adults go to emergency departments for fall-related injuries, at a cost of \$4 billion. NIDCD supports a longitudinal study that measures

vestibular function in older adults. NIDCD also is sponsoring the Acute Video-Oculography for Vertigo in Emergency Rooms for Rapid Triage (AVERT) clinical trial to help diagnose vertigo, dizziness, and other balance problems. The team of researchers is using a diagnostic medical device (video-oculography) in the triage of patients who go to the emergency room with complaints of vertigo and/or dizziness. The device measures abnormal eye movements to differentiate benign causes of the dizziness or imbalance from dangerous causes, such as stroke. This study offers the potential for improving standards of care in the diagnosis and treatment of patients with vertigo or dizziness, leading to better outcomes at lower costs (*U01 DC013778*).

Dysfunction of the vestibulo-sympathetic reflex (VSR) is extremely common and potentially life-threatening, particularly in the elderly, and it is present in such disorders as orthostatic hypotension. When individuals with this disorder stand up, their blood pressure decreases, resulting in lightheadedness, dizziness, falling, and fainting. Orthostatic hypotension occurs in 50 percent of people older than age 70. NIDCD supports research understanding the neural circuitry underlying the VSR and its involvement in orthostatic hypotension. This program is now advancing research into investigating devices and treatments by exploring prosthetic and pharmacotherapeutic strategies (*R01 DC008846*).

Linear acceleration detectors of the vestibular system, the otolithic organs, detect the forces produced by head tilt and by linear (front-to-back, side-to-side) head movements. How the vestibular and the nervous systems resolve gravitational from linear accelerations, to accurately perceive motion and control balance, currently is under active study by NIDCD-supported scientists (*R01 DC012813*, *R01 DC004260*, and *R21 DC014518*).

Vestibular migraine, a variant of migraine in which dizziness is a prominent feature, affects about 1 percent of the general population and 10 percent of patients seen in dizziness and headache

clinics. Like conventional migraines, vestibular migraines are more prevalent in females. Little is known about the clinical course of this disorder or the functional impairment that it causes, and there is no proven therapy. NIDCD-supported investigators are conducting a Phase II clinical trial to assess the efficacy of rizatriptan in treating vestibular migraines. If successful, this study will provide the first data for an evidence-based treatment of vestibular migraines and set the stage for larger Phase III trials (*U01 DC013256*).

Ménière's disease is a vestibular disorder of the inner ear that causes severe dizziness (vertigo), ringing in the ears (tinnitus), hearing loss, and a feeling of fullness or congestion in the ear. Ménière's disease can develop at any age, but it is more likely to first occur in adults between ages 40–60 and is more common in women. NIDCD estimates that approximately 615,000 individuals in the United States currently are diagnosed with Ménière's disease and that 45,500 cases are newly diagnosed each year. Endolymph fluid buildup in the labyrinth is believed to contribute to vertigo and other symptoms of Ménière's disease. Researchers are hoping to develop methods for manipulating inner ear fluids that could lower endolymph volume and reduce or eliminate dizziness (*R01 DC001368*).

NIDCD research is attempting to develop vestibular prosthetic devices and minimally invasive surgery techniques to control imbalance and vertigo while preserving hearing and other functions. Dysfunctions of the vestibular system can occur independently or with hearing loss. NIDCD has encouraged translational research towards development of a vestibular implant similar to the cochlear implant. In FY 13, NIDCD issued an FOA to encourage continued research and development efforts for translation of electrical stimulation of the vestibular nerve to studies in human subjects to replace balance and positional information lost through disorders like Ménière's disease or vestibular migraines. These efforts are continuing today and have expanded NIDCD research in this area (*R01 DC014002*, *R01 DC013536*, and *R01 DC013069*).

NIDCD-Issued FOAs Active in 2015–2016

PA-13-102 (R01) and PA-13-103 (R21): Disorders of Human Communication: Effectiveness, Outcomes, and Health Services Research

The goal of these FOAs is to accelerate the translation of research discoveries into practice, increase access to health care, and enhance the delivery, quality, and effectiveness of care with the purpose of improving personal and public health.

PAR-13-277: NIDCD Clinical Research Center Grant (P50)

This FOA targets applicant institutions with demonstrated ability to conduct clinical research in human communication disorders to apply for Clinical Research Center Grants. Applications are encouraged in NIDCD's seven scientific programs—hearing, balance, smell, taste, voice, speech, and language.

RFA-DC-14-002: NIDCD National Temporal Bone, Hearing & Balance Pathology Resource Registry (U24)

The NIDCD temporal bone registry is a national research resource for human otopathology. Its fundamental purpose is to coordinate information about specimens of the human ear and its disorders. The registry coordinates specimen collection, information recording, and data management of specimens, and provides public information, including an up-to-date website about human ear research. It is not a simple database or tissue bank for human ear specimens. This foa supports these functions to enhance and promote critically needed research on the middle ear and inner ear that cannot be done in living humans.

PA-14-009: NIDCD Research Grants for Translating Basic Research into Clinical Tools

The intent of this FOA is to provide a new avenue for basic scientists, clinicians, and clinical scientists to jointly initiate and conduct translational research projects. The scope of the FOA includes a range of activities to encourage translation of basic research findings, which will impact the diagnosis,

treatment, and prevention of communication disorders.

PA-14-090 (R21) and PA-14-091 (R01): NIDCD Research on Hearing Health Care

This FOA encourages research leading to accessible and affordable hearing health care. The overarching emphasis is on the acquisition of knowledge that can be rapidly translated into new or enhanced approaches for access, assessment, or interventions with a goal of delivering better hearing health care outcomes. Applications that seek quality approaches that are effective, affordable, and deliverable to those who need them—as well as implementable and sustainable in settings beyond the research environment—are encouraged.

PA-14-235(R21) and PA-14-236 (R01): Advancing Research in Voice Disorders

These FOAs encourage research focused on advancing our scientific knowledge of the human larynx and human voice production in health and disease and optimal ways to prevent, evaluate, diagnose, and clinically manage voice disorders.

RFA-DC-16-001: Open Design Tools for Speech Signal Processing (R01)

This FOA invites Research Project Grant applications to develop novel acoustic signal processing algorithms for speech enhancement that employ the substantially greater amounts of computing power likely to be available in future generations of hearing aids, cochlear implants, personal sound processors, and consumer electronic devices.

RFA-DC-16-002: Open Design Tools for Speech Signal Processing (R43/R44)

This FOA solicits Small Business Innovation Research grant applications to develop and support the use of portable acoustic signal processing tools that provide substantial amounts of computing power and reconfigurable real-time speech enhancement software that operates in real-world environments. This research tool must incorporate open-source design principles for key hardware and software components to support rapid dissemination, reconfiguration, and enhancement of

tools that enable acoustic psychophysical research studies beyond those widely performed today.

RFA-DC-17-001: NIDCD National Human Ear Tissue Laboratory Resource for Hearing and Balance Research (U24)

This FOA will establish a laboratory as a national technological resource for auditory and vestibular researchers who use human inner and middle ear tissues for a range of basic and clinical studies. The Laboratory will develop and provide technical services for procuring, preparing, sectioning, and distributing high-quality human ear tissues; develop and disseminate techniques for improved tissue preservation and for imaging human middle and inner ear structures, including cellular and membranous components; and provide opportunities for technical instruction in the special skills needed to prepare ear and use tissues from postmortem human temporal bones. A cooperative agreement will coordinate interactions with the research community to maximize impact and novelty while avoiding duplicative efforts. This resource will benefit a broad spectrum of research projects, including clinical and translational, by providing a critical link towards the translation of animal studies to the human ear and eventually the clinic, for NIDCD's mission to help prevent, detect, diagnose, and treat deafness and other communication disorders.

Workshops Held in 2015–2016

2016

Language and Literacy Development in Early Dual Language Learners

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and NIDCD held a scientific workshop held August 18–19, 2016, on language and literacy development in early dual-language learners. The workshop consisted of formal presentations concerning variability in bilingual development, assessment and intervention, and neurocognitive development;

in-depth discussions; and separate sessions aimed at identifying research gaps and opportunities.

2015

Synaptopathy and Noise-Induced Hearing Loss: Animal Studies and Implications for Human Hearing

NIDCD held a workshop May 4–5, 2015, on noise-induced cochlear synaptopathy, including the aging of noise-exposed ears, and the implications of recent animal studies for human hearing.

Towards Augmentative and Alternative Communication and Brain-Computer Interface Synergy

NIDCD held a programmatic workshop on September 17, 2015, to explore ways to move towards synergy between the Augmentative and Alternative Communication and the Brain-Computer Interface research fields.

Awards Cited

Plexico, Laura. *Multi-System Measurements of Hormonal Influence of Voice Production*.

(Grant No. R03DC013664). NIDCD grant, Auburn University, Auburn, Alabama.

Hunter, Eric J. *Gender Differences and Speech Accommodation in Occupational Settings*.

(Grant No. R01DC012315). NIDCD grant, Michigan State University, East Lansing, Michigan.

Kimberley, Teresa J. *A Multimodal Assessment of Neurophysiology in Focal Dystonia*.

(Grant No. R01DC015216). NIDCD grant, University of Minnesota, Minneapolis, Minnesota.

Verdolini, Katherine. *Prospective Study on Prevention and Treatment of Voice Problems in Teachers*.

(Grant No. R01 DC008567). NIDCD grant, University of Pittsburgh, Pittsburgh, Pennsylvania.

Simonyan, Kristina. *Voice Tremor in Spasmodic Dysphonia: Central Mechanisms and Treatment Response*.

- (Grant No. R01DC012545). NIDCD grant, Mount Sinai School of Medicine, New York, New York.
- The University of Alabama at Birmingham. *The Natural History of CMV-Related Hearing Loss and the Feasibility of CMV Screening as Adjunct to Hearing in the Newborn (CHIMES) Study*.
- (Contract Award no. HHSN263201200010C). NIDCD grant, The University of Alabama at Birmingham, Birmingham, Alabama.
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- (Grant No. U24 DC013983). NIDCD grant, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.
- Linthicum, Fred H., and Giovannini, Marco. *The Otopathology of Hearing Loss: Genotype-Phenotype Correlation in Human Temporal Bone*.
- (Grant No. U24DC011962). NIDCD grant, University of California, Los Angeles, California.
- McKenna, Michael J. *Optopathology by Light Microscopy and Molecular Techniques*.
- (Grant No. U24DC011943). NIDCD grant, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.
- Cureoglu, Sebahattin. *Pathology and Pathogenesis of Otitis Media Syndromic Ear and Ménière's Disease*.
- (Grant No. U24DC011968). NIDCD grant, University of Minnesota, Minneapolis, Minnesota.
- Ishiyama, Akira. *NIDCD National Human Ear Tissue Laboratory Resource for Hearing and Balance*.
- (Grant No. U24 DC015910). NIDCD grant, University of California, Los Angeles, California.
- Newman-Toker, David E. *AVERT Acute Video-Oculography for Vertigo in Emergency Rooms for Rapid Triage*.
- (Grant No. U01DC013778). NIDCD grant, Johns Hopkins University, Baltimore, Maryland.
- Holstein, Gay R. *Chemical Anatomy and Synaptology of Vestibulo-Sympathetic Pathways*.
- (Grant No. R01DC008846). NIDCD grant, Mount Sinai School of Medicine, New York, New York.
- Dickman, J. David. *Multisensory Integration of Vestibular and Magnetic Signals*.
- (Grant No. R01DC012813). NIDCD grant, Baylor College of Medicine, Houston, Texas.
- Angelaki, Dora. *Neural Mechanisms of Vestibular Function*.
- (Grant No. R01DC004260). NIDCD grant, Baylor College of Medicine, Houston, Texas.
- Angelaki, Dora and Pitkow, Zachary S. *Cortical Feedback to the Vestibular Brainstem*.
- (Grant No. R21DC014518). NIDCD grant, Baylor College of Medicine, Houston, Texas.
- Baloh, Robert W. and Staab, Jeffrey P. *A Phase II Trial on Rizatriptan for Vestibular Migraine*.
- (Grant No. U01DC013256). NIDCD grant, University of California, Los Angeles, California.
- Salt, Alec N. *Inner Ear Fluid Interactions*.
- (Grant No. R01DC001368). NIDCD grant, Washington University in Saint Louis, Missouri.
- Rubinstein, Jay T. *Optimization of a Human Vestibular Prosthesis*.
- (Grant No. R01DC014002). NIDCD grant, University of Washington, Seattle, Washington.
- Della Santina, Charles C. *Multichannel Vestibular Prosthesis Pilot Early Feasibility Trial*.
- (Grant No. R01DC013536). NIDCD grant, Johns Hopkins University, Baltimore, Maryland.
- Lewis, Richard F. *Vestibular Contributions to Estimated Head Motion and Orientation*.
- (Grant No. R01 DC013069). NIDCD grant, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

National Institute of Dental and Craniofacial Research (NIDCR)

Executive Summary

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to promote the general health of the American people by improving dental, oral, and craniofacial health through research and research training. NIDCR funds clinical and basic research to understand, prevent, and treat oral diseases and craniofacial conditions, including those that disproportionately or solely affect women. Among these diseases are orofacial pain conditions, including temporomandibular joint disorders (TMD), osteoporosis of the craniofacial complex, and autoimmune salivary gland diseases. NIDCR also supports research on the oral health of pregnant women, mothers, and their children, and research on craniofacial and tooth development in unborn children. This report highlights accomplishments and initiatives in key areas related to women's health and research focused on advancing the understanding of sex as a biological variable and gender differences.

In fiscal years (FY) 15 and 16, NIDCR supported a variety of studies designed to identify risk factors and characterize diseases affecting women. This includes a robust orofacial pain research program, spanning the basic to clinical sciences. Investigators are studying how various sex hormones affect TMD and pain sensitivity in basic and preclinical studies, while clinical researchers are investigating factors that increase the risk of developing TMD and transitioning to chronic TMD in a longitudinal cohort study called Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA). Recently, in the second phase of the study (OPPERA II), researchers identified a population subgroup

that has a higher risk of developing TMD, which may stimulate research toward prevention of TMD in this subgroup. NIDCR-funded investigators also have made recent advances in studying osteoporosis, which disproportionately affects women, including identifying sex differences in the pathophysiology of osteonecrosis of the jaw, a condition associated with several drugs used to treat osteoporosis. NIDCR supports a number of studies on Sjögren's syndrome (SS), an autoimmune disease with dramatic oral health consequences that affects women nine times more frequently than men. This includes support of the Sjögren's International Collaborative Clinical Alliance (SICCA) biorepository, which distributes clinical samples to investigators worldwide. NIDCR also supports research to define the best methods to eliminate disparities in oral health that often impact women and their children.

Recognizing the importance of gene-gene, gene-environment, and behavioral interactions, the Institute has long emphasized basic, genetic, behavioral, social science, and epidemiological research. Researchers supported by NIDCR during FY 15 and FY 16 continue to identify genes associated with such craniofacial anomalies as cleft lip and palate and other developmental anomalies, such as amelogenesis imperfecta, a condition that affects tooth development. This could lead to improved prevention, diagnosis, and treatment in pregnant women at risk for giving birth to children with these abnormalities. NIDCR also supports basic science studies examining growth and development of teeth, cartilage, and bone that provide the scientific foundation for understanding oral diseases.

Accomplishments and Activities

Pain Research

For many years, NIDCR-supported research has explored many aspects of pain—ranging from basic science studies about pathophysiology to efforts to develop new therapies for acute and chronic pain—including conditions that primarily affect women. Findings from these studies demonstrate that men and women respond differently to painful stimuli, that distinct immune cells may mediate pain differently in men and women, and that women are more likely than men to develop certain chronic pain conditions. Human and animal studies are described in the following sections.

Temporomandibular Joint and Muscle Disorders

Temporomandibular joint and muscle disorders are a diverse group of orofacial conditions associated with persistent orofacial pain and jaw dysfunction. Approximately 5 to 10 percent of the U.S. population will seek care for TMD in their lifetime. Although most cases resolve with minimal or no treatment, some individuals develop a chronic, painful disorder that is associated with significant jaw dysfunction and emotional and financial burden.

Chronic TMD is more prevalent in females than males, and women report higher levels of pain than men. Using a rodent model, NIDCR-funded investigators showed that the female sex hormone estradiol has a profound effect on numerous genes important in pain modulation and regulation of nerve inflammation (Umorin, 2016). Other work has suggested that cartilaginous cell proliferation in the temporomandibular joint (TMJ) is not mediated by differences in estradiol levels between male and female mice (Robinson, 2016). Ongoing studies are examining the mechanics of the joint to understand how forces affecting the TMJ disc differ in males and females.

Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA)

In 2004, NIDCR funded the OPPERA study, a large, multisite prospective clinical study that sought to identify biological, psychological, and social factors that increase the risk of developing TMD and transitioning to chronic TMD. The OPPERA study confirmed risk factors previously reported and identified new risk factors, including genes associated with pain signaling and various types of pain receptors. This study confirmed the role of Catechol-O-methyltransferase (COMT), an enzyme responsible for breaking down molecules that transmit pain signals, in TMD. OPPERA also assessed risk factors for initial development of TMD (first onset TMD) and found that multiple overlapping health conditions were predictors. These results are being confirmed with data generated in the second phase of OPPERA, which follows individuals with first onset TMD, to explore in greater depth genetic risk factors for chronic and first onset TMD.

Recently, OPPERA II researchers have identified a subgroup of the general population with higher risk of developing TMD (and possibly other chronic pain conditions), using a short questionnaire and a few simple measurements. Identifying individuals at risk for developing chronic pain conditions permits the development of proactive pharmacological and/or behavioral approaches that could mitigate risk (Bair, 2016). The study also found that individuals with chronic painful TMD have lower blood levels of an anti-inflammatory adipokine, omentin-1, suggesting that TMD pain may be mediated by systemic inflammatory pathways (Harmon, 2016). Omentin-1 levels are reduced in several inflammatory conditions, including osteoarthritis, inflammatory bowel disease, and obesity. Further elucidation of the mechanisms by which omentin-1 and similar inflammatory mediators contribute to persistent pain and development of pain could potentially yield diagnostic markers and therapeutic interventions.

Other Examples of NIDCR-Supported TMD Research

- TMJ disc dysfunction occurs in approximately 30 percent of TMD patients, with the mean age of onset between ages 25–35. Articular tissue failure in synovial joints is thought to involve mechanical fatigue and, thus, be dependent on magnitudes and frequencies of applied mechanical stress. Recently published work demonstrated that magnitudes of energy input to TMJ tissues during function were significantly higher in patients with pain and disc displacement (+P+DD), compared to patients without pain and with/without DD (-P+DD, -P-DD) (Gallo, 2015). The frequency of energy input to TMJ tissues, as measured by percent of time the jaw muscles were active, was significantly higher at night for -P+DD females, compared to healthy (-P-DD) females and males (Iwasaki, 2015). This finding suggests sex and TMD diagnostic group differences in muscle activity could be predictive determinants of TMJ integrity and of development of degenerative joint disease.
- A recent cross-sectional analysis of females with TMJ osteoarthritis found several local and systemic biomarkers were significantly correlated with morphological flattening of the lateral pole of the condylar articular surface, suggesting this bone resorption profile could contribute to the initial diagnosis of TMJ osteoarthritis. Development of a Bone Texture Tool method as an open-source software package to aid clinicians in diagnosis is currently underway (*R21 DE025306*, Paniagua). NIDCR-funded researchers now are comparing TMJ images of approximately 600 patients (mostly female) treated for TMD over the past 6 to 10 years to new images taken with cone beam computed tomography, and will utilize proteomics technology to determine the degree to which progressive change in the joint structures contributes to pain and dysfunction in TMD patients.
- The National Dental Practice-Based Research Network (PBRN) conducts oral health research studies in dental practices on topics of importance to practitioners and their patients. A practice-based research study is being conducted to measure the prevalence of pain in the orofacial regions in dental patients visiting a general dentist. Researchers found that 6.6 percent of patients reported pain in the muscles and TMJ within the previous year, and this pain was more commonly reported in women (Horst, 2015). A follow-up prospective PBRN study will seek to identify practitioner treatment decisions for patients with TMD pain and assess change in pain over time with different treatments for TMD pain. This study also will assess the influence of practitioner and patient gender upon practitioner treatment decisions and patient response to treatment (*U19 DE022516*, Gilbert).
- A Phase II randomized clinical trial is investigating whether a variation in the gene that encodes the enzyme COMT alters a person's response to propranolol used as a pain reliever. This research will help determine whether doctors can tailor propranolol treatment to individuals with TMD based on their genetic differences, and determine if this non-opioid medication is effective in reducing TMD pain (*U01 DE024169*, Tchivileva).

Neuropathic Pain

Neuropathic pain is a complex, chronic pain that may occur when nerve fibers are damaged or become dysfunctional. Little is known about the role that sex and gender may play in neuropathic pain processes. NIDCR-supported investigators studying interactions between immune cells and neurons in a mouse model of persistent neuropathic pain found that male and female animals used different cell types to relay pain signals from the immune system to the nervous system. Female mice used adaptive immune cells (T cells), while male mice used microglia. In the female mouse model, microglia were not required to elicit pain sensitivity, and T cell preference could be reversed

by testosterone administration. These findings suggest two separate mechanisms of immune-neuronal interactions in the mouse spinal cords. An important implication of these findings is that distinct strategies targeting neuroimmune signaling might be required for the treatment of chronic pain in men versus women (Sorge, 2015).

A continuing challenge in chronic pain is lack of clarity on how the transition from acute to chronic neuropathic pain occurs and how to prevent and reverse this transition. Spinal cord synaptic plasticity and long-term potentiation have been strongly implicated in chronic neuropathic pain development. While accumulating evidence points to an important role for glial cells in the pathogenesis of neuropathic pain, little is known about whether signaling by astrocytes, the most abundant glial cell type in the central nervous system (CNS), also is sex-dependent in chronic pain. NIDCR is currently funding a study comparing sex differences in spinal cord astrocyte signaling in neuropathic pain using biochemical, behavioral, and electrophysiological approaches (R01 DE022743, Ji).

Several animal studies have implicated complement proteins in both neuropathic and inflammatory pain models, but their role in human pain mechanisms remains unknown. NIDCR currently is funding a study using human dental pulp to test the hypothesis that the neurotransmitter serotonin preferentially elicits release of complement peptides from the peripheral tissues of women, compared to men, leading to a sexually dimorphic increase in capsaicin-sensitive receptor activity in trigeminal sensory neurons and a concomitant increase in orofacial pain. Findings from this study could provide mechanistic insights into sexually dimorphic pain conditions where serotonin has been implicated, such as trigeminal neuralgias, migraine, fibromyalgia, and vestibulodynia (R01DE026139, Hargreaves).

Burning mouth syndrome (BMS) is a chronic neuropathic pain condition characterized by ongoing burning pain within the mouth with

no obvious cause. BMS is more prevalent in perimenopausal/postmenopausal females, and a multifactorial etiology has been implicated. NIDCR currently is funding a clinical study to assess multiple potential CNS abnormalities for their impact on BMS presentation. By combining data from multiple levels of CNS function, this study will seek to identify CNS markers that may contribute to the pathophysiology and clinical presentation of this poorly understood orofacial pain condition that primarily affects women (R21 DE023964, Seminowicz).

Chronic Overlapping Pain Conditions (COPCs)

Women are at greater risk for most common forms of chronic pain and evidence suggests significant rates of overlap among a cluster of pain disorders predominantly affecting women. This suggests that chronic pain conditions are complex disorders that share symptoms and mechanisms with other pain conditions and may require further elucidation. In September 2014, two Funding Opportunity Announcements (FOAs) were issued soliciting research on COPCs. These FOAs encourage epidemiologic, clinical, and translational research to increase our understanding of the natural history, prevalence, biological mechanisms, psychological variables, and clinical risk factors—including sex and gender—responsible for the presence of multiple chronic pain conditions. In collaboration with the Office of Research on Women's Health (ORWH), NIDCR currently is funding two Trans-NIH High Priority, Short-Term Awards (R56) in Women's Health.

The first study, from an Early Stage Investigator, is assessing whether serum-derived exosomal microRNAs, which can modulate expression of inflammatory mediators, contribute to COPCs. The project uses dental pulpitis (acute tooth nerve pain) as an acute pain model and assesses patients diagnosed with >3 of the following conditions, which are more prevalent in females: TMD, episodic migraine, vulvar vestibulitis, fibromyalgia, and irritable bowel syndrome. If successful, the

proposed research could identify a microRNA profile that could discriminate between localized pain and an underlying condition that predisposes patients to chronic pain (*R56 DE025399*, Khan). The second study is using a well-defined human cohort to evaluate the contribution of proteins, microRNAs, and genes to the etiology of TMDs and five overlapping pain conditions: tension-type headache, low back pain, irritable bowel syndrome, pelvic pain, and widespread bodily pain. Findings could yield new insights into the mechanisms underlying TMD and COPCs and identify novel targets for development of therapeutics for maladaptive overlapping pain conditions in women (*R56 DE025298*, Nackley).

At a Chronic Overlapping Pain Working Group meeting held in September 2015, efforts focused on developing a case definition for “chronic overlapping pain conditions” and identifying common data elements for future clinical research. These efforts set the stage for standardization of diagnostic criteria and assessments, allowing for comparisons of varied pain cohorts and identification of common risk factors across chronic pain conditions. As a result of this effort, NIDCR funded an administrative supplement, with co-funding from the National Institute of Neurological Disorders and Stroke and National Center for Complementary and Integrative Health, to digitize and implement a modified version of the Complex Medical Symptoms Inventory, which includes diagnostic criteria for 10 COPCs. An assessment tool that can be completed by patients in a clinical or research setting will facilitate identification of biopsychosocial and genetic factors underlying COPCs.

Pain Management

Well-controlled experimental studies suggest that patient demographic characteristics play a causal role in providers’ pain management decisions, but that providers are unaware of this influence. Using an innovative virtual-patient technology, researchers studied pain management decisions among 154 dentists and physicians. Clinicians

varied by sex/gender, age, race/ethnicity, and duration of experience; virtual patients varied by sex/gender, age, and race/ethnicity. Results indicate that clinician demographics may play a significant role in pain management decisions. Compared to male clinicians, female clinicians were more likely to recommend pain treatment with non-opioid analgesics, and this effect was pronounced for black virtual patients (Bartley, 2015). To further these findings, a national survey study of dentists in the PBRN will explore the impact of sex/gender and other demographic characteristics upon dentists’ opioid prescribing practices and implementation of risk mitigation strategies (*U01 DE022516*, Gilbert).

Mineralized Tissue Studies in Health and Disease

The study of teeth, bone, and other mineralized tissues has been a mainstay of NIDCR research since the Institute’s inception, because these tissues are important to oral health and to the growth and development of the entire body. Bone is an active and dynamic tissue that continuously remodels throughout life. In aging bone, an imbalance of resorption over formation often induces loss of bone mass, and can lead to osteoporosis, a skeletal disease that affects bone architecture and increases the risk of fracture. Osteoporosis disproportionately affects women. Other diseases that affect mineralized tissues of the craniofacial complex include dental caries (decay), periodontal (gum) disease, and drug-induced osteonecrosis.

Development and Maintenance of Mineralized Tissue

NIDCR-funded investigators are studying the basic biological processes involved in the development and maintenance of bone, cartilage, and/or teeth.

- Bone growth, development, and mineral balance are orchestrated by a complex repertoire of molecular switches. Problems with any of the components may lead to debilitating bone disorders and serious consequences, such as fractures resulting from osteoporosis.

Important pathways establishing this balance, such as transforming growth factor-beta (TGFB) signaling, control expression of many genes during fetal development through regulation of hormone secretion (Martinez-Armenta, 2015). Estrogen has been known to regulate a TGFB-inducible early response gene (*TIEG*), but the exact molecular mechanism was unknown. Available animal models for bone loss include *TIEG* knockout mice, which display sex-specific osteopenic phenotypes characterized by low bone mineral content and density in females. A group of NIDCR investigators using this mouse model determined that loss of *TIEG* decreased thyrotropin-releasing hormone expression, impairing the actions of estrogen on bone (Hawse, 2014). These results implicate *TIEG* in mediating estrogen signaling throughout the skeleton in female mice.

- The extracellular collagen-degrading matrix metalloproteinase MMP-13 is important for maintaining bone quality and is a target regulated by TGFB. NIDCR researchers studying molecular processes associated with bone quality received supplemental funds to compare sex differences in bone remodeling, which is particularly important during lactation, when there is great demand to release calcium stores from bone. This work also has implications for understanding bone changes and fragility that accompany steroid-induced osteoporosis (*R01 DE019284*, Alliston).
- It has been reported that females experience dental caries at a higher prevalence and severity over the lifespan, though the role of genetics in this sex difference is not known. NIDCR researchers used a family-based study design to investigate gene-by-sex interactions in dental caries. Data on caries experience in primary and permanent dentition was collected from 2,663 individuals in 740 families in the Center for Oral Health Research in Appalachia Cohort 1. Investigators found that genetics played a smaller role in caries risk in the primary dentition of girls, compared to boys. Analysis of permanent dentition demonstrated

that while overall heritability was not different between sexes, different sets of genes were involved in caries risk in each sex (Shaffer, 2015).

- NIDCR-funded investigators are identifying microbial factors affecting the genetic diversity and potential selection of *mutans streptococci* (MS) strains, a group of cariogenic bacteria associated with dental caries, following caries preventive and restorative therapy in children. Through an administrative supplement grant, the investigators are assessing sex-specific differences in MS strains and cariogenicity pre- and post-restorative therapies and sex-specific differences in responsiveness to specific treatments (*R15 DE024317*, Machida).
- Using an existing data set from a prospective study of mothers with monthly monitoring of vitamin D during pregnancy and oral examinations of their children after birth, NIDCR-funded investigators are assessing the influence of maternal circulating vitamin D levels during pregnancy upon enamel defects (hypoplasia) of those teeth formed *in utero*, and subsequent susceptibility to dental caries (*R03 DE025082*, Reed).

Osteonecrosis of the Jaw (ONJ)

Bisphosphonates (BPs) are drugs that inhibit the activities and functions of osteoclasts and perturb the differentiation of osteoblasts. Intravenous BPs are primarily used to treat and control pain associated with cancer metastasis to bone, Paget's disease, and multiple myeloma. Oral BPs are used to prevent bone loss and are prescribed for patients with osteoporosis or osteopenia. In 2003, case reports suggested use of BPs could lead to development of nonhealing, exposed necrotic bone in upper or lower jaws, a clinical condition that was named medication-induced ONJ. Most cases of medication-induced ONJ are related to intravenous BP use in cancer patients, but several cases are associated with oral BP. In 2009, cases began to surface of medication-induced ONJ in patients treated with the antiresorptive drug denosumab,

which inhibits the osteoclastogenic factor RANKL. Solicitations for research on ONJ resulted in a number of studies examining the etiology and epidemiology of ONJ.

- Early investigations centered on risk factors for development of ONJ, epidemiologic assessment of ONJ in osteoporotic/osteopenic patients and cancer patients using BPs, the fate and role of BP in a variety of cells, and the pathophysiologic mechanisms of ONJ. Further studies are investigating how ONJ involves the oral mucosa and the immune system (Tseng, 2015; Park, 2015). A research team is funded through an administrative supplement to examine sex differences, assessing how the number and function of myeloid cells is affected by female sex hormones, and if the heterogeneity of myeloid cells in females and males influences the severity of ONJ (*R01 DE022552*, Nishimura).
- Models for ONJ are essential to study the pathophysiology of this condition and discover pathways for prevention and treatment. NIDCR-funded investigators are refining animal models to reflect various risk factors, including inflammation (such as seen in periodontal disease) and osteoporosis, both of which affect women differently than men. Building upon published work examining the role of periodontitis and bisphosphonate treatment, NIDCR-funded researchers have found a higher incidence of ONJ in female rats, compared to males, under these combined experimental conditions and are optimizing the animal model (Aguirre, 2015). Other projects are exploring imaging methods and techniques that can detect early signs of ONJ before bone lesions are visible in the mouth. These advanced techniques have allowed one research group to demonstrate that systemic chelation can remove the bisphosphonate pamidronate from bone in rats, which may offer an opportunity to prevent full lesion development (Howie, 2015). Work is underway to examine other processes, such as osteomucosal healing involving both hard

and soft tissues, lymphocytes and other cells of the innate immune system, and the growth of lymphatic vessels that may play important roles in the pathogenesis of ONJ.

Periodontal Health in Women

NIDCR funded an ancillary study to the Women's Health Initiative Observational Study (WHI-OS), the Osteoporosis and Periodontal Disease (OsteoPerio) study, to examine periodontal disease status and progression in a subsample of 972 postmenopausal WHI-OS participants. Biospecimens collected from participants in the OsteoPerio study will be used to examine the composition and diversity of the subgingival microbiome at three time points; determine the extent to which the oral microbiome composition changes over time; identify which oral microbiome compositions are associated with periodontal disease presence, severity, and progression over time; and determine the influence of key personal characteristics on the oral microbiome composition and its relationship to periodontal disease status and progression. The proposed study fills a critical gap in our knowledge of the role of the subgingival microbiome in periodontal disease severity and progression at older ages. There is no other prospective epidemiologic study as large and rich with data resources to address contemporary questions about the oral microbiome and its role in periodontal disease in postmenopausal women (*R01 DE024523*, Wactawski-Wende).

Oral Human Papilloma Virus (HPV) Infection

A prior study within the nationally representative, cross-sectional U.S. National Health and Nutrition Examination Survey 2009–2010 cycle found that the prevalence of oral oncogenic HPV infection was three times higher among men than women, consistent with the higher risk for HPV-positive oropharyngeal cancer among men in the United States. Data from an NIDCR-supported study suggest that the higher burden of oral oncogenic HPV infections and HPV-positive oropharyngeal

cancers among men arises in part from a higher number of lifetime sexual partners and stronger associations with sexual behaviors among men (Chaturvedi, 2015).

Researchers wondered if HPV causes a similar proportion of oropharyngeal cancers among women, Asians, Hispanics, and blacks as it does among white men, and investigated HPV's role in non-oropharyngeal head and neck cancers. To answer these questions, NIDCR investigators conducted a cohort study of 863 patients with newly diagnosed squamous cell cancer of the oral cavity, oropharynx, larynx, or nasopharynx. They found HPV is the cause of most oropharyngeal cancers in women as well as in men, whites, Asians, Hispanics, and blacks. From 1995 to 2012, the proportion of HPV-associated oropharyngeal (but not non-oropharyngeal) head and neck cancers increased among all sex and race groups, establishing that HPV is an important cause of oropharyngeal cancer, not just among white men, but also among women and nonwhites (D'Souza, 2016).

Autoimmune Diseases and Sjögren's Syndrome (SS)

Autoimmune disorders cause an unintended destruction of the body's own tissues and disproportionately affect women. Sjögren's syndrome (SS), an autoimmune disease characterized by reduced secretions from salivary and lacrimal glands, affects an estimated 1–4 million people, 90 percent of whom are women. Patients with SS have increased numbers of lymphocytes and other immune cells in their salivary and lacrimal glands and an increased risk for developing malignant lymphoma, which occurs an estimated 40 times more frequently in patients with SS.

In 2003, NIDCR, the National Eye Institute, and ORWH provided support for the Sjögren's International Collaborative Clinical Alliance (SICCA). The SICCA is an integrated research network and large international SS patient registry

that spans seven countries (Argentina, China, Denmark, India, Japan, the United Kingdom, and the United States). The SICCA registry, designed by an international expert panel of ophthalmologists, rheumatologists, and oral medicine/pathology specialists, used standardized tests to evaluate more than 1,900 enrolled participants. All had possible signs and/or symptoms of SS typical of patients seen in a clinical practice and were drawn from ethnically diverse patient populations worldwide. In August 2016, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for Primary Sjögren's Syndrome (pSS) were published. This is the first set of criteria for pSS to be approved by both the ACR Board of Directors and the EULAR Executive Committee. These criteria have been assessed quantitatively using patient data, and have undergone validation on an independent population, which included patients from the SICCA registry. This registry provides data and linked biospecimens to investigators throughout the world to promote research on SS. In one NIDCR-supported study, investigators examined differentially methylated regions in labial salivary gland biopsies from women in the SICCA Registry. Genome-wide methylation analysis revealed that methylation was altered in almost 8,000 genes. In 57 genes, many of which are involved in immune system processes, the differentially methylated positions were enriched in the promoter region, implicating several genes and pathways that may be involved in SS disease-related processes (Cole, 2016).

NIDCR intramural scientists have been following a cohort of patients with SS to better understand the natural history of the disease. Efforts have been focused on identifying the genetic disease mechanisms of SS through collection and analysis of clinical data and biospecimens over time. Recent progress made by NIDCR intramural investigators includes:

- Through bioinformatics analysis, NIDCR intramural investigators identified that increased expression of bone morphogenetic

protein 6 resulted in the loss of expression of aquaporin 5, a water channel critical for salivary gland fluid secretion. This finding led investigators to develop a novel therapy for the treatment of SS using animal models of SS and gene therapy. By increasing the salivary gland expression of aquaporin, water permeability of the gland increased and resulted in the restoration of secretory gland function and resolution of the hallmark salivary gland inflammation and systemic inflammation associated with disease. Secretory function also increased in the lacrimal gland, suggesting this local therapy could treat the systemic symptoms associated with primary SS (Lai, 2016).

- Chronic low-level viral infections have been suspected in the development of SS, since multiple studies have shown stimulation of antiviral response pathways in SS tissues. Because a causal link between a viral infection and development of pSS had not been identified, investigators studied SS-affected salivary gland tissue to identify potential viral-mediated triggers in the pathogenesis of SS. Two distinct viral profiles were identified, including the increased presence of hepatitis delta virus (HDV) in 50 percent of SS patients. Expression of HDV antigens resulted in reduced salivary flow, increased focal lymphocytic infiltrates, and development of autoantibodies, providing further support of a viral-mediated etiopathology in the development of pSS (Weller, 2016).

Oral Health Disparities Research

NIDCR's strategic plan includes as a goal the elimination of disparities in oral health. Vulnerable populations include women of racial and ethnic minority backgrounds, those with low income, and those with developmental or acquired disabilities. In addition, NIDCR supports research on the oral health of children, including the impact of primary caregivers, often mothers, on the oral health of their children.

NIDCR awarded 10 research grants in 2015 aimed at eliminating inequities in access to care and improving the oral health of children. These awards support the “Multidisciplinary and Collaborative Research Consortium to Reduce Oral Health Disparities in Children” (RFAs *DE-15-006* and *DE15-007*). Studies will explore the integration of oral health into public health and primary health care settings; assess the effectiveness of preventive programs, such as school-based oral health care and managed care; and test new technologies, such as text messaging and electronic health records to enhance disease prevention and health promotion. Several of the projects are designed to motivate mothers and caregivers and teach best practices for care of children's teeth.

Mother-to-child transmission (MTCT) of MS, the primary bacteria causing dental caries, is widely accepted as the primary route of infection, though other sources of transmission have been suspected. One NIDCR-funded study investigated the genetic diversity and transmission of MS in 169 index children and 425 household family members. Thirty-four unique genotypes were observed, and 117 child and household isolates were evaluated for shared genotypes. Index children had 1-9 genotypes, and those with multiple genotypes were 2.3 times more likely to have dental caries currently or in the past. Only 28 percent of index children shared all genotypes within the household, while 72 percent had at least one genotype not shared with anyone in the household. In 55 percent of cases, children shared a genotype with more than one family member. This study presents evidence that there is child-to-child and intrafamilial transmission of MS, in addition to MTCT (Momeni, 2016).

There is a complex relationship between maternal behaviors, maternal oral health, and children's oral health. Intervening to improve parent/caregiver oral health behaviors may improve oral health status of their children. One NIDCR-supported trial tested a behavioral intervention to increase dental attendance among rural Oregonian low-income women and their children. Four hundred women

were randomized into one of four conditions to receive prenatal or postpartum motivational interviewing/counseling (MI) or prenatal or postpartum health education (HE). Counselors also functioned as patient navigators. Primary outcomes were dental attendance for the mother during pregnancy and for the child by age 18 months. Maternal attendance was 92 percent in the prenatal MI group and 94 percent in the prenatal HE group, rates that did not differ. Children's attendance was 54 percent in the postpartum MI group and 52 percent in the postpartum HE group. Both study groups had much higher attendance than statewide self-reported rates from the Oregon Pregnancy Risk Assessment Monitoring System. Although MI did not lead to greater attendance when compared to HE alone, high attendance may be attributable to the counselors' patient navigator function (Riedy, 2015). Three ongoing studies are testing other behavioral interventions directed at pregnant women or mothers of very young children to determine if the interventions will reduce dental decay in study participants' children.

Human Immunodeficiency Virus (HIV) Linked to Oral Health

The study of the oral manifestations of HIV infection has been of great interest for NIDCR because oral changes in HIV-infected individuals are frequent, varied, affect quality of life, represent the first signs of infection, and may persist with antiretroviral therapy. The impact of HIV/AIDS on women has grown substantially since the beginning of the pandemic.

The Pediatric HIV/AIDS cohort study (PHACS) is following HIV-exposed uninfected children to evaluate the long-term safety of fetal and neonatal exposure to antiretroviral prophylaxis. PHACS includes 20 centers in the United States and has enrolled more than 2,500 mother/child dyads. NIDCR is funding an ancillary study to PHACS to assess dental caries, periodontal attachment loss, and soft tissue disease in study participants. Biospecimens also are being collected. Study findings will offer insights about the natural history

of disease and its oral manifestations. Further, NIDCR-supported researchers are examining the gut and oral mucosal microbiota in infants who were born to HIV positive mothers treated with antiretroviral therapy to determine if the altered microbiome of infected mothers influences growth and development of exposed uninfected children.

Craniofacial Anomalies

Craniofacial abnormalities, such as cleft lip/cleft palate (CL/CP), ectodermal dysplasias, and amelogenesis and dentinogenesis imperfecta, may be the result of spontaneous or inherited genetic variants. The causes often are complex, involving environmental factors and gene-gene and gene-environment interactions.

Nonsyndromic CL/CP is a common birth defect with multifactorial etiology, involving both heritable and environmental exposures. Previous studies have demonstrated that maternal smoking increases the risk of a child being born with CL/P, but the effects of passive maternal smoking exposure are not well understood. NIDCR-funded scientists demonstrated that passive smoking was significantly associated with CL/P, and the increased risk was consistent for different populations and types of CL/P. This research emphasizes the importance of identifying maternal environmental risk factors for CL/P to prevent development of these conditions in children (Kummet, 2016).

NIDCR supported a large, multiethnic, international genome-wide association study (GWAS) of nearly 6,500 participants of African, Asian, European, and South and Central American ancestry. Genomic regions were identified on chromosomes 2, 17, and 19, providing leads for future research on genetic factors involved in developing CL/P (Leslie, 2016). NIDCR investigators also performed a GWAS analysis of 3,585 individuals from Ghana, Ethiopia, and Nigeria. Genetic association findings on a panel of 48 candidate genes suggested that several loci identified in other populations may play a role in orofacial clefting in Africans (Gowans, 2016).

Amelogenesis imperfecta (AI) is a rare heritable disease that affects enamel formation, producing teeth with soft, thin, or brittle enamel. Causal mutations have been identified in about half of nonsyndromic cases of AI, but the etiology is unknown for the rest. In two recent studies, investigators studied AI families and identified two novel genes that disrupt proteins expressed in ameloblasts, the cells that produce enamel (Parry, 2016; Seymen, 2016). These findings suggest that these newly identified genetic mutations may lead to AI disease presentation.

NIDCR Activities that Support the Goals of the NIH Strategic Plan for Women's Health Research

The following examples support **Goal 1: "Increase Sex Differences Research in Basic Science Studies"** and selected objectives.

1.1 Encourage genetic and epigenetic studies to identify sex differences in gene expression.

NIDCR researchers are exploring the role of genetics to support clinical observations of sex/gender differences in specific oral diseases. In one study, investigators examined differentially methylated regions in labial salivary gland biopsies from women in the SICCA Registry, a registry and biorepository of SS patients. Genome-wide methylation analysis identified 57 genes, many of which are involved in immune system processes, with differentially methylated positions enriched in the promoter region. These findings implicate several genes and pathways that may be involved in SS disease-related processes and warrant further research (Cole, 2016). Another study assessed gene-by-sex interactions for dental caries in 2,663 individuals in 740 families from a large cohort study of women and their children who have been followed from pregnancy through the child's sixth birthday. It was found that genetics played a smaller role in caries risk in the primary dentition of girls, compared to boys, and that different sets of genes were involved in caries risk for each sex (Shaffer,

2015). These findings have led the investigators to study gene-by-environment interactions separately by sex/gender.

1.4 Include sex parameters in the design of experiments using animal models. To better understand the mechanism underlying the complex, chronic pain condition called neuropathic pain, NIDCR-supported investigators studied interactions between immune cells and neurons in male and female mouse models. The investigators found that female mice used T cells, while male mice used microglia, to relay pain signals from the immune system to the nervous system. In the female mouse model, microglia were not required to elicit pain sensitivity, and T cell preference could be reversed by testosterone administration. These findings suggest two separate mechanisms of immune-neuronal interactions in the spinal cords of these mice and demonstrate the need to include both male and female animals in studies of pain.

Examples below support **Goal 3: "Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women"** and selected objectives.

Objective 3.9 Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions. There is a complex relationship between maternal behaviors, maternal oral health, and children's oral health. As discussed earlier, one NIDCR-supported trial tested a behavioral intervention to increase dental attendance among rural Oregonian low-income women and their children using a patient navigator. Dental attendance increased and was similar in both groups, suggesting that the high dental attendance may be attributable to the counselors' patient navigator function (Riedy, 2015). Baseline data from another trial found caries scores were greater with older children, lower in females ($p=0.01$), and lower in those with higher caregiver scores on oral

health behavior questions. Intervening to improve parent/caregiver oral health behaviors may improve oral health status of their children. Three ongoing clinical trials are testing behavioral interventions in pregnant women or mothers of very young children to determine if the interventions will reduce dental decay in study participants' children.

Initiatives: Funding Opportunity Announcements (FOAs)

Factors Underlying Differences in Female and Male Presentation for Dental, Oral, and Craniofacial Diseases and Conditions (R01), PA-16-295; and (R21), PA-16-296: These FOAs encourage research on mechanisms underlying the manifestations of sex-based differences in dental, oral, and craniofacial (DOC) diseases and conditions. They encourage studies aimed at understanding immune reactivity, genetic variation, environmental triggers, aging, and hormonal changes as they affect sex-based differences in DOC-related diseases and conditions.

Immune System Plasticity in the Pathogenesis and Treatment of Complex Dental, Oral, and Craniofacial Diseases (R01), PAR-15-192; and (R21), PAR-15-193: These FOAs encourage research projects to elucidate the role of immune system plasticity in health and in the pathogenesis of DOC diseases. The goal is to advance knowledge of the immunological basis of DOC diseases, and to develop tools and technologies for precise modulation of the immune system to restore or maintain health. New knowledge derived from this research may facilitate development of novel immunomodulatory therapies to prevent disease onset or reverse disease progression.

Pharmacogenomics of Orofacial Pain Management (R01), RFA-DE-16-001: This FOA encourages research on the genetic basis of variability in therapeutic drug responses and adverse events in individuals with painful conditions of the dental and orofacial region. The objectives are to determine the role of genetic variability in pharmacokinetics, pharmacodynamics,

and drug toxicities that contribute to and predict the clinical outcomes of analgesic treatment of individuals with acute and chronic pain conditions.

Research on Chronic Overlapping Pain Conditions (R01), PA-14-244; and (R21), PA-14-243: The purpose of these FOAs is to encourage epidemiological, clinical, and translational research that will increase our understanding of the natural history, prevalence, biological mechanisms, psychological variables, and clinical risk factors responsible for the presence of multiple chronic pain conditions in people with pain.

Biology of the Temporomandibular Joint in Health and Disease (R01) PA-14-358, (R21) PA-14-359: The purpose of these FOAs is to encourage research that will advance our understanding of the TMJ in health and disease and to stimulate research that complements previous efforts and focuses on the biology of joint function and the tissues that make up the TMJ.

Neurobiology of Migraine (R01) PA-14-068, (R21) PA-14-069: These FOAs are issued by the National Institute of Neurological Disorders and Stroke in conjunction with the NIH Pain Consortium. They solicit R01 and R21 grant applications from institutions/organizations to perform innovative research that will elucidate the mechanisms underlying migraine; expand our current knowledge of the role of genetic, physiological, biopsychosocial, and environmental influences in migraine susceptibility and progression; and explore new therapeutic targets and therapies for acute migraine management and longer term prevention.

Mechanisms, Models, Measurement, & Management in Pain Research, PA-16-188 (R01); PA-16-187 (R21): The purpose of these FOAs, issued by the National Institute of Nursing Research in conjunction with members of the NIH Pain Consortium, is to inform the scientific community of the pain research interests of the various NIH Institutes and Centers (ICs) and to stimulate and foster a wide range of basic, clinical, and

translational studies on pain as they relate to the missions of these ICs.

Small Research Grants for Establishing Basic Science-Clinical Collaborations to Understand Structural Birth Defects (R03), PAR-16-323:

The purpose of this FOA is to promote initial establishment of basic science-clinical collaborations by providing small grants to teams of basic scientists, physician scientists, and/or clinicians. These interdisciplinary teams may include, but are not limited to the following: developmental biologists, cell biologists, geneticists, genomicists, physician scientists (including individuals with veterinary degrees), clinicians, epidemiologists, biostatisticians, and/or bioinformaticists.

Multidisciplinary and Collaborative Research Consortium to Reduce Oral Health Disparities in Children: A Multilevel Approach, (UH2/UH3) RFA-DE-15-006, (U01) RFA DE-15-007:

The overall goal of these initiatives is to establish effective interventions or programs to reduce or eliminate oral health disparities and inequalities in vulnerable U.S. children between ages 0–21 years. Multidisciplinary teams of investigators will refine and test an intervention or evaluate outcomes of an existing program or policy intended to reduce health disparities and inequalities.

Workshops, Conferences, Symposia, and Consortia

Gene-Environment Interaction in Orofacial Clefting

A workshop on influence of gene-environment interactions on craniofacial birth defects was held September 6–7, 2016. Organized by NIDCR in collaboration with the Centers for Disease Control and Prevention, the *Eunice Kennedy Shriver* National Institute of Child Health and Development, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the National Institute of Environmental Health Sciences, the workshop brought together

researchers from a variety of scientific disciplines to identify areas of opportunity in gene-environment research and to identify additional resources that would aid research in this field.

Women in Dental Academia Symposium

In 2015, NIDCR organized a symposium at the American Association for Dental Research meeting titled “Glass Ceiling or Sticky Floor: Barriers for Women in Dental Academia.” This symposium involved speakers from academia and NIH, highlighted workforce diversity/inclusion and NIH funding statistics, and included an open discussion about challenges for women entering and re-entering the academic and research workforce.

10th and 11th Annual NIH Pain Consortium Symposia

The 10th annual NIH Pain Consortium Symposium was held at NIH May 26–27, 2015. The symposium titled “Looking Back to the Future: Advances in Pain Research in Brain Imaging, Neural-glia Mechanisms, Genetics and Epigenetics, Novel Therapy Development, and Cognitive and Emotional Influences” brought together panels of basic, translational, and clinical researchers to discuss the cognitive and emotional aspects of pain, genetics and epigenetics of pain, pain signatures and predictors from imaging research, neuron-glia mechanisms of chronic pain, and novel treatments for pain. On May 31 and June 1, 2016, NIH hosted the 11th Annual NIH Pain Consortium Symposium titled “Innovative Models and Methods” and focused on existing and future models and methods to better understand pain mechanisms that could lead to the development of improved treatments. Panels of basic, translational, and clinical researchers addressed lessons learned in translational research, bridging the gap between models and the clinic, and applying new approaches to pain research. At each symposium, a poster session included a broad selection of current pain research findings presented by young investigators.

Eighth Scientific Meeting of the TMJ Association

The Eighth Scientific Meeting of the TMJ Association, co-sponsored by NIDCR, took place

September 11–13, 2016, in Bethesda, Maryland. The theme was “How Can Precision Medicine Be Applied to Temporomandibular Disorders and Its Comorbidities?”

MDEpinet TMJ Patient Roundtable

The MDEpinet TMJ Patient Roundtable, organized by the TMJ Association and the U.S. Food and Drug Administration (FDA), held on June 16, 2016, was a first-of-its kind collaboration in the TMD area, bringing stakeholders together to address data on implant performance, surgical outcomes, and adverse events in an effort to: (1) develop outcome and assessment and reporting tools based on patient input; (2) explore the multidisciplinary-interdisciplinary intersection of patient biology, anatomy, genetics, and physiology with TMJ medical devices and clinical patient-centered outcomes to better target therapies; and (3) develop evidence to incorporate patient-centered data into clinical care. Participants included TMD patients, patient advocates, industry, clinicians, and representatives from NIH, FDA, and the Agency for Healthcare Research and Quality.

Trans-NIH Sex as a Biological Variable Working Group

Along with the NIH effort to improve rigor and reproducibility, a working group was formed in 2015 to develop and implement policies requiring applicants to consider sex as a biological variable in the design and analysis of NIH-funded research involving animals and cells. Led by Dr. Janine Clayton, the working group provided input and feedback to this policy, with representation from NIDCR. This policy has been developed and was implemented for applications submitted January 25, 2016, and thereafter, as announced in the publication of notice number *NOT-OD-15-102* (Consideration of Sex as a Biological Variable in NIH-Funded Research).

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National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Executive Summary and Overview

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports biomedical and behavioral research to address some of the most common, costly, and chronic diseases and conditions affecting the U.S. and global populations, including diabetes, obesity, endocrine and metabolic diseases; digestive diseases and nutritional disorders; and kidney, urologic, and hematologic diseases. Many of the diseases and conditions within NIDDK's research mission affect women solely, disproportionately, or in unique ways. For example, only women develop gestational diabetes mellitus (GDM); women lose their comparative cardiovascular disease risk protection when they develop chronic diabetes; African-American women experience the highest rates of obesity; obesity increases risk for myriad health problems of special interest for women, including cardiovascular disease, gallbladder disease, and GDM; women are more prone to autoimmune disorders, including autoimmune thyroid and liver diseases; bowel and bladder control problems are much more prevalent in women; and women are most highly affected by chronic pain syndromes associated with the bladder (interstitial cystitis/bladder pain syndrome [IC/BPS]) and gut (irritable bowel syndrome [IBS]). NIDDK supports a diverse portfolio of research important to women's health, including studies of—

- Diabetes in women (including type 1, type 2, and GDM)
- Diabetes health complications, including urologic problems, sexual dysfunction, and depression
- Obesity prevention and treatment
- Thyroid and parathyroid conditions and diseases

- Endocrine regulation of bone metabolism and osteoporosis
- IBS
- IC/BPS
- Fecal and urinary incontinence
- Kidney diseases and kidney failure
- Liver and biliary diseases
- Urinary tract infections (UTIs)

Sex/gender differences research also is revealing new information about how susceptibility, onset, progression, or treatment efficacy for diseases and conditions within NIDDK's mission may differ between women and men. Similarly, microbiota and microbiome studies intersect with a number of these areas and are providing new insights.

The scope of NIDDK's women's health research crosses the Institute's three extramural research divisions—the Division of Diabetes, Endocrinology, and Metabolic Diseases; the Division of Digestive Diseases and Nutrition; and the Division of Kidney, Urologic, and Hematologic Diseases—as well as NIDDK's Division of Intramural Research. Their efforts are enhanced by activities of NIDDK's Office of Obesity Research, Office of Minority Health Research Coordination, and Office of Nutrition Research. NIDDK and the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) also work together to foster research in many of these areas.

Some NIDDK-supported research, such as the study of the relationship of obesity and diabetes to cardiovascular disease and the study of diabetes during pregnancy, also may have an important impact on diseases and conditions that are primarily within the mission of other NIH Institutes and Centers (ICs), and the Institute will often seek to synergize IC efforts. NIDDK promotes public health education and awareness through the efforts

of its Office of Communications and Public Liaison. Key efforts include the National Diabetes Education Program, a joint effort of NIDDK and the Centers for Disease Control and Prevention (CDC), the National Kidney Disease Education Program, and the Weight-control Information Network. Finally, NIDDK conducts strategic planning efforts for research in major areas of its portfolio on a regular basis; many of these are germane to women's health, and include input and/or partnership from ORWH. Examples of women's health and sex differences research accomplishments and activities supported by NIDDK in fiscal years (FY) 2015 and 2016 follow, categorized under diabetes, obesity, healthy pregnancy program, microbiota and microbiome studies, chronic pain conditions, kidney disease, and urologic health.

Accomplishments and Activities

Diabetes

Type 2 Diabetes Prevention—How a Factor Specific to Women Affects Intervention Efficacy

Information important to diabetes prevention in women continues to emerge from the Diabetes Prevention Program (DPP) and its long-term follow up, the DPP Outcomes Study (DPPOS). In 2002, the DPP clinical trial results showed that, in a racially, ethnically, and age-diverse cohort of obese and overweight adults with elevated blood glucose levels, an intensive lifestyle intervention (ILI; i.e., exercise and diet to induce moderate weight loss) reduced the risk of developing type 2 diabetes by 58 percent. The diabetes drug metformin reduced diabetes risk by 31 percent (Knowler et al, 2002). Sixty-eight percent of the DPP study participants were women, of whom 16 percent had a history of GDM, which has enabled researchers to study the efficacy and long-term effects of DPP interventions in women with this risk factor. ORWH support facilitated recruitment and retention of these women. In a previous report, DPP researchers

found that ILI was more effective than metformin in the DPP participants as a whole and in parous women without GDM, but that metformin was as effective as ILI in women with a history of GDM—i.e., metformin was much more effective in women with a history of GDM than in those who had not had GDM with previous pregnancies (Ratner et al., 2008). A report from DPPOS has extended these findings further: After 10 years of observational follow-up, risk for developing type 2 diabetes remained higher in women with a history of GDM, and both ILI and metformin were very effective in reducing progression to diabetes in those women. In contrast, only ILI, and not metformin, was effective in delaying diabetes onset in parous women without a history of GDM (Aroda et al., 2015). This difference has implications for clinical care. DPPOS also has been examining intervention effects on other outcomes, including diabetes complications and comorbid conditions, such as depression. Renewed for a third 5-year period and also co-funded by ORWH, DPPOS will investigate whether starting metformin during prediabetes leads to lower rates of cardiovascular disease and cancer. The DPPOS cohort is 67 percent female, and sex/gender differences in the rates of these outcomes will be examined.

Impact of Youth Diabetes on Pregnancy

Girls are disproportionately represented in the pediatric population with type 2 diabetes—a difference not observed in adults with the disease. Both diabetes, especially if not well-controlled, and young age are known to confer high risk to mothers and their infants. Despite the rising prevalence of type 2 diabetes in the pediatric population, however, data on rates and outcomes of pregnancy in girls with type 2 diabetes are limited. New findings about the impact of diabetes on girls and pregnancy have emerged from the NIDDK-supported Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) Study. This clinical trial compared the efficacy of three treatment arms (metformin, the only U.S. Food and Drug Administration-approved oral diabetes drug for treatment in children, metformin plus rosiglitazone,

and metformin plus an ILI) in a diverse cohort of youth ages 10–17 years; about 65 percent of the cohort was female. Key trial findings included a higher than expected failure rate for all treatments and that type 2 diabetes is actually more aggressive in youth than in adults (TODAY Study Group et al., 2012). Because one of the treatment arms involved use of a pregnancy class C drug, part of informed consent for the TODAY trial emphasized avoidance of pregnancy; however, a higher than anticipated number of pregnancies occurred during the trial (*note, once a pregnancy was detected at a study visit, the participant no longer received study drugs until postpregnancy/lactation*). In a retrospective analysis of available data, TODAY researchers found that, of the 452 female participants enrolled in the TODAY Study, 46 (10.2 percent) had 63 pregnancies during study participation, a rate consistent with the overall rate of teen pregnancy in the United States at the time of the study. The mean age at first pregnancy was 18.4 years, with a mean diabetes duration of 3.4 years. Poor pregnancy outcomes were observed, with 26.4 percent of pregnancies ending in a miscarriage, stillbirth, or intrauterine death, and 20.5 percent of the live-born infants having a major congenital anomaly. Whereas the former is consistent with what has been observed in adult women with diabetes, the latter is much higher and suggests that pregnancies in girls with type 2 diabetes may be especially prone to these anomalies, although the reasons remain uncertain (obesity and glucose control being possible candidates) (Klingensmith et al., 2016). These findings emphasize both the importance of type 2 diabetes prevention in youth and the need for further data on pregnancy outcomes and long-term health of children born to girls and young women with type 2 diabetes. TODAY2, the observational follow-up on the trial, is collecting data on new pregnancies prospectively.

Paving the Way to Improving Urologic Complications in Women with Type 1 Diabetes

Diabetes affects nearly every organ and tissue in the body, with a spectrum of ensuing health

complications. A better understanding of urologic complications is of particular interest for women, who are already disproportionately affected by noncancerous urologic diseases and conditions. Insights into urologic complications in women with type 1 diabetes continue to emerge from the Diabetes Control and Complications Trial and its ongoing observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC). One report has found that the incidence of urinary incontinence (UI) reported by women at year 17 of EDIC was associated with poorer blood glucose control during the first 10 years of EDIC, while adjusting for other clinical factors (Lenherr et al., 2016a). This is the first study to demonstrate a direct association between blood glucose control and UI. Similarly, among 572 women evaluated at EDIC year 17 (mean age 50.7 +/-7.2 years), researchers found a positive association between poorer blood glucose control during the preceding year and the number of UTIs reported during the same period, also while adjusting for other clinical factors (Lenherr et al., 2016b). Both findings suggest that improved glucose control—already important to other aspects of health in people with diabetes—could reduce future risk of urologic problems in women with type 1 diabetes.

Obesity

Leveraging Look AHEAD (Action for Health in Diabetes)—Examining Weight Loss and Health in Older Women and Men with Type 2 Diabetes

Research will build on the Look AHEAD clinical trial, which studied the effects of an ILI (healthy eating, increased physical activity) for weight loss in overweight/obese adults with type 2 diabetes; nearly 60 percent of the 5,100 participants were women. Spearheaded by NIDDK, Look AHEAD past co-sponsors included the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Nursing Research, ORWH, the National Institute of Minority Health and Health Disparities, and CDC. The intervention, now complete, led to

many health benefits, although it did not reduce the incidence of cardiovascular morbidity or mortality. In its new follow-up phase (approximately 3,800 participants), co-funded by NIDDK and the National Institute on Aging (NIA), Look AHEAD is evaluating whether the intervention has longer term effects on increasing lifespan, reducing health care costs, and other aspects of healthy aging. Sex/gender analyses will be run on all outcomes.

Weight and Fracture Risk in Women

Both conditions of severe underweight, as in anorexia nervosa (AN), and excess weight heighten certain fracture risks, but as bone mineral density in obese women often is normal or high when compared to that of lean women (unlike in women with AN), the underlying causes for this similarity must differ. Researchers comparing vertebral strength in women with AN, lean women, and obese women found that lean and obese women had similar strength, while that of AN women was lower. They also examined vertebral loads and calculated measures reflecting fracture risk during different activities (e.g., standing, holding, lifting, bending) in the three groups. Vertebral loads were highest in obese women and lowest in AN women for standing, holding, and lifting, but were highest in AN women for bending. Measures reflecting fracture risk were highest in obese women for standing and lifting, whereas women with AN had the highest measure for bending. These and other results suggest that examining the load-to-strength ratio helps explain increased fracture risk in both low-weight and obese women (Bachmann et al., 2016).

Physical Activity, Fat Accumulation, and Sex Differences

Fundamental and clinical studies together are revealing sex-specific aspects of the biology underlying energy balance and obesity. For example, researchers working in female mice recently identified—among estrogen-responsive hypothalamic neurons in the brain believed to be involved in metabolism and reproductive success—a subpopulation of neurons that is

dedicated to driving physical activity in females. Notably, disrupting development of these neurons resulted in female-specific obesity and inactivity (Correa et al., 2015). Advances also have been made in the genetics of fat accumulation and distribution through studies employing genomic scans involving hundreds of thousands of individuals, most of European ancestry, including finding that a subset of the genomic variants identified for each of these two aspects of fat biology showed sex-based differences in their impact (Locke et al., 2015; Shungin et al., 2015).

Benefits and Risks of Weight-Loss Surgery to Treat Obesity

One treatment approach for extreme obesity is bariatric surgery—a form of weight loss surgery that involves altering the capacity and/or the anatomy of the digestive system. More than 80 percent of persons undergoing this surgery are female, and the majority of patients are white. Increasing evidence suggests that bariatric surgery is not only a useful tool for promoting and sustaining substantial weight loss, but that it also can be beneficial for treating type 2 diabetes, and studies are ongoing to better characterize and understand this effect. For example, results from an NIDDK-supported study in which 71 percent of the participants were female have shown that of two types of bariatric surgery—Roux-en-Y gastric bypass (RYGB) and laparoscopic adjustable gastric banding (LAGB)—RYGB is much more effective at inducing long-term type 2 diabetes remission. The study also suggests that factors in addition to weight loss may play a role in the greater likelihood of diabetes remission with RYGB (Purnell et al., 2016). These findings emerged from research conducted in the Longitudinal Assessment of Bariatric Surgery (LABS)-2, a prospective study of patients undergoing weight-loss surgery at one of 10 different hospitals across the United States. Obesity is a risk factor for UI, which is much more common in women than men, and another study from LABS-2 has examined the impact of bariatric surgery on improvement and remission of UI in women and men in the first 3 years after

surgery. The researchers reported that although the prevalence of UI post-surgery was higher at 3 years than at 1 year, it still was significantly lower than at baseline (prior to surgery). They also found that improvements were associated with weight loss, younger age, and absence of a severe walking limitation (Subak et al., 2015). These NIDDK-supported studies provide further insight into potential health benefits and risks of a treatment used predominantly by women.

Healthy Pregnancy Program

Numerous observational studies have linked preexisting overweight/obesity and/or excessive gestational weight gain during pregnancy to short-term and long-term adverse health consequences in both mothers and offspring. Additional research is needed, however, to identify effective interventions that will improve weight, glucose levels, and other pregnancy-related outcomes in mothers and determine whether these interventions affect obesity and metabolic abnormalities in the offspring. An estimated 7 percent of women will develop GDM during pregnancy; about half of these women will develop type 2 diabetes 5–10 years postpartum (Kim et al., 2002), and offspring of GDM-affected pregnancies are at increased risk for obesity and diabetes. Moreover, results from the Hyperglycemic and Adverse Pregnancy Outcome (HAPO) study suggested that elevated maternal glycemia even below levels diagnostic of GDM is associated with adverse pregnancy outcomes. To help address these key issues surrounding obesity and diabetes/hyperglycemia during pregnancy, NIDDK supports a Healthy Pregnancy Program, which encompasses the following efforts:

- **The LIFE-Moms Consortium.** LIFE-Moms has been testing lifestyle interventions in overweight and obese pregnant women that may reduce inappropriate gestational weight gain and/or improve metabolic status, with potential short- and long-term health benefits for mothers and offspring. The consortium consists of seven clinical studies in a broad

range of populations, including minority and socio-economically disadvantaged groups, and a research coordinating unit. Different intervention strategies are being tested, such as home visits by parent-educators and individual or group lifestyle programs in clinical settings. The individual trials have completed their intervention programs through the end of pregnancy (delivery), and it is anticipated that the first results will become available in 2017. Follow-up is continuing through 1 year postdelivery for the women and 1 year of age for the offspring. This effort is co-sponsored by NIDDK (serving as lead), NHLBI, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Complementary and Integrative Health, ORWH, and the Office of Behavioral and Social Sciences Research (OBSSR).

- **The HAPO Follow-Up Study (HAPO-FUS).** HAPO-FUS is a multisite observational study, conducted at 10 of the original HAPO sites, that is leveraging the well-characterized HAPO study population to determine whether hyperglycemia during pregnancy less severe than GDM influences later levels of obesity in children and development of diabetes in mothers after giving birth. HAPO-FUS has completed recruitment, with 4,810 mother-child pairs; results of the analyses are expected to be reported in summer 2017. This study is co-sponsored by NIDDK and NICHD.
- **The Post-Gestational Diabetes Awareness Campaign.** This ongoing effort of the National Diabetes Education Program is part of its “*Small Steps, Big Rewards. Prevent Type 2 Diabetes*” campaign. One goal for this educational component is to help women with a history of GDM and children affected by GDM adopt and maintain healthy behaviors. Another is to expand outreach to health care professionals who are counseling women and families affected by GDM. FY 15–16 efforts included outreach to women with a history of

GDM through social media efforts, promotions around Mother's Day/Women's Health Week, and a blog post authored by the NIDDK Director titled "It's Never Too Early to Prevent Type 2 Diabetes."

In related efforts, the Intervention Nurses Start Infants Growing on Healthy Trajectories (INSIGHT) randomized clinical trial (NCT01167270), which is comparing a home-based responsive parenting (RP) intervention for infant prevention of weight gain that is primarily focused on mothers to a control intervention, has already found RP to be associated with reduced rapid weight gain in offspring during the first 6 months after birth and reduced overweight status at age 1 year (Savage et al., 2016). Additionally, in FY 16, NIDDK initiated plans for a small scientific workshop at which participants will focus on the early diagnosis and overall pharmacological management of GDM. It is hoped this workshop will address current gaps in knowledge and lay the foundation for future research initiatives.

Microbiota and Microbiome in Health and Disease

Research to understand the trillions of microbes living in various body niches—e.g., gut, urogenital tract—and their interaction with their hosts is providing new insight into health and disease states and is already showing potential for treatment strategies. Obesity, digestive diseases, and nutrition have been some of the immediate targets, but studies of the microbiota (microbes) and microbiome (the microbial genetic material) are providing insights into other conditions as well. For example, researchers working in a female mouse model have found evidence that the intestinal microbiota modulates inflammatory responses caused by sex steroid deficiency that lead to trabecular bone loss. Furthermore, treatment of the sex steroid-deficient mice with probiotics protected against this bone loss (Li et al., 2016). If these findings hold true in humans, it could lead to a new approach for preventing postmenopausal bone loss. Microbiota composition also is under

study. For example, a recent study looked at, among other factors, the impact of mode of delivery (vaginal versus cesarean) on microbiota diversity in offspring, and found that after the first few months of life, infants delivered by cesarean section had less diverse and less mature gut microbial communities than did vaginally delivered infants (Bokulich et al., 2016). Although the long-term implications of such differences on health and disease remain to be understood, such knowledge could potentially assist women and their health care providers in optimizing outcomes for their offspring in the future. In addition to recent activities encouraging new research on the gut microbiota/microbiome and host interactions in digestive diseases and nutrition, a new grant will focus on the relatively recently discovered "female urinary microbiota" that exists in the bladder of many adult women, and whether it plays a role in UI (1R01DK104718-01A1). Notably, this grant received critical funding from ORWH through its R56 program.

Chronic Pain Conditions

IBS

The functional gastrointestinal disorder IBS causes pain and constipation or diarrhea and is more common in women than in men. Although diet and stress contribute to this disorder, its underlying causes are unknown. Symptoms may be influenced by abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. A key goal for research is to understand the interplay of gut and brain pathways in these disorders and to build upon this knowledge to design effective treatments. Researchers also are examining sex and gender differences in this interplay. Pivotal work in these areas has been conducted by investigators at a Specialized Center of Research (SCOR) at the University of California, Los Angeles, co-funded by NIDDK and ORWH. A recent study from this center suggests that people with IBS engage brain regions involved in threat appraisal and emotion more than healthy people do when facing

an uncertain threat of pain; this difference was primarily seen in women with IBS when compared to their healthy counterparts (Hong et al., 2016). These results provide clues into the role of brain response to uncertainty in symptom experience in those with IBS. Another study has shown that early adverse life events are associated with IBS, providing evidence of a strong relationship between several types of childhood trauma and the risk of developing IBS later in life (Park et al., 2016). Likewise, further research from this SCOR showed that, in an animal model, stress in early life (ELS) causes changes in the brain that cause the animals to be more sensitive to abdominal pain later in life. Notably, although when grouped by ELS versus non-ELS, male and female animals showed no differences in the physical response to pain, the researchers did find sex-based differences in brain activation responses in these groups. They also found that ELS exposure appeared to affect male and female brain function differently (Holschneider et al., 2016). In addition to supporting these studies, NIDDK also is leveraging this SCOR to build upon the success of the IBS Outcome Study, a multicenter clinical trial with the goal of determining whether self-administered cognitive behavioral therapy is helpful in reducing IBS symptoms and overall burden. NIDDK has been supporting a study that will combine the recruitment, assessment, and treatment components of the IBS Outcome Study (IBSOS) with the brain imaging technology at the SCOR to investigate the neurobiological mechanisms underlying cognitive behavioral therapy for IBS. The study also will develop tools to predict which patients may benefit from these treatments (R01DK096606). The IBSOS itself recently demonstrated that people with IBS exhibit variations in memory of pain and other symptoms over time; these findings could help inform both clinical research and clinical practice (Lackner et al., 2014).

Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

The multicenter MAPP Research Network is conducting innovative, collaborative studies of urologic chronic pelvic pain syndrome (UCPPS), which encompasses the two most common chronic urological pain disorders, IC/BPS in women and men, and chronic prostatitis/chronic pelvic pain syndrome in men. Since its inception in 2008 and renewal/expansion in 2014 with co-support from ORWH, the Network's unique approach has entailed searching "beyond the bladder/prostate" to find the causes of these conditions, including studying the possible relationships between these conditions and other chronic pain disorders, such as IBS, fibromyalgia, and chronic fatigue syndrome. For example, MAPP Research Network findings germane to women with IC/BPS include new insights into the course of UCPPS, such as symptom variability over time (Stephens-Shields et al., 2016), potential biomarkers for pain and for IC/BPS itself (Schrepf et al., 2015; Parker et al., 2016), the importance of self-reported symptom "flares" in assessing these conditions and in patient quality of life in women (Sutcliffe et al., 2015), and initial insights into lower urinary tract microbiota differences between women reporting flares and those who did not (Nickel et al., 2016). Network scientists also have continued to report on a variety of differences in brain structure and function between women with IC/BPS and their healthy counterparts (Farmer et al., 2015; Martucci et al., 2015), as well as brain microstructural differences distinguishing UCPPS from another pain syndrome common in women, IBS (Woodworth et al., 2015). Many of the findings from Phase I of the Network currently are being pursued through a multifaceted Trans-MAPP Symptoms Patterns Study to determine their potential role(s) in symptom manifestation, maintenance, and amelioration. For more information, please see the MAPP Research Network website: www.mappnetwork.org.

New Insights into Pain Pathways in Women and Men

Clarifying underlying causes of symptoms in chronic pain conditions is helpful for clinical treatment. Researchers recently examined possible autonomic nervous system (ANS) contributions to chronic pelvic pain (CPP) conditions in women. Nerves that are part of the ANS regulate unconscious activities, such as heart rate, blood pressure, digestion, and bladder function. If ANS nerves malfunction or become damaged, however, a person can experience such symptoms as dizziness, increased or decreased sweating, and problems with urination. Overall, and in combination with earlier research, the study results suggest that women with CPP (IC/BPS and/or myofascial pelvic pain), particularly women with IC/BPS, may have systemic neural changes, rather than nerve problems restricted to, for example, the bladder. The indicator of this systemic change, called vagal tone withdrawal, can potentially be addressed therapeutically (Chelimsky et al., 2016). Another study looked at whether being male or female can influence pain sensitivity (pain stimulus threshold) and/or pain inhibition (degree of stimulus response). The researchers found significant differences between healthy women and men both in their sensitivity to pain and in pain inhibition, even after controlling for differences in sleep quality and depressive symptoms. Men were more tolerant of pain and showed more efficient pain conditioning than women. These results suggest that there are underlying biological differences between women in men in pathways affecting pain experience that could help explain observed differences in chronic pain condition prevalence and symptom severity. Future research could help clarify this and also help determine whether targeting pathways involved in pain sensitivity and pain inhibition in different ways in women and men—e.g., by using different therapies, or by administering the same intervention in different amounts—could help better alleviate pain burden in women (Bulls et al., 2015).

Sex/Gender Differences in Kidney Disease

Researchers continue to assess sex and gender differences in the healthy and diseased kidney. For example, NIDDK scientists studying autosomal-dominant polycystic kidney disease (ADPKD) observed sex differences in the severity of the disease in mice. Specifically, they found that in mice with a knockout in the gene homologous to human *PKD1* (the primary gene affected in the human disease), adult females had less severe kidney cystic disease, and more severe liver cystic disease, when compared to male counterparts; this observation is consistent with reports in humans. They also found evidence of correlation between the partial protection in females and differences in lipid metabolic pathways. Notably, global gene expression profiles in normal male and female mouse kidneys differed almost as much as those of normal and cystic kidneys (Menezes et al., 2016). In addition to advancing understanding of underlying mechanisms in ADPKD, the results highlight the importance of controlling for sex in treatment studies using mouse models. A female-protective effect generally is observed in chronic kidney diseases in humans—i.e., prevalence and progression in males is worse for many of these diseases—but information about differences in acute kidney injury is less clear. Planning has begun for a new NIDDK initiative, the Kidney Precision Medicine Project, that may help to provide new insights into both sex and gender differences in chronic and acute kidney disease. More information is available at www.niddk.nih.gov/research-funding/research-programs/Pages/kidneyprecisionmedicine.aspx.

Urologic Health

Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium

Problems affecting the bladder and the urethra, including UI, UTIs, overactive bladder, and IC/BPS, as well as many others, occur much more frequently in women than in men. Researchers and health

care providers use the term lower urinary tract symptoms, or LUT symptoms, to refer to symptoms associated with any type of lower urinary tract dysfunction or condition, as well as those with as-yet unidentified cause. LUT symptoms and their associated conditions not only have a direct negative impact on health, but also exacerbate or contribute to other chronic health problems in women, including obesity, diabetes, and depression. To date, the majority of public and private research efforts have focused on management and treatment of severe LUT symptoms. NIDDK is spearheading a Women's Urologic Health Research Program at the NIH with an emphasis on prevention of LUT symptoms in women. Input and support for this effort has come from the U.S. Department of Health and Human Services (HHS) Office of Women's Health (OWH), multiple NIH ICs, other federal agencies, external scientific and clinical experts from multiple disciplines, and professional and health advocacy groups. In collaboration with NIA, OBSSR, and ORWH, NIDDK established the Prevention of Lower Urinary tract Symptoms (PLUS) Research Consortium in 2015. This multicenter, multidisciplinary consortium is undertaking qualitative and quantitative research studies necessary to establish the scientific basis for future prevention-intervention research targeting LUT symptoms and conditions in women and girls, including obtaining information from girls and women of various ages to define a healthy bladder and identify normal bladder behaviors, and looking at protective factors for lifelong bladder health and risk factors for various types and degrees of conditions that manifest in LUT symptoms.

Urinary Tract Infections

Women are especially prone to UTIs, primarily due to differences in female and male anatomy of the urinary tract, and many women suffer from recurrent infections. The leading cause of UTIs is exposure to uropathogenic *Escherichia coli* (*E. coli*) bacteria, also referred to as UPEC. Although UTIs are currently treatable with antibiotics, the emergence of antibiotic-resistant microbes, combined with the personal and medical costs of

care, makes finding better therapeutic strategies a priority. Researchers, including scientists at a SCOR at Washington University in St. Louis that is co-supported by ORWH and NIDDK, continue to gain insights into host and bacterial factors that contribute to UPEC UTIs. For example, SCOR scientists recently uncovered evidence that many UPEC isolated from human infections may use a combination of a cytotoxic molecule, a virulence gene regulating system, and manipulation of a host cell death pathway to fine-tune the timing and degree of infected host cell exfoliation to optimize their own ability to infect new bladder cells and establish persistent infection (Nagamatsu et al., 2015). Another research team has identified several “fitness” genes expressed by UPEC to protect themselves from human host defenses (Subashchandrabose et al., 2014); such genes represent potential new therapeutic targets for UTI prevention or treatment. Other approaches may emerge from knowledge of a host cell pathway involved in removal of invading pathogens (Miao et al., 2015), as well as from the finding that excessive activity by neutrophils during a bladder infection may actually predispose the bladder to recurrent UTIs—and that there may be a way to modulate this activity (Hannan et al., 2014). At the same time, a study in mice suggests that *E. coli* that can invade and multiply in the urinary tract but do not cause symptomatic UTIs may be an effective “probiotic” therapy against UPEC. The researchers found that administering the asymptomatic bacteria to mice infected with UPEC could both reduce UPEC numbers and measures of pelvic pain. One particular asymptomatic isolate from humans was not only comparable to a standard course of ciprofloxacin antibiotic treatment, but provided early and dramatic pain relief that the antibiotic does not (Rudick et al., 2014).

Supporting Implementation of the NIH Strategic Plan for Women’s Health Research

NIDDK Activities Mapped to the Strategic Plan

Sex/Gender Differences in Kidney Disease—ADPKD Study Strategic Plan Goals and Objectives:

Goal 1— Increase Sex Differences Research in Basic Science Studies

Top objective:

- 1.4 Include sex parameters in the design of experiments using animal models.

Other objectives:

- 1.1 Encourage genetic and epigenetic studies to identify sex differences in gene expression.
- 1.2 Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

PLUS Research Consortium Strategic Plan Goals and Objectives:

Goal 3— Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women

Top objective:

- 3.5 Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

Other objectives:

- 3.1 Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan.

- 3.8 Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

Other NIDDK Activities Relevant to the Strategic Plan

As noted under “Accomplishments,” NIDDK has fostered both basic and clinical research resulting in advances in understanding sex/gender differences in disease areas within its mission. In addition to continued sex/gender analysis in basic research and in or ancillary to large-scale clinical studies, a number of new efforts will promote analysis of sex/gender differences. For example, NIDDK made career development awards for research focused on fundamental sex differences in the enteric nervous system that could contribute to sex differences in gastrointestinal motility (1K08DK110532-01), sex differences in adipogenic potential of adipose tissue myeloid cells in humans (1K01DK109053-01A1), and sex differences in hepatic gene expression in human adults and children that could affect viral gene therapy approaches for treating genetic liver diseases (1K01DK107607-01A1), and is newly supporting a research project in animal models focused on sex differences in visceral hypersensitivity (pain) (1R01DK103759-01) and another using cell and animal models to study kidney function and hypertension that will also continue advancing our understanding of sex differences in this organ (1R01DK107694-01). NIDDK also participated in the ORWH-led effort to provide administrative supplements for research on sex/gender differences in both FY 15 and FY 16, and the Institute will continue to work with ORWH to identify new opportunities to promote sex/gender differences research.

NIDDK Positions Relevant to Women's Health

NIDDK's scientific staff includes a Program Director for Women's Urologic Health who—with input from ORWH, the HHS Office of Women's Health, and other NIH ICs—is developing the prevention-focused research program to improve women's urologic health described previously. NIDDK's Healthy Pregnancy Program involves the efforts of program directors from two extramural research divisions plus the NIDDK Office of Obesity Research. A Women's Health Liaison to ORWH in NIDDK's Office of Scientific Program and Policy Analysis coordinates efforts across the Institute and works with ORWH to foster partnerships in areas of joint interest.

Inclusion Efforts

NIDDK activities that have expanded or lay the foundation to expand participation of girls and women in clinical research in trials include the Women's Urologic Health Research Program and the PLUS Consortium, which are bringing girls and women into clinical research focused on prevention of urologic symptoms across the lifespan, with the anticipated accompanying benefit of improved overall health.

Career Development Efforts In Science, Technology, Engineering, and Mathematics (STEM) Fields

Ongoing research training initiatives developed by the NIDDK Office of Minority Health Research Coordination focus on developing and training new and young investigators. Specifically, efforts and programs focus on individuals who are underrepresented in biomedical research, including

students with disabilities, those from disadvantaged backgrounds, and those from certain racial and ethnic minorities in the United States. Although not focused solely on girls and women, these initiatives—Short Term Research Experience for Underrepresented Persons (STEP UP) (high school), STEP UP (undergraduate), and Diversity Summer Research Training Program—encourage entry into NIDDK-relevant STEM areas by girls and women who might not otherwise have an opportunity to do so. In FY 15–16, girls and women constituted the majority of participants in all three programs.

Information and Education Initiatives

NIDDK continues to support a number of education and awareness campaigns important to women's health. In addition to efforts already cited under “Accomplishments,” these include:

The Weight-control Information Network (WIN) program, “*Sisters Together: Move More, Eat Better.*” For FY 15–16, the *Sisters Together* Program Guide was promoted via social media and Web-based newsletters to raise awareness about the content and to encourage groups and individuals to consider creating a community-based program.

Outreach and Promotion Related to Women's Health. In FY 15–16, NIDDK sought to raise awareness and provide evidence-based information about diseases and conditions commonly affecting women through a variety of channels, including “eblasts” to raise awareness of national health observances, Facebook posts to promote NIDDK publications related to women's health and to highlight National Women's Health Week, and distribution of publications related to women's health at conferences and health fairs and during National Women's Health Week.

FY 15–16 Funding Initiatives, Workshops, and Conferences

Requests for Applications (RFAs)

Psychosocial and Behavioral Mechanisms in Bariatric Surgery (R01) (RFA-DK-16-017). The purpose of this RFA is to support research to measure psychosocial and behavioral variables in individuals undergoing bariatric surgery to understand how they predict success and risk and examine mechanisms of behavior change. RFA sponsor: NIDDK.

Identification of Mechanisms Mediating the Effects of Sleep on Diabetes-Related Metabolism in Humans (R01) (RFA-DK-16-005). The purpose of this RFA is to invite applications that investigate the mechanisms mediating the interactions between sleep and diabetes-related metabolism using deep metabolic phenotyping approaches in healthy human populations and those with metabolic and/or sleep disorders. RFA sponsors: NIDDK and ORWH.

As noted under Accomplishments, NIDDK also renewed the DPPOS for a third 5-year period through two limited competition RFAs (RFA-DK-15-503, RFA-DK-15-505), funded a follow-up study to the TODAY clinical trial (RFA-DK-15-504), and funded a follow-up study of Look AHEAD (RFA-DK-15-501).

Program Announcements (PAs)

NIDDK participated in the following:

- Administrative Supplements for Research on Sex/Gender Differences (Admin Supp.) (PA-15-034, PA-16-066).
- Underactive Bladder in Aging (R01) (PA-15-049).
- Advancing Mechanistic Probiotic/Prebiotic and Human Microbiome Research (R01) (PA-15-135).

- Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (Admin Supp.) (PA-15-321).
- Mechanisms, Models, Measurement, and Management in Pain Research (R01) (PA-16-188).

Conferences and Workshops

Functional Bowel Disorders Workshop: Future Research Directions in Pathophysiology, Diagnosis and Treatment: June 23–24, 2016. The purpose of this workshop was to review recent advances in functional bowel disorders, including IBS, and to identify new directions for research.

Kidney Precision Medicine Meeting: May 23–25, 2016. In recognition of the heterogeneity of kidney diseases, how they present in individuals, and limited therapies, the purpose of this meeting was to bring together experts from multiple fields to help inform a research effort that could lead to more precise treatment of acute and chronic kidney disease. Biological sex was one of the variables discussed. A meeting summary is available at: www.niddk.nih.gov/news/events-calendar/Documents/KPMP%20Meeting%20Summary.pdf.

Behavioral Phenotyping of Physical Activity and Sedentary Behavior: December 1–2, 2015. The purpose of this meeting was to understand and identify promising research opportunities in behavioral and psychological phenotyping related to variation in physical activity and sedentary behavior in the context of obesity prevention and treatment or weight-loss maintenance.

Workshop on Behavioral and Psychosocial Factors in Women with Urinary Incontinence: March 30, 2015. The purpose of this workshop was to convene clinical and psychosocial researchers and explore the effect of individual differences in behavioral and psychosocial (nonbiologic) factors on the treatment trajectory and response in women with UI and to identify new research opportunities.

A meeting summary is available at: www.niddk.nih.gov/news/events-calendar/Pages/workshop-behavioral-factors-women-ui.aspx.

Urinology Think Tank: February 9, 2015. The purpose of this small meeting was to review and discuss the likelihood that urine has an active biological role that extends beyond its existences as the fluid of waste and excess water, which is relevant to current questions regarding the interaction of diet and lower urinary tract symptoms. A meeting summary is available at: www.niddk.nih.gov/news/events-calendar/Pages/urinology-think-tank_02-2015.aspx.

Research Needs for Effective Transition in Lifelong Care of Congenital Genitourinary Conditions: February 2, 2015. The purpose of this multidisciplinary workshop was to identify research needs for improving the quality of care provided for adolescents/young adults with complex chronic conditions involving the genitourinary systems as they transition to independence and the adult health care delivery system; many of the research needs identified focus on women and are outlined in a published workshop summary report (Hsieh et al., 2017).

Health Disparities in Women

Several of the diseases that disproportionately affect racial and ethnic minority populations in the United States are high-priority research areas for NIDDK. Some of these diseases, such as obesity and type 2 diabetes, also affect women and men differently within these disproportionately affected groups. The NIDDK Office of Minority Health Research Coordination oversees Institute efforts to address these disparities. (Website: www2.niddk.nih.gov/OMHRC/OMHRCHome/OMHRCHome.htm.)

Several major NIDDK-supported research efforts pertain to health disparities in women—for example, the DPP/DPPOS and TODAY/TODAY2 study cohorts, which have more females than males—are highly ethnically and racially diverse, reflecting the disproportionate burden of diabetes

in racial and ethnic minority girls and women. Moreover, a recent report demonstrated successful translation of the DPP ILI to predominantly low-income Hispanic women in an urban community health center setting (Van Name et al., 2016). LIFE-Moms emphasized participant recruitment from disproportionately affected minorities and low socioeconomic status populations in the United States. A newly funded AREA award will examine disparities in diabetes comorbidities and multiple chronic conditions that are leading causes of death, including intersections with gender (1R15DK104260-01A1), while another project will examine factors and variables, including gender, influencing diabetes risk in Chinese immigrants (1R01DK104176-01A1). NIDDK's intramural research program also supports projects highly relevant to health disparities in women, such as differences in fat metabolism between African-American and white women that are relevant to effectively diagnosing vascular disease risk, and studies of obesity and GDM in Pima Indian women through participation in DPPOS, Look AHEAD, and LIFE-Moms, and through other efforts. In addition to support for pertinent “Information and Education Activities” already described, NIDDK communications activities important to health disparities in women include providing a variety of health information publications in Spanish and other languages.

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National Institute on Drug Abuse (NIDA)

Executive Summary

As the foremost authority on drug use disorders, sponsoring the vast majority of the world's research on the subject, the National Institute on Drug Abuse (NIDA) supports science that addresses the most fundamental and essential questions about drug use disorders. The Institute does this by monitoring emerging trends, identifying and studying underlying biological and social factors and consequences, and determining how best to use this knowledge to develop, test, and implement prevention and treatment programs. Within NIDA's mission is a focus on studying issues specific to women and identifying and studying sex/gender differences in both clinical and preclinical research. Research over the past few decades has shown that there are male/female differences in the initiation and progression of drug use disorders, the risk and protective factors, and the consequences of drug use disorder, as well as that intervention outcomes may be enhanced by sex/gender-specific considerations. In recognition of the important role of sex/gender differences in drug use disorders, NIDA continues its commitment to support research to identify sex/gender-specific aspects of drug use and addiction across the lifespan and to apply these findings to improve outcomes for both men and women.

This fiscal year (FY) 15–16 biennial report highlights NIDA's research on women and sex/gender differences and its activities to promote research in this area, including science, technology, engineering, and mathematics (STEM) efforts, which have been very successful in attracting women in biomedical science. NIDA's featured programs and research advances include both basic and clinical neuroscience and are shedding light on sex differences in biological and behavioral mechanisms, as well as the consequences of addiction. A striking feature of the research presented in this report is a translational emphasis. Brain imaging studies with smokers, for example,

are revealing sex differences in the neurobiological underpinnings of nicotine addiction—findings that hold promise for achieving sex-based nicotine cessation treatments. NIDA's cannabis studies, which are so important given the changes in marijuana laws across the Nation, are showing sex differences in marijuana use in a variety of measures. Studies of children who are prenatally exposed to drugs continue to find that effects of those exposures often differ in boys and girls. Studies of individuals with co-occurring substance use disorders and infectious disease are revealing outcomes that are of special concern for women.

Collectively, these and other research advances described herein continue to provide evidence demonstrating the importance of conducting research specific to women, taking a sex/gender-based research approach, and analyzing data separately for males and females. Ultimately, this approach will provide the information needed to tailor prevention and treatment interventions that will optimize outcomes for both men and women. This is at the heart of the Precision Medicine Initiative laid out in the *New England Journal of Medicine* perspective article by Dr. Francis Collins, the Director of the National Institutes of Health (NIH), and Dr. Harold Varmus, then Director of the National Cancer Institute, in which they described precision medicine as “prevention and treatment strategies that take individual variability into account” (Collins and Varmus, 2015). Sex is the most basic, fundamental individual difference. Thus, NIDA is pleased to present examples of research that exemplify the Precision Medicine Initiative.

Most of NIDA's scientific research advances highlighted in this report reflect the goals of the NIH Strategic Plan for Women's Health Research, Strategic Goal 1, “Increase sex differences research in basic science studies.” The Institute's research also addresses some of the other trans-NIH strategic goals for research on women's health.

The Women and Sex/Gender Differences Research Program at NIDA

NIDA's Women and Sex/Gender Differences Research program was established in 1995. The Program Coordinator, along with NIDA's Women and Sex/Gender Research Group (WGRG), leads the scientific efforts at NIDA to promote research on women and sex/gender differences in drug use. The WGRG has membership representing research areas that span from molecular biology and genetics to risk and protective factors, prevention, consequences, and treatment and services, as well as members representing grant review, NIDA publications, and minority programs. From its inception, the overarching goals of NIDA's Women and Sex/Gender Differences Research program have been to infuse the study of women and sex/gender differences research throughout all areas of drug use research, to disseminate resultant findings, and to target the next generation of drug use researchers. The program uses a variety of strategies, including funding opportunity announcements, travel awards, symposia, scientific presentations, and publications, as well as a landing page, [Substance Use in Women](#), on NIDA's website specifically devoted to this research.

NIDA's Women and Sex/Gender Differences Research Program Coordinator represents NIDA on the Office of Research on Women's Health (ORWH) Coordinating Committee for Research on Women's Health and leads NIDA's efforts on several ORWH programs, including the Specialized Centers of Research (SCOR) on Sex Differences program, the Building Interdisciplinary Research in Women's Health program, the Administrative Supplements for Research on Sex/Gender Differences program, and the Trans-NIH High Priority, Short-Term Awards (R56) for Women's Health program. The Coordinator also serves on the Trans-NIH Sex as a Biological Variable Working Group.

Featured Research Programs

NIDA is pleased to partner with ORWH in its SCOR on Sex Differences program. This program consists of research centers across the country that integrate basic, clinical, and translational research approaches with a primary sex-based focus. The three ORWH SCORs that are administered by NIDA are located at the Medical University of South Carolina (MUSC), the University of Minnesota, and Yale University. Each center has at least three highly integrated, synergistic research projects. All three centers focus on nicotine addiction, and two also emphasize cocaine addiction. All are interdisciplinary and translational, having at least one preclinical project and at least two clinical projects. The SCORs are taking a precision medicine perspective, studying factors that may impact the effectiveness of a potential medication, such as stress and impulsivity, and may do so differentially in males and females.

The SCOR at MUSC, led by Dr. Kathleen Brady, focuses on three neuropeptides—oxytocin, orexin, and corticotrophin-releasing factor—as potential mechanisms underlying the stress response in men and women with cocaine use disorder and as potential targets for sex-based medications for the treatment of both cocaine addiction and nicotine addiction. The SCOR contains two clinical projects and two animal model projects. One set of clinical studies, utilizing brain imaging techniques, is investigating oxytocin as a potential cocaine medication for stress-based relapse. Oxytocin is a hypothalamic neuropeptide that has been shown to mediate behavioral responses to stress and to play a role in neuroadaptations that occur following long-term drug use. Other clinical studies are examining the influences of sex hormone and oxytocin administration on the relationships among stress, craving, and smoking resistance. A set of preclinical studies is examining orexin and oxytocin as neuropeptide substrates that may underlie sex and estrous cycle-dependent differences in cocaine taking and reinstatement of cocaine seeking. Another set of preclinical studies is focused on the role of norepinephrine and the

corticotrophin-releasing factor in stress reactivity in cocaine self-administration. The sex-based and stress-based focus of this SCOR has potential to lead to sex-based treatments for both nicotine and cocaine addiction. **[Objectives: 1.4, 1.5, 1.6, 1.7, and 2.6]**

The SCOR at the University of Minnesota, led by Dr. Marilyn Carroll, focuses on interactions among sex differences, hormonal status, impulsivity, and drug-motivated behavior to study potential treatments for nicotine and cocaine addiction.

Three medications that have been shown to reduce impulsivity are being examined: progesterone, atomoxetine, and varenicline. A preclinical project is studying sex differences in an animal model of nicotine and cocaine relapse and will determine whether medications that reduce impulsivity also will reduce drug seeking. In addition, the project will consider hormonal factors, including naturally occurring hormonal fluctuations during pregnancy and postpartum. A clinical study is investigating sex differences in the effect of exogenous progesterone on impulsivity and smoking cessation, and another clinical study is investigating sex differences in the effect of exogenous progesterone combined with atomoxetine on impulsivity and on preventing relapse to marijuana use, comparing outcomes in individuals who do and do not co-use cigarettes. **[Objectives: 1.4, 1.5, 1.6, and 1.7]**

The SCOR at the Yale University School of Medicine, led by Dr. Sherry McKee, is aimed at developing effective smoking cessation treatments, especially for women. In preliminary human laboratory studies and a small smoking cessation efficacy trial, Dr. McKee demonstrated that guanfacine can effectively reduce smoking rates in both men and women, but via different mechanisms. In males, guanfacine appears to modulate nicotine reinforcement, whereas in females the drug appears to mitigate negative affect and stress. The Yale SCOR now is studying sex differences in the drivers of smoking and relapse, both behavioral and neurobiological, via an animal model project and a human brain imaging project linked to a human laboratory

project and larger Phase II smoking cessation trial with guanfacine. Together, these projects will probe the noradrenergic system's effects on stress-reactivity and nicotine reinforcement, testing the hypotheses that different brain systems modulated by noradrenergic activity are activated by smoking in women and men and that guanfacine, an α -2a noradrenergic agonist, can preferentially target these sex-sensitive systems to improve smoking cessation outcomes. **[Objectives: 1.4, 1.5, 1.6, 1.7, and 2.6]**

Together, these SCORs hold promise for the development of sex-based treatment for smoking cessation and cocaine addiction. Now in their fifth year of funding, progress made by the three NIDA SCORs will be highlighted at the annual meeting of the College on Problems of Drug Dependence, June 17–22, 2017, in Montreal, Canada, in a symposium titled “Sex as a Biological Variable: Research Findings from the NIH Office of Research on Women’s Health and NIDA Center Grants—Ahead of Its Time or Long Overdue?” The symposium will feature progress presentations from the principal investigators of each of the three SCORs. **[Objectives: 1.9 and 4.5]**

Research Accomplishments

Nicotine and Smoking

Differences in smoking between men and women are well documented, including the health consequences, quit success rates, barriers to cessation, and success with nicotine replacement treatments. The studies below highlight research exploring mechanisms that may contribute to these sex differences, as well as medication strategies to promote smoking cessation.

Preclinical Study Suggests that Reducing Nicotine Withdrawal-Induced Stress May Lead to More Effective Smoking Cessation Treatments for Women. These findings were demonstrated in a rodent model by researchers studying the role of ovarian hormones in stress-associated gene expression and dopamine markers believed to

promote withdrawal in females. During withdrawal, intact females exhibited an increase in anxiety-like behavior, genes associated with stress, the dopamine receptor, and the estrogen receptor. These behavioral and neurobiological changes, however, were absent in ovariectomized female rodents, suggesting that ovarian hormones alter responses to stress and changes in gene expression during withdrawal (Torres et al., 2015). **[Objectives: 1.1, 1.4, 1.5, 1.6., and 1.7]**

Sex Differences in the Brain’s Dopamine Signature of Cigarette Smoking. A novel technique allows researchers to quantify changes in the brain’s release of the neurotransmitter dopamine during smoking and create real-time “movies.” In males, but not females, consistent and rapid dopamine release occurred in the right ventral striatum—associated with drug reinforcement. In females, dopamine release occurred rapidly in the right dorsal putamen—associated with habit formation—whereas in males, the rise in dopamine release was slow and moderate, if an increase occurred at all. These findings are in accord with other studies indicating that smoking in men is due to nicotine reinforcement, whereas in women, smoking occurs for other reasons, such as mood and emotion regulation and reactivity to cues. Follow-up research is aimed at using this new real-time method of imaging dopamine to evaluate the effects of smoking cessation treatments in males and females (Cosgrove et al., 2014). **[Objectives: 1.5, 1.6, and 2.6]**

Anxiety Sensitivity May Contribute to Motivation to Quit Smoking Among Women, but Not Men. Smoking cessation is influenced by many factors, including motivation to quit (MTQ). Investigators examined the relationship between anxiety sensitivity (AS) and MTQ among individuals enrolled in a residential substance use treatment center. The findings suggest that AS is significantly related to MTQ for women, but not for men, such that women higher in AS were more motivated to quit smoking. To the extent that MTQ can serve as an important indicator for initiating a cessation attempt among smokers in residential substance use

treatment, AS may serve as an important target for cessation interventions among women in treatment (Dahne et al., 2015). **[Objectives: 1.5, 1.6, and 1.8]**

Adversity Is Associated with Reduced Chance of Quitting to Smoke and Relapse After a Quit Attempt. NIDA- funded research is examining the link between adversity and quitting smoking. One study using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) demonstrated that past-year stressful life events are strongly related to a lower likelihood of smoking cessation for women, but not men, who have a history of childhood adversity, compared to those who do not. In a second study within nonsmokers and smokers who relapsed within the first month of a quit attempt, but not abstainers, females had significantly higher adversity scores than males. Both studies highlight stress as a target for smoking cessation treatments (behavioral or pharmacologic) for women with high lifetime or past-year adversity (Smith et al., 2016a) (Lemieux et al., 2016). **[Objectives: 1.5, 1.6, and 1.8]**

Smoking Cessation Medications May Diminish Gender Differences in Successful Quitting. Beyond clinical trial data, very little research examines gender differences in medication effectiveness among the general population of smokers. Analysis of longitudinal data of 7,825 smokers from the International Tobacco Control Four-Country Surveys conducted in the United Kingdom, Canada, Australia, and the United States revealed that although there were no gender differences in the likelihood of desire to quit, plans to quit, or quit attempts, women had 31 percent lower odds of successfully quitting smoking than men. Successful quitting was lowest in women who did not use any smoking cessation medications (13% women vs. 20% men), and no different from men when medications were used, thus highlighting the benefit of medication use among women trying to quit smoking. Although research indicates that women may have more difficulty quitting than men, these data indicate that the use of smoking cessation medications may help diminish this difference (Smith et al., 2015). **[Goal: 1]**

Sex Differences in Smoking Cessation

Medications: What Works Best? Three types of pharmacotherapies currently are approved by the U.S. Food and Drug Administration (FDA) for smoking cessation: (1) five variants of nicotine replacement therapy (transdermal nicotine [TN], gum, lozenge, nasal spray, and oral inhaler); (2) varenicline; and (3) sustained-release bupropion. A head-to-head comparison previously showed that varenicline was more efficacious than TN and bupropion, with no difference in efficacy between TN and bupropion. Building upon that analysis, which was not sex-specific, NIDA-funded scientists performed a sex-based meta-analysis of 28 studies and 14,389 smokers. Their findings replicated the overall findings of the prior head-to-head report. Their sex-based analysis revealed that, relative to placebo, women and men achieved similar outcomes when treated with varenicline. Moreover, they found that for women, varenicline was more efficacious than TN and bupropion, whereas for men, varenicline did not have a statistically significant benefit over TN or bupropion. These results suggest that varenicline should be used as a first-option smoking cessation treatment for women (Smith et al., 2017). **[Objectives: 1.6 and 2.7]**

Cannabis Use

NIDA funds a wide range of research on marijuana (cannabis) and its main psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), as well as chemicals related to THC (cannabinoids). Prior epidemiological research indicates that although the severity of a cannabis use disorder (CUD) is higher for men, women proceed to CUD more quickly than men after first use, a phenomenon called “telescoping.” This faster progression to CUD in women may be related to laboratory research showing greater sensitivity among women who were daily users to the abuse liability effects of smoked cannabis than among men. Below are studies exploring sex differences in the analgesic effects of cannabis, mental health conditions associated with cannabis use, and a newly funded preclinical study exploring synthetic cannabis.

Women Less Sensitive Than Men to Analgesic Effects of Cannabis. In a laboratory study, 42 cannabis users were given cannabis containing from 0 to 5.6 percent THC and then assessed for pain using a cold water test. Active cannabis increased pain tolerance (how long it took to remove hand from cold water) in both men and women for a short time after smoking, and it reduced pain sensitivity (how long it took to report pain) in men, but not women. No sex differences were seen in THC’s abuse liability effects in this study, as in a prior study by these researchers, which was likely due to the study’s methodological features involving use of the cold water procedure to assess THC’s analgesic effects. This study suggests that sex-dependent differences should be noted when considering cannabis as a potential therapeutic for pain, and potentially raises concerns for women who would seek to use cannabis to treat pain (Cooper and Haney, 2016). **[Objectives: 1.5, 1.6, and 1.8]**

Risk of Co-Occurring Internalizing Symptoms and CUD Higher Among Women in Late Adolescence and Middle Age Than in Men.

NIDA-funded researchers compared internalizing and suicide risks in 437 men and 163 women seeking CUD treatment from late adolescence through middle adulthood. Co-occurring risks were higher in women than men during late adolescence and middle age, but not early adulthood, suggesting that the structure of risk for CUD may differ in men and women across the lifespan and that women presenting for CUD treatment during late adolescence and middle adulthood may uniquely benefit from interventions designed to address these elevations in anxiety and suicide risk (Foster et al., 2016). **[Objectives: 1.5, 1.6, and 1.8]**

Reductions in Cannabis Use Prospectively Associated with a Reduction in Depression Symptoms in Study of Female Emerging Adults.

Major depressive disorder is the most common mental health disorder among young adults and is significantly more common in women than in men. Previous studies have indicated that the risk for depression is associated with increased cannabis

use, but it is not known if a reduction in cannabis use is associated with a reduction of depression symptoms. This question was addressed in a study of 332 female self-reported cannabis users ages 15–18 years. They were assessed for depression symptoms and cannabis use at baseline and at 3- and 6-month follow-up. Researchers found that a reduction in the frequency of cannabis use was associated with a decrease in depression symptoms for those women with mild, moderate, or severe depression, compared to those with minimal depressive symptoms (Moitra et al., 2016). **[Objectives: 1.5, 1.6, and 1.8]**

University of Arkansas Receives NIDA Grant to Study Health Effects of Synthetic Cannabinoids.

Synthetic cannabinoids (SCBs) are very popular emerging drugs, marketed to teens and first-time drug users as “safe” and “legal” alternatives to marijuana. However, clinical reports have indicated that SCB use results in several symptoms that are different from marijuana and are life-threatening. Dr. Paul Prather of the University of Arkansas was awarded a grant by NIDA to study chemicals produced by the breakdown of SCBs in the body that may contribute to the harmful effects of these dangerous drugs. Behavioral results from this research using the mouse model will be studied separately for males and females (1R01DA03914301A1). **[Objectives: 1.4 and 1.5]**

Prescription Opioid Misuse and Opioid Use Disorders (OUD)

Opioids are a class of drugs used to decrease pain. The rise in prescription opioid availability, illicitly made synthetic opioids, and heroin use has contributed to an increase in the prevalence of OUD and opioid-related deaths. Between 1999 and 2010, overdose deaths from prescription opioids increased more than 400 percent among women, compared to an increase of 237 percent among men. Between 2002 and 2013, heroin use among women increased 100 percent, compared to an increase of 50 percent among men. These

disparities led to research to better understand opioid use in men versus women. Indeed, NIDA research has shown, for example, that the pathways to OUD often are different in men and women. Much of NIDA’s research on the male-female differences are described in the U.S. Department of Health and Human Services’ (HHS) Office on Women’s Health White Paper: Opioid Use, Misuse, and Overdose in Women. Highlighted below are studies that explored (1) sex differences in behavior among chronic pain patients with co-occurring OUD, (2) the risk of OUD among women in the criminal justice system, and (3) the role of gender on mortality risk among persons with OUD. Finally, a preclinical study is highlighted that sheds light on why there is a greater frequency and severity of chronic pain in women and suggests a new novel treatment approach. Highlights of recent NIDA research on opioid use during pregnancy are presented in the section on prenatal drug exposure.

Sex Differences Among Chronic Pain Patients with a History of Concurrent Opioid Use.

Sex differences in the demographic, diagnostic, and behavioral attributes of patients with co-occurring chronic pain and OUD are not well characterized. In a NIDA-supported study of chronic pain patients with a history of concurrent opioid use, women reported significantly more physical limitations and psychological changes—such as negative emotional states—associated with pain. In contrast, men tended to endorse certain external aberrant behaviors—such as use of alcohol or illicit drugs, increasing dose of their medication without authorization, and contact with street culture—with a greater frequency than women. Recognition of the distinct characteristics of treatment-seeking men and women with OUD could help guide changes in pain management before OUD begins or escalates (Manubay et al., 2015). **[Objectives: 1.5, 1.6, and 1.8]**

Prescription Opioid Misuse Among Victimized Women on Probation and Parole.

Victimized women on probation and parole report high rates of prescription opioid misuse (POM) and comorbid

mental and physical health problems. In a NIDA-funded study from a sample of 406 women on probation and parole, 41.6 percent of women reported lifetime POM, and 20 percent reported past-year POM. Compared to women who did not report POM, those who did were more likely to be white, have poorer general health, and have more severe psychological distress. Each unit increase in the measure for physical pain was associated with a 30-percent increase in the odds of misuse, and participants who met diagnostic criteria for post-traumatic stress disorder were 60 percent more likely to report misuse than individuals who did not. Routine screening for prescription drug misuse, as well as treatment of physical pain and psychological distress, may decrease the risk of POM and prescription opioid use disorder among women on probation or on parole (Hall et al., 2016). **[Objective: 3.5]**

Gender Differences in Mortality Among Patients Treated for OUD. Understanding and addressing the gender-specific risks of OUD may improve the treatment process and also reduce the risk of premature mortality for both women and men. A NIDA-funded study analyzed linked vital statistics data obtained for all individuals first enrolled in publicly funded pharmacological treatment for OUD in California from 2006 to 2010. Women had a greater increased risk of mortality, compared to the general population. Among men, mortality risk was decreased by full-time employment and increased by non-daily heroin use (relative to daily use) and medical problems. Concurrent opioid and methamphetamine/cocaine use increased mortality risk among women and decreased it among men (Evans et al, 2015). **[Objective: 1.5]**

Preclinical Study Sheds Light on Greater Frequency and Severity of Chronic Pain in Women and Suggests Novel Approach to Pain Treatment. Epidemiological studies consistently demonstrate a greater prevalence among women than men of chronic pain disorders, and in clinical studies women exhibit higher self-reported severity of pain. An animal model study had shed light on these sex differences and suggests a novel

treatment approach to treating pain. In rats, investigators found that activating the mu-opioid receptor, the major opioid receptor mediating pain relief, increased the release of endomorphin 2 (an endogenous opioid), which added to the analgesic effect produced by the opioid drug; however, this effect was sex-specific and occurred only in males. This outcome suggests that males are able to harness the body's own opioid analgesia better than females and that this may account for the greater frequency and severity of chronic pain experienced by women, compared to men. How to facilitate harnessing the body's own opioid analgesia in females remains to be explored. Building upon this new research finding could lead to sex-based and novel drug treatments that relieve pain by activating the body's own endorphins, thereby avoiding or lessening prescription opioid abuse (Kumar et al., 2015). **[Objectives: 1.4 and 1.5]**

Treatment

As described in studies highlighted below, treatment studies are showing that by factoring sex as a variable into research, we are finding whether established as well as promising treatments are equally effective in males and females. A treatment study of mothers with a substance use disorder (SUD) shows the benefit of including her children as part of family therapy. A brain imaging study may provide clues for better treatment for women. Sex-based data from large surveys of emergency departments point to the utility of screening, brief intervention, and referral to treatment within hospital emergency departments. Finally, a preclinical study with female rodents provides evidence for possible therapeutic benefit of resistance exercise for women with an SUD.

Contingency Management Treatments Are Equally Efficacious for Both Sexes in Intensive Outpatient Settings. A secondary data analysis was conducted to examine possible sex differences in substance use treatment outcomes among participants ($N = 920$) from five clinical trials randomized to contingency management (CM) for abstinence or standard care treatment. Women

presented with higher problem severity across a number of domains (e.g., employment, drug, psychiatric) at intake. Men reported more years of alcohol use and significantly higher alcohol and legal problem severity. Despite these differences in treatment entry characteristics, men and women responded equally well to intensive outpatient treatment in general, and to CM specifically, across three treatment outcomes: treatment retention, longest duration of abstinence, and the percent of negative urine samples submitted (Rash and Petry, 2015). **[Objective: 1.6]**

Men and Women Derive Similar Benefits from Participating in a Computer-Assisted Psychosocial Intervention. Researchers in NIDA's Clinical Trials Network (CTN) conducted a sex-based secondary analysis of data from a multisite effectiveness trial of a computer-assisted behavioral intervention, Therapeutic Education System (TES), composed of 62 Web-delivered, multimedia modules, covering skills for achieving and maintaining abstinence, plus prize-based incentives for abstinence and treatment adherence. Participants were randomly assigned to 12 weeks of treatment as usual (TU) or to modified TU plus TES, which substituted for 2 hours of TU per week. Men and women experienced no differences in treatment outcomes. Women, however, reported higher acceptability scores at week 4, but no gender differences were detected at weeks 8 or 12. Acceptability was positively associated with abstinence among women. Findings suggest that men and women derive similar benefits from participating in a computer-assisted intervention, which is a promising outcome as technology-based treatments expand (Campbell et al., 2015). **[Objective: 1.6]**

Treatment-Seeking Mothers in Outpatient Family Systems Therapy with Their 8- to 16-Year-Old Children Outpatient Treatment for Substance Use Disorders Have Faster Recovery. Researchers randomly assigned 183 treatment-seeking mothers to receive either family systems therapy (which included their children ages 8–16 years) or women's health education (mothers only).

At treatment follow-up, mothers who participated in family systems therapy had a quicker decline in alcohol, marijuana, and cocaine use. This is the first effort to successfully document a family systems therapy for substance-using mothers with minor children in their care. In a follow-up study, researchers are examining the impact family systems therapy has on children, and preliminary data also suggest benefits for their mental health (Slesnick and Zhang, 2016). **[Objective: 1.6]**

Brain Imaging Studies May Hold Promise for Better Treatment Strategies for both Women and Men. Using magnetic resonance imaging, researchers are studying structural brain images of men and women with previous stimulant use disorder. Even after a prolonged period of abstinence, female former users had widespread brain differences (that is, less gray matter volume in frontal, limbic, and temporal regions of the brain) when compared to their healthy control counterparts, whereas men demonstrated no significant brain differences. Lower gray matter volume was associated with more impulsivity, greater behavioral approach to reward, and also more severe drug use. The results may provide clues to the biological processes underlying the clinical course of stimulant use in men and women and may lead to more effective treatments for both (Regner et al., 2015). **[Objectives: 1.6 and 2.6]**

Women of Reproductive Age with SUD Are More Likely to Present to the Emergency Department with Injuries Than Those Without SUD. Data from a large, statewide, multisource health care utilization data set of 1,748,027 individual women who received medical or SUD treatment services from 2002 to 2008 were used to examine patterns of injury requiring emergency department (ED) visits among SUD-positive and SUD-negative women. Almost two-thirds of SUD-positive women (65.1%) had any type of injury, compared to 44.8 percent of SUD-negative women. For four specific injury types, the proportion injured was almost double for SUD-positive women (49.3% vs. 23.4%). Specifically, differences for motor vehicle incidents were 22.5 percent for SUD-positive

women versus 12.5 percent for SUD-negative women; for falls, 26.6 percent versus 11.0 percent; for self-inflicted injury, 11.5 percent versus 0.8 percent; and for purposefully inflicted injury, 11.5 percent versus 1.9 percent. In each of the injury categories, injury rates among SUD-positive women were lowest for alcohol disorders only and highest for alcohol and drug disorders combined. The high rates of injury identified among women with SUD suggest the utility of including a brief, validated screen when injured women present to the ED (Bernstein et al., 2014). **[Objective: 2.5]**

Gender and Prescription Opioid Misuse in the Emergency Department. The Substance Abuse and Mental Health Services Administration’s Drug Abuse Warning Network (DAWN) collects data from a nationally representative sample of hospitals throughout the United States. For the 2011 DAWN, data from ED visits were identified that involved nonmedical use of prescription drugs, of which 38.8 percent were found to involve opioids. The ED opioid visits data were analyzed to compare characteristics between women and men. There were no sex differences in the prevalence of opioid-related ED visits, in the number of opioid-related visits involving a secondary drug, or in the types of opioids ingested. There were sex differences, however, in clinical outcomes, depending on specific drug combinations. Women who presented with prescription opioid misuse with concurrent use of either illicit drugs or antidepressants were more likely to require general hospital admission. Among men, presentations for opioids with alcohol and with heroin increased the odds for general hospital admission. This study underscores an important role for the ED in screening, brief intervention, and referral to treatment (Choo et al., 2014). **[Objective: 1.8]**

Resistance Exercise Reduces Motivation for Cocaine in Study of Female Rodents. In substance-using populations, aerobic exercise is associated with positive outcomes and reduces drug self-administration in laboratory animals. This preclinical study examined the effects in female rats of resistance exercise on cocaine

self-administration and on the expression of brain-derived neurotrophic factor (BDNF) expression, which is a marker of neuronal activation regulated by aerobic exercise that moderates the motivation to seek and take cocaine. The resistance training involved wearing vests of various weights and climbing ladders. Compared to sedentary rats, exercising rats self-administered significantly less cocaine and were less motivated to work for cocaine. This reduction in motivation to seek cocaine was correlated with lower BDNF in the nucleus accumbens core, which is a brain region important for learning and reward. These data raise the possibility that strength training may decrease cocaine use in humans (Strickland et al., 2016). **[Objectives: 1.4 and 1.6]**

Prenatal Exposure to Drugs

Research shows that substance use during pregnancy can lead to negative health consequences for unborn babies and infants, effects that are sometimes sex-specific. Many substances pass easily through the placenta—so anything that the pregnant woman ingests is taken in to some degree by the baby. The studies below describe offspring outcomes of prenatal exposure to THC (the main psychoactive ingredient in marijuana), tobacco smoke, and cocaine. Additionally, studies are highlighted describing progress in novel opioid medication detection methods to address medication-assisted opioid treatment among nursing mothers. Finally, an editorial by NIDA’s Director that urges safer opioid prescribing practices for pregnant women is highlighted.

Cross-Generational Sex-Specific Effects of THC Exposure on Gene Expression. Findings from rat models have demonstrated that adolescent exposure to THC affects reward-related behavior and striatal gene expression in male offspring that were not exposed to THC during their own lifespan. Researchers have now expanded on these findings in males by analyzing the female brain for specific abnormalities associated with cross-generational THC exposure. In both sexes, results revealed a switch from altered gene expression

in the ventral striatum during adolescence to the dorsal striatum in adulthood. Females, however, exhibited stronger correlation patterns between genes and also showed locomotor disturbances not evident in males. These findings indicate that cross-generational consequences of parental THC exposure can occur both similarly and differently in unexposed male and female offspring (Szutorisz et al., 2016). **[Objectives: 1.1, 1.4, and 3.4]**

Sex, Age, and Stress Effects of THC During the Periadolescent Period in the Rat. In human adolescents, marijuana use often is associated with anxiety, depression, psychotic-like symptoms, and other mood disorders. Age of onset of cannabis use and stress history also can affect the response to cannabis. In a preliminary study of rats exposed to THC during the periadolescent period, changes were found in anxiety-like, depression-like, and psychotic-like symptoms, as well as in cannabinoid receptor-1 expression. Both antidepressant and anti-anxiety effects of THC were observed and varied depending upon early exposure to stress, when the animals were tested during the periadolescent period, and the sex of the animal. Rodent models such as these can shed light on our understanding of the association of cannabis use in adolescents and mental health symptoms, which often differ between males and females (Silva et al., 2016). **[Objectives: 1.4, 1.5, and 1.6]**

Lower Levels of Focused Attention in Infants with Prenatal Tobacco Exposure. Tobacco is one of the drugs most commonly used during pregnancy, delivering significant amounts of chemical toxins to the fetus via the maternal bloodstream. A recent NIDA-funded study of a sample of 203 mothers and their infants found that infants with fetal tobacco exposure (FTE) exhibited lower levels of focused attention at 9 months than nonexposed infants. Among exposed babies, behavior reactivity to frustration, but not infant sex, was associated with the lowest levels of focused attention. FTE was determined via nicotine metabolites reflecting fetal exposure primarily in the third trimester. Results suggest that persistent smoking throughout pregnancy is

a stronger risk factor for infant focused attention than smoking only in the early stages of pregnancy. Thus, smoking cessation interventions for pregnant women, even in the third trimester, may have a positive effect on attentional outcomes in their babies (Shisler et al., 2016). **[Objectives: 1.4, 1.5, and 1.6]**

Prenatal Cocaine Exposure Differentially Affects Stress Responses in Girls and Boys and Associations with Future Substance Use. Among 193 low-income 14- to 17-year-olds, half of whom were prenatally cocaine exposed (PCE), sex-specific associations were found between biobehavioral stress responses to a laboratory stressor and substance use 6–12 months later in PCE children, compared to non-PCE children. PCE history was associated with higher stress responses for girls than for boys, and higher stress responses were associated with future substance use for girls. In contrast, PCE boys showed lower biobehavioral stress responses than PCE girls, and their lower stress responses predicted future substance use. Overall, findings suggest different biobehavioral stress response risk profiles for adolescent PCE girls versus boys, with heightened arousal for girls and blunted arousal for boys associated with future substance use (Chaplin et al., 2015). **[Objectives: 1.5 and 1.6]**

Measuring Opioid Use Disorder Treatment Medications in Breastmilk and Correlations with Maternal Concentrations. NIDA intramural researchers have developed a fully validated technique to investigate the relationship between breastfeeding and outcomes in children of mothers who are treated with combination buprenorphine/naloxone therapy. The comprehensive, highly sensitive and specific method detects multiple buprenorphine markers in a small specimen volume. In a follow-up study, 11 pregnant women were treated for OUD with sublingual buprenorphine/naloxone. Findings demonstrated that the medications were transferred to the fetus during prenatal exposure and that the quantity of naloxone transferred from maternal circulation is minimal and highly correlated with maternal

concentrations (Swortwood et al., 2016) and (Wiegand et al., 2016). [Objectives: 3.3 and 3.5]

Maternal Buprenorphine Maintenance and Lactation. As part of a larger study evaluating fetal and infant effects of maternal buprenorphine treatment, women with OUD—who were buprenorphine-maintained as part of substance use treatment and who wanted to breastfeed their infants—were evaluated for concentrations of buprenorphine and metabolites in human milk and in maternal and infant plasma. Data from the study demonstrated low concentrations of buprenorphine and metabolites in human milk and lend support to the recommendation for lactation among stable buprenorphine-maintained women. However, the correlation between maternal dose and maternal plasma and human milk buprenorphine concentrations bears further study (Jansson et al., 2016). [Objectives: 3.3 and 3.5]

NIDA Editorial Urges Safer Opioid Prescribing Practices for Pregnant Women. In a recent editorial, NIDA Director Nora Volkow, M.D., urges that the known association of opioids with neonatal abstinence (NAS), suggests that they should be prescribed only for short-term use for pregnant women in severe pain. If long-term use is unavoidable, such as for women in need of buprenorphine or methadone maintenance therapy for heroin addiction, then careful assessment and monitoring should be in place to minimize the risk of overdose, NAS, and misuse. NAS is characterized by central nervous system hyperirritability and autonomic nervous system dysfunction and often requires medication and an extended hospital stay. A prior multicountry study of pregnant women with opioid dependence reported that neonates exposed *in utero* to buprenorphine required significantly less morphine and shorter hospital stays for the management of NAS than neonates exposed to methadone (Volkow, 2016).

Co-Occurring SUD and Infectious Disease

Substance use increases the risk of infectious disease transmission, including the transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV). The studies below highlight sex differences among persons with co-occurring SUD and infectious disease, including sex differences in HIV care among recent detainees with SUD, cognitive ability among persons with co-occurring HIV and SUD, and the incidence of global HCV among persons who inject drugs.

Distinct Challenges Affect Women's HIV Treatment Outcomes After Jail. Women who are infected with HIV and are transitioning back to communities after serving jail time are less likely than their male counterparts to have a regular HIV care provider, to take and regularly adhere to an HIV medication regimen, and to have suppression of the virus. HIV treatment outcomes of 590 men and 277 women were compared 6 months after their release from jail at 10 sites in nine states. The findings add to previous evidence that HIV treatment for women leaving jail should be tailored to their specific needs (Meyer et al., 2014). [Objectives: 1.6 and 1.8]

Impairments in Visual Memory and Decisionmaking Are More Prominent in Women with Co-Occurring HIV and SUD. Substance use is a major risk factor for HIV-1 infection. The presence of substance use also has been shown to exacerbate cognitive impairments due to HIV-1 infection. To investigate possible sex differences in cognitive impairment in individuals with co-occurring HIV and SUD, researchers administered to HIV-positive and HIV-negative men and women with SUD the Brief Visuospatial Memory Test–Revised (BVMT-R) to measure episodic memory and the Game of Dice Task to measure decisionmaking under risk. There were no differences based on sex or HIV status on BVMT-R performance, but HIV-positive women performed significantly more poorly on memory-delayed recall. This effect was most prominent among HIV-positive

women with cocaine use disorder. When tested for decisionmaking under risk, HIV-positive participants made significantly poorer decisions than HIV-negative participants, but this deficit appeared more prominent among HIV-positive women. These findings are consistent with recent speculation that impairments in memory and decisionmaking may be more common among HIV-positive women, particularly those with a history of drug (cocaine) use disorder (Keutmann et al., 2017) and (Martin et al., 2016). **[Objectives: 1.5, 1.6, and 1.8]**

Higher Incidence of HCV in Females Compared to Males Who Inject Drugs. Among people who inject drugs (PWID), women have been shown to have higher incidence of HIV and risk behaviors than men. To determine the female-to-male (F:M) HCV incidence among PWID, researchers performed a meta-analysis of 28 studies that enrolled 9,325 PWID. The results showed a higher pooled HCV incidence rate (per 100 person-years observation) in females, compared to males (20.36 and 15.20, respectively). The overall F:M ratio was 1.36:1. In studies that recruited participants from community settings, the F:M ratio was 1.24, which was lower than that reported in the clinical settings (1.72). The F:M ratio also varied by geographic location from 4.0 in China to 1.17 in the United States. These findings raise questions and concerns regarding sex differences with respect to the risk of HCV. Both behavioral and biological studies are needed to investigate causes and potential mechanisms, as well as sex-specific prevention approaches to HCV infection (Esmacili et al., 2017). **[Objectives: 1.5 and 1.6]**

Health Disparities

Below are examples of NIDA-supported research that is providing information on prevention of substance use and SUD among racial and ethnic subgroups. Additionally, the section on STEM activities highlights NIDA programs that target advancing the research careers of minority investigators.

Substance Use Disorders Extremely Common Among Previously Incarcerated Youth. A longitudinal study of 1,829 randomly sampled 10- to 18-year-olds who entered detention in Cook County, Illinois, from 1995 to 1998 examined how lifetime and past-year prevalence of SUD differed by sex, race/ethnicity, and substances used as the group entered young adulthood. More than 90 percent of males and nearly 80 percent of females had an SUD at some point in their lifetime. The participants were re-interviewed up to nine times over 16 years and were assessed for SUD. Males had higher lifetime prevalence of alcohol and marijuana use disorder, whereas females had higher lifetime prevalence of cocaine, opiate, amphetamine, and sedative disorders. Additionally, the prevalence of SUD among females declined more rapidly than among males. Cocaine use disorder was more than 30 times more likely among non-Hispanic whites than among African-Americans. Overall, prevalence of any SUD dropped as youth aged (Welty et al., 2016). **[Objectives: 1.8 and 3.9]**

Intervention Yields Sustained Health Benefits for American Indian Teen Mothers and Their Children. Family Spirit, a program that teaches parenting skills to American Indian teen mothers, improved participants' children's emotional and behavioral development throughout their first 36 months of life. Participants received teaching visits in their own homes from trained American Indian paraprofessionals, from pregnancy through 3 years postpartum. A comparison group of mothers received upgraded pediatric care, compared with the norm on their reservations. Intervention participants also had lower rates of depression, fewer behavior problems, and less illicit drug use than mothers in the control group, indicating that this intervention has positive effects on young mothers and their children (Barlow et al., 2015). **[Objective: 3.9]**

Increasing Perception of Leisure Opportunities for Girls (But Not Boys) Reduces Risk of Substance Use. HealthWise SA: Life Skills for Young Adults is a school-based prevention program designed to reduce substance use and risky sexual

behavior by targeting youth's leisure, healthy decisionmaking, self-management skills, life skills, drug-refusal skills, and emotion regulation. In an underresourced community in South Africa, implementation of HealthWise between 8th and 10th grade was associated with a decreased likelihood of initiating alcohol and cigarette use and an increased amount of perceived leisure opportunities among girls, but not boys. While the effects on substance use outcomes have been demonstrated in prior research, this is the first study to demonstrate how experimentally targeting leisure through an intervention can increase perceived leisure opportunities and thereby prevent early substance use initiation for a specific population (Motamedi et al., 2016). **[Objective: 3.9]**

STEM Activities

Special NIDA-sponsored activities targeting women junior investigators and aimed at nurturing their research careers have been very successful. In addition, NIDA and the National Institute on Aging (NIA) have formed a partnership to support women intramural scientists at the NIH Biomedical Research Center in Baltimore, Maryland.

NIDA's Intramural Research Program (IRP)

Scientific Director's Fellowship for Diversity in Research (SDFDR) at NIDA's IRP. The SDFDR is an IRP fellowship for underrepresented postbaccalaureate and postdoctoral students. This mechanism promotes mentorship of young scientists from underrepresented populations by NIDA IRP scientists. Career development plans are customized to ensure each Fellow's success in the pursuit of careers in science and medicine. Fellows participate in research and present their findings at local and national meetings. Postbaccalaureate Fellows are supported for 2–3 years and postdoctoral fellows are supported for 3–5 years. In 2015 and 2016, one of four (25%) postdoctoral Fellows and six of eight (75%) postbaccalaureate Fellows supported by this program were female.

Estimated funding of the program is \$352,000. **[Objective: 4.5]**

Recruitment and Training for Underrepresented Populations (RTURP) Program at NIDA's IRP. The RTURP is an intramural program that provides training opportunities for students from underrepresented populations who are interested in the science of drug use and addiction. The program accepts students from high school to graduate school for 8–10 weeks of intense training. Such activities as lectures, seminars, weekly lunches, professional workshops, and poster presentations are offered to students throughout the summer. In 2015 and 2016, two of two (100%) graduate students, 10 of 17 (59%) college students, and 11 of 15 (73%) high school students supported by this program were female. Estimated funding of the program is \$80,000. **[Objective: 4.5]**

Women Scientist Advisory (WSA) Board. The NIDA-NIA WSA meets on a regular basis to support women intramural scientists at the NIH Biomedical Research Center in Baltimore, Maryland. The group supports and fosters women actively working in science through an exchange of ideas and three annual awards for women scientists: WSA Investigator Award, WSA Staff Scientist Award, and WSA Fellows Award. **[Objective: 4.5]**

NIDA's Office of Research Training

NIDA Director's Travel Award at the College on Problems of Drug Dependence (CPDD) Annual Scientific Conference. The NIDA Director's Travel Award program partially defrays the cost of travel for NIDA-supported National Research Service Award Fellows, trainees, and NIDA diversity-supplement recipients to attend the annual CPDD meeting. In 2015, 15 of the 20 (75%) awards went to women; in 2016, 10 of the 20 (50%) awards were made to women. **[Objective: 4.5]**

Grant-Writing and Career Workshop at the CPDD Annual Scientific Conference. NIDA's Grant-Writing and Career Workshop, held in conjunction with the CPDD conference, capitalizes upon the expertise gathered for the CPDD meeting

to provide young investigators with the tools and resources necessary to become successful substance use researchers. This workshop demonstrates NIDA's continued commitment to the next generation of these researchers. In 2014, 42 of 80 (53%) participants were women. In 2015, 31 of 60 (52%) participants were women. **[Objective 4.5]**

NIDA's Office of Diversity and Health Disparities

Four STEM efforts focusing on underrepresented populations were sponsored by NIDA's Office of Diversity and Health Disparities (ODHD).

NIDA Summer Research Internship Program.

This program provides research internships for high school and undergraduate students with a goal of recruiting underrepresented populations into research. Internships include a paid 8-week intensive, hands-on drug use and addiction research experience that provides students with the opportunity to gain an understanding of the research process. The experience may include laboratory experiments, formal courses, data collection activities, data analysis, patient recruitment, manuscript preparation, literature reviews, and library research. The program exposes students to drug use research and encourages them to pursue careers in biomedical and behavioral research. Internships are conducted with NIDA-funded investigators across the country. In 2015, NIDA awarded 62 internships, 44 (71%) of which were to women. In 2016, 51 (75%) of 69 internships were awarded to women. **[Objective: 4.5]**

Administrative Supplements to Enhance Diversity. This diversity supplement program was established to improve diversity in the scientific research workforce by supporting and recruiting undergraduate students, predoctoral and postdoctoral Fellows, and investigators from groups that have been shown to be underrepresented in the sciences, including disabled individuals. In 2015, NIDA funded 27 diversity supplements, 14 (52%) of which were awarded to women. In 2016,

21 (75%) of the 28 diversity supplements funded were awarded to women. **[Objective: 4.5]**

NIDA Diversity Scholars Network (NDSN).

The NDSN is a rigorous and comprehensive mentorship program aimed at improving the funding of outstanding underrepresented early-stage investigators conducting drug use research. The NDSN program consists of two sessions that support a cohort of scholars in gaining research grants or equivalent funding to build a sustainable independent research career. In 2015, 19 early-stage investigators participated in the NDSN program, 15 (79%) of whom were women. In 2016, 18 early-stage investigators participated, 10 (56%) of whom were women. **[Objective: 4.5]**

NIDA Diversity Scholars Travel Award. NIDA's ODHD sponsors a travel award to help defray the costs of attending the annual Society for Neuroscience (SfN) meeting. As part of this award, recipients are required to attend the Frontiers in Addiction Research NIDA-National Institute on Alcohol Abuse and Alcoholism (NIAAA) Mini-Convention held prior to SfN. In 2015, 11 (65%) of 17 travel awards were made to women. In 2016, seven (54%) of 13 travel awards were made to women. **[Objective: 4.5]**

NIDA's Women and Sex/Gender Differences Research Program

Women and Sex/Gender Differences Research Junior Investigator Travel Award Program at the CPDD Annual Scientific Conference. To promote entry of junior investigators into drug use research on women and sex/gender differences, NIDA has sponsored a travel award program to assist awardees in defraying the cost of attending the annual meeting of the CPDD since 2000. Award applicants are required to be the first author on their research submission to CPDD, and the research must focus on women or include a sex/gender analysis of data. In 2015, 80 percent of the applicants were women, and in 2016, 78 percent were women. Twenty awards were made in both

2015 and 2016, of which 85 percent (2015) and 75 percent (2016) went to women. **[Objective: 4.5]**

Clinical Trials Network

To complement the clinical trials described in Research Accomplishments, this section discusses NIDA's CTN and how it is advancing research on women and sex/gender differences. This section also describes a multisite trial that could provide a new smoking medication for women.

NIDA's CTN is a national consortium of drug use researchers and providers who conduct research to generate the evidence needed for the integrated management of patients with substance misuse or SUD at general medical settings and linked specialty care treatment settings. The CTN currently consists of 13 research Nodes (i.e., grantee institutions) affiliated with approximately 60 academic institutions and more than 240 health care clinics—including hospitals, primary care settings, specialty clinics, and Federally Qualified Health Centers—throughout the United States. During 2015–2016, the CTN conducted several analyses on gender differences of multiple trials, publishing more than 15 manuscripts from this work, addressing such topics as (1) gender differences in mortality rates and ratios among treatment-seeking clinical trials participants, (2) gender differences in psychological problems among men and women seeking treatment for cannabis use disorder, (3) differences between men and women on measures of stimulant use and associated disorders, (4) gender-based outcomes and acceptability of a computer-assisted psychosocial intervention for SUD, and (5) gender differences among individuals with SUD and co-occurring disorders.

In addition, investigators are planning gender analyses for 10 ongoing or recently completed multisite trials. Several years ago, the CTN established a Gender Special Interest Group, which has continued to play a key role in the overall gender research across the CTN studies and in identifying substance use research areas that could benefit from additional attention to gender-related outcomes. This group presented two symposia in 2015, showcasing some of the recent findings from CTN studies. A total of 36 data sets are now available online (datashare.nida.nih.gov). NIDA encourages researchers (including early career investigators) to take advantage of these data sets for addressing gender-specific questions. In addition, as new trials are planned, NIDA invites scientists to work with the trial investigators to plan ancillary or platform studies that can provide needed information on issues that can affect women in drug use treatment. **[Objective 1.6]**

Phase 2 Multicenter Trial of AZD8529 for Smoking Cessation in Female Smokers.

This study, supported by NIDA's Division of Therapeutics and Medical Consequences, is evaluating the efficacy and safety of AZD8529, a potent and selective positive allosteric modulator of the metabotropic glutamate receptors, in female smokers who are seeking treatment for smoking cessation. Previous findings suggested that agents that modify glutamate signaling play roles in treating addictive disorders. AZD8529 showed positive findings in treatment for nicotine addiction in preclinical animal models. Due to toxicology findings related to the male reproductive system in animals, it was decided to evaluate the efficacy of this drug in females only in this exploratory clinical study. This is a 19-week, randomized Phase II clinical study conducted at nine sites in the United States to enroll 210 female smokers. Study enrollment is completed and results are pending. **[Objective 2.7]**

NIDA-Issued Funding Opportunity Announcements (FOAs) on Women and Sex/Gender Differences

- **Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence, PA-14-038 (R01), PA-14-036 (R21), PA-14-037 (R03).** The goal of these FOAs, issued by NIDA and NIAAA, is to advance research on male-female differences in drug and alcohol abuse and addiction and on factors specific to women. Both human and animal model research is sought. The expiration date is May 8, 2017; the FOAs will be revised and reissued.
- **Drug Abuse Dissertation Research, PA-16-443.** The goal of this NIDA FOA is to enhance the diversity of the drug abuse research workforce by providing dissertation awards on topics related to the study of basic and clinical neuroscience, development, epidemiology, prevention, treatment, services, or women and sex/gender differences as they relate to drug abuse. The expiration date is January 8, 2020.
- **Pilot and Feasibility Studies in Preparation for Drug and Alcohol Abuse Prevention Trials (R34), PA-15-250 (R34) and grants.nih.gov/grants/guide/pa-files/PA-15-177.html.** The purpose of this FOA, issued by NIDA and NIAAA, is to encourage pilot and preliminary research in preparation for larger scale services research effectiveness trials. Special emphasis is placed on taking a sex/gender-based research approach. The expiration date is May 8, 2018.
- **Drug Abuse Prevention Intervention Research, PA-15-080 (R21); PA-15-081 (R03); PA-15-082 (R01).** The purpose of these FOAs is to encourage grant applications for research that will employ rigorous scientific methods to test theoretically derived hypotheses to increase understanding of the science of drug use prevention within diverse populations and settings and across the lifespan. Special emphasis is placed on taking a sex/gender-based research approach. The expiration date is September 8, 2017.

Other Activities That Support Implementation of the NIH Strategic Plan for Women's Health Research

Scientific Presentations

[Objective: 1.9]

- “Sex/Gender Research at NIH: What’s on the Horizon?” At the workshop, *Moving Beyond “Mice to Men”: Innovations in Translational Gender-Sensitive Tobacco Research*, held at the annual meeting of the Society for Research on Nicotine and Tobacco, February 25–28, 2015.
- “Sex/Gender Matters in Your Drug Abuse Research.” NIDA Meeting with the HHS Humphrey Fellows, NIDA Headquarters, April 1, 2015, Rockville, Maryland.
- “The Use of Both Female and Male Animals in NIH-Funded Research.” Invited presentation for the Animal Forum session at the annual meeting of the College on Problems of Drug Dependence, June 13–18, 2015, Phoenix, Arizona.
- “Intimate Partner Violence and HIV: Intersectionality and Accumulation of Risk.” American Psychological Association Annual Meeting, August 7, 2015, Toronto, Canada.
- “NIH’s New Policy on Sex as a Biological Variable: What It Is and Why It Matters.” Eastern Psychological Association, March 3–5, 2016, New York, New York.
- “Sex/Gender Differences in Drug Addiction and Why It Matters.” At the NIH Office of Research on Women’s Health Preconference Workshop, “Transforming Women’s Health: From Research to Practice.” Academy of Women’s Health 24th Annual Congress, April 14–17, 2016, Washington, D.C.
- “What You Need to Know to Help Your Grantees with the Sex as a Biological Variable Policy.” NIDA Headquarters, July 26, 2016, Rockville, Maryland.

- “Factoring Sex into Drug Abuse Research: Why It Matters.” NIDA ODHD meeting, “*Diversity Scholars Network Mock Review Workshop*,” NIDA Headquarters, September 23, 2016, Rockville, Maryland.

NIDA Staff: Scientific Symposia Organized

[Objective: 1.9]

- “Substance Abuse Treatment Clinical Trials: Does Gender Matter?” CPDD, June 13–18, 2015, Phoenix, Arizona.
- “Females and Flowers: Sex Differences in the Dependence-Related Effects of Delta-9-THC.” CPDD, June 13–18, 2015, Phoenix, Arizona.
- “Gender Matters: The Value of Tailoring Prevention and Treatment Interventions.” American Psychological Association (APA), August 6–9, 2015, Toronto, Ontario, Canada.
- “Sex Differences in Marijuana’s Effects in Human and Animal Studies: Equal Opportunity for Abuse?” APA, Toronto, Ontario, Canada, August 6–9, 2015.
- “Gender Differences in Addiction Treatment: Results from the NIDA CTN.” American Academy of Addiction Psychiatry, December 2015, Huntington Beach, California.
- “Imaging the Male and Female Addicted Brain: Structural and Functional Differences and Implications for Precision Medicine.” CPDD, June 11–16, 2016, Palm Springs, California.
- “Imaging the Human Male and Female Addicted Brain: Implications for Precision Medicine.” APA, August 4–7, 2016, Denver, Colorado.

NIDA Staff: Scientific Publications

- Allen A, McRae-Clark AL, Saladin ME, et al. (2016). Determining menstrual phase in human biobehavioral research: a review with recommendations. *Experimental and Clinical Psychopharmacology*, 24(1), 1–11.

- Miller LR, Marks C, Becker JB, et al. Considering sex as a biological variable in NIH-supported research. *FASEB Journal* (in press).
- Weinberger AH, Smith PH, Allen SS, et al. (2015). A systematic and meta-analytic review of research examining the impact of menstrual cycle phase and ovarian hormones on smoking and cessation. *Nicotine & Tobacco Research*, 17(4), 407–21.

NIDA Staff: Service on NIH or HHS Committees

[Objective: 1.9]

- Steering Committee for HHS/Office of the Assistant Secretary/Office on Women’s Health, *National Meeting on Opioid Use, Abuse, and Overdose in Women*, September 29–30, 2016, Crystal City, Virginia.
- HHS Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders
- Trans-NIH Sex as a Biological Variable Working Group
- ORWH Coordinating Committee for Research on Women’s Health

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National Institute of Environmental Health Sciences (NIEHS)

Executive Summary

“Your environment is your health.” This statement summarizes why it is important to understand the ways in which our environment plays a role in our health and biology. The mission of the National Institute of Environmental Health Sciences (NIEHS) is to discover how the environment affects people’s health and to promote healthier lives. NIEHS investigators conduct studies to understand better how women are affected by environmental exposures, how exposures and disease progression may impact women and men similarly or differently, and how an individual’s sex and gender may influence both susceptibility to disease and the eventual outcome. The scope of women’s health research has become a dynamic, multidisciplinary area of study within environmental health sciences. There are striking sex/gender differences in the prevalence, progression, and outcome of numerous conditions, including diabetes, obesity, cardiovascular diseases, substance use disorders, depression and brain disorders, infectious diseases, cancer, and autoimmune diseases.

Certain health conditions, including menopause and pregnancy, are unique to women; some diseases, such as endometriosis, ovarian cancer, and cervical cancer occur only in women; breast cancer is overwhelmingly found in women, and certain autoimmune diseases and osteoporosis occur to a great extent in women, compared to men. Many or most of these conditions and diseases may be environmentally mediated. These disparities between women and men are influenced by biological sex and gender identity, as well as by developmental, cultural, environmental, and socioeconomic factors. Women’s health and sex differences research, therefore, encompasses not only clinical studies, but also a full spectrum of scientific investigations, such as molecular, genetic, and other basic and laboratory studies, as well as

investigations into healthy lifestyles and behavior, risk reduction, and disease prevention. With this information in hand, women can better determine how to alter the lifestyle factors that lead to these exposures and diseases and provide better protection for themselves and their children. On a wider scale, society can better define standards that protect women from the environmental triggers of these diseases and develop better gender-specific and sex-specific interventions and therapies.

Accomplishments and Activities

Environmental Exposure and Decreased Ovarian Reserves in Rural South African Women

NIEHS researchers examined environmental exposures of 420 reproductive-age women in rural South Africa and the effect of exposure on ovarian health to understand whether environmental exposure affects disease pathogenesis. This study found decreased ovarian health was associated with exposure to pyrethroid pesticides, commonly used to control for malaria. Although studies have shown exposure to pyrethroids is associated with adverse effects on male reproductive health, this was the first epidemiological study to assess pesticide exposures in relation to female reproductive health. Additional studies are needed to determine whether anti-Müllerian hormone levels can be used as a biomarker for exposure of the ovaries (Whitworth et al., 2015).

Maternal Age at Delivery Associated with Epigenetic Signature

NIEHS researchers and their collaborators in Norway began to evaluate the biological

mechanisms underlying an increased risk of adverse birth outcomes in the offspring of older mothers using the Norway Facial Clefts study, the Norwegian Mother and Child Cohort Study (MoBa), and the Sister Study. Using an epigenome-wide association study, they found maternal age at delivery was associated with decreased methylation at four sites in the newborn epigenome. This finding was then replicated in samples from the independent MoBa study. To examine whether the epigenetic signature of maternal-age effects persisted, the researchers examined epigenetic changes in adult women from the Sister Study and found the same epigenetic signature, suggesting that these maternal age-related epigenetic changes persist from birth for more than 40 years (Markunas et al., 2016).

Nail Polish as a Source of Exposure to Flame Retardant/Plasticizer Chemical

Triphenyl phosphate (TPHP) is a chemical component in nail polish that can be used as a flame retardant or plasticizer. A small cohort was used to examine TPHP exposure through fingernail painting. TPHP was found in eight of 10 nail polish samples, and one polish containing TPHP was used for fingernail painting in the cohort. Inhalation and dermal routes of exposure were assessed. This work indicated a significant increase in TPHP metabolite presence after fingernail painting that was significantly reduced upon protective glove use, suggesting the dermal route was the primary source of TPHP exposure. Further work is needed to determine what the potential health effects are of TPHP exposure, and this work suggests glove use may prevent exposures (Mendelsohn et al., 2016).

Maternal Exposure to Phthalates and BMI in Resulting Offspring

Using pooled data from three prospective cohort studies, researchers examined maternal phthalate exposure and childhood body mass index (BMI). They found prenatal exposure to phthalates was associated with greater than twice the odds of increased BMI in 4–7-year-old children. In addition,

this work revealed sexual dimorphism for some of the metabolites examined suggesting prenatal exposures may have sexually dimorphic effects on physical development (Buckley et al., 2016).

Two-Hit Exposure to Polychlorinated Biphenyls and Sex-Specific Effects in the Brain

Scientists funded by NIEHS examined the effects of polychlorinated biphenyls (PCBs), persistent man-made chemicals with a range of toxicity, after prenatal and subsequent peripubertal exposures using a rodent model. They found sexually dimorphic effects with females showing social and anxiety behavior in puberty and males showing alterations in sociosexual preferences in adulthood. Prenatal exposures had more effects than prepubertal exposures, and prepubertal exposures modified the outcomes of the prenatal exposures. This work suggests the brain is susceptible to PCB exposures in prenatal and prepubertal life stages and the effects can differ based on sex (Bell et al., 2016a). The same laboratory also examined the mechanisms underlying these effects. After prenatal and prepubertal exposures, rodents were examined for serum hormone levels, gene expression, and DNA methylation in adulthood. They found exposures resulted in unique neuromolecular phenotypes and that males were more profoundly affected by exposures (Bell et al., 2016b).

Exposure to Greenness Linked to Decreased Mortality in Women

NIEHS-funded scientists examined data from the U.S.-based Nurses' Health Study prospective cohort of 108,630 women and found women with the highest density of vegetation near their homes had a 12 percent lower death rate. Women in the most "green" areas had a 41 percent lower death rate for kidney disease, 34 percent lower death rate for respiratory disease, and 13 percent lower death rate for cancer (James et al., 2016).

Sex-Specific Effects of Developmental Exposure to Lead

Using the Cincinnati Lead Study cohort, NIEHS-funded research examined the methylation status of imprinted genes known to play a role in normal development in DNA extracted from participant's blood whose lead levels were assessed about 30 years prior. The majority of the Cincinnati Lead Study cohort was born to black women. This work found that the mean and maximum lead concentrations were associated with the DNA methylation of 50 percent of imprinted genes examined. Also, sex-specific effects were seen for two of the imprinted genes (Li et al., 2015).

Sex-Specific Effects of Developmental Exposure to Arsenic

NIEHS-funded research examined developmental low-level arsenic exposure in male and female mice and looked at the epigenetic effects in the adult brain and found exposure to environmentally relevant levels of arsenic during development results in sex-specific epigenetic changes in the brain that persist into adulthood (histone acetyltransferases affected in male mice, histone deacetylases affected in female mice). This work exposes potential sex-specific mechanisms of arsenic toxicity and the long-term impact of fetal exposures to environmentally relevant levels of arsenic that may affect susceptibility to disease in adulthood (Tyler et al., 2015).

Low-Level Maternal Arsenic Exposure and Birth Outcomes

NIEHS grantee research analyzed 706 mother-infant pairs exposed to low-level arsenic in drinking water and diet and found decreased head circumference at birth was associated with increased levels of arsenic in the mother's body. A significant three-way interaction was seen between maternal weight status, infant sex, and arsenic exposure on birth weight, with increased arsenic exposure linked to decreased birth weight in females born to overweight mothers (Gilbert-Diamond et al., 2016).

Maternal Folate Levels Linked to Altered DNA Methylation in Newborns

Scientists at NIEHS performed an epigenome-wide analysis of newborns and found increased levels of maternal folate, an essential vitamin for fetal development, was associated with altered methylation of 320 genes involved in a variety of processes, including tumor progression, neurological function, and developmental diseases. This work emphasizes the potential benefit of folate supplementation for pregnant women and their resulting offspring (Joubert et al., 2016b). In a separate study, NIEHS scientists determined that supplemental intake at or above the recommended dosage, in combination with a folate-rich diet, achieves a total folate intake level associated with a slightly increased risk of pediatric asthma (Parr et al., 2016).

Maternal Smoking During Pregnancy Leads to Altered Epigenome in Newborns

As part of the Pregnancy and Childhood Epigenetics consortium, NIEHS scientists shed new light on the links between maternal smoking during pregnancy and epigenetic modifications in newborns. Researchers combined epidemiologic and epigenetic data from 13 different studies and used a statistical method called meta-analysis to determine associations between maternal smoking during pregnancy and genome-wide changes in DNA methylation in newborn blood. Using the Illumina450K platform, researchers measured DNA methylation at more than 450,000 CpG sites along the DNA sequence to determine the epigenetic modification. More than 6,000 of these CpG sites were differentially methylated relative to maternal smoking during pregnancy. Although many were linked to genes that had already been related to maternal smoking, nearly 3,000 had never been associated with smoking in either children or adults before this study (Joubert et al., 2016a).

Breast Cancer and the Environment: Prioritizing Prevention

The Breast Cancer and Environmental Research Act established the Interagency Breast Cancer and Environmental Research Coordinating Committee, which examined research on the current state of breast cancer and the environment. The Committee published a comprehensive report in February 2013 summarizing its findings and listing seven recommendations to highlight the need for coordinated, targeted efforts to identify and mitigate the environmental causes of breast cancer. In 2015, NIEHS scientists described evidence for a data gap in early life exposures and breast cancer risk over a lifetime suggesting more research is needed in this area to effectively prevent breast cancer (Fenton and Birnbaum, 2015).

Additional experiments set the foundation for future work using rat models to assess mammary gland effects when NIEHS scientists showed mammary gland development differs between rat strains and these differences should be taken into consideration when designing experiments, timing exposures, and interpreting data (Stanko et al., 2016). To understand the role of key biological mechanisms and pathways, NIEHS research leveraged data from The Cancer Genome Atlas to show correlations between the developmentally regulated gene *LIN28*'s expression and breast cancer subtypes, including *HER2*-positive breast cancer, suggesting *LIN28* may be a therapeutic target for some subtypes of breast cancer. This work shed light on the mechanistic role of *LIN28* in some breast cancer subtypes (Yang et al., 2015).

Origins of Ovarian Theca Cells

Research at NIEHS applied genetic lineage tracing techniques in the mouse to trace the origin of theca cells, which are endocrine cells in the ovary. This high-profile work determined that theca cells arise from two distinct cellular contributions within and outside of the ovary. This work also identified the molecular signaling pathway that allows theca cells to make androgen. Taken together,

this research may provide insight into how such ovarian disorders as premature ovarian failure and polycystic ovarian syndrome come to fruition (Liu et al., 2015).

Biomarker Development to Evaluate Estrogenic Chemicals

NIEHS scientists used ovariectomized adult mice to model prepubertal girls and postmenopausal women to build a screen that includes biomarkers to identify the estrogenic activity of chemicals and classify chemicals as short- versus long-acting estrogens. Using a natural phytoestrogen as the positive control for short-acting estrogens and estradiol as the positive control for long-acting estrogens, this work identified a biomarker panel to tease apart estrogenicity and relative strength of endocrine disruptors (Hewitt et al., 2015).

Agricultural Health Study

The Agricultural Health Study (AHS), funded by NIEHS, the National Cancer Institute, the U.S. Environmental Protection Agency (EPA), and the National Institute for Occupational Safety and Health, works to understand how agricultural, lifestyle, and genetic factors affect the health of farming populations. More than 89,000 farmers and their spouses in Iowa and North Carolina have been involved in AHS since 1993. Several AHS reports of particular relevance for women's health were published during FY 15–16, and the findings included the following:

- Pesticide, solvent, or fertilizer exposure among female spouses of licensed pesticide applicators in AHS had an increased risk of developing rheumatoid arthritis. Exposure to livestock as a child and an adult had a protective effect in women (Parks et al., 2016b).
- Personal use of organophosphate insecticides was linked to an increased risk for hormonally related cancers—including breast, thyroid, and ovary—among a cohort of 30,003 female spouses of pesticide applicators in AHS (Lerro et al., 2015).

NIH Strategic Plan for Women's Health Research

NIEHS funds a large array of studies that explores variations due to sex as an integral part of the search for knowledge across the entire research spectrum, beginning at the most basic laboratory level. NIEHS research regarding sex differences encompasses diverse fields, including genetics, immunology, endocrinology, developmental biology, cell biology, epidemiology, microbiology, biochemistry, and toxicology, as well as in behavioral and social sciences. Below are examples of NIEHS research activities that further knowledge in this area. The activities support the implementation of the Office of Research on Women's Health (ORWH) Strategic Plan Goal 1: Increase Sex Differences Research in Basic Science Studies.

Endocrine Disruptors

NIEHS is funding numerous human studies examining the health effects on the developing fetus related to prenatal exposures to environmental chemicals. Many studies to date have reported small but significant changes as it relates to reported sexually dimorphic behaviors. In some studies, pregnant women exposed to a specific class of endocrine disruptors show changes in girls and not in boys as it relates to depression, but yet play behavior changes are reported in boys and not girls. Larger studies are being conducted to see if specific endocrine disruptors like phthalates and bisphenol A may perturb the developing fetal endocrine system and increase the risk for behavioral disorders. This effect may be related to changes in the gestational sex steroid milieu as noted in animal studies. Outcomes to be addressed include, but are not limited to, visual and spatial abilities, and to determine whether males or females are more vulnerable to specific chemicals. *Supports ORWH Strategic Plan objectives 1.2, 1.7, and 1.8.*

National Toxicology Program

The general toxicology assessments conducted by the National Toxicology Program (NTP) usually involve exposures of rats and mice of both sexes to test articles for periods of 14 days or 13 weeks. Assessments almost always performed include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The NTP long-term toxicology and carcinogenesis studies (bioassays) in rodents generally employ both sexes of rats (Harlan Sprague Dawley) and mice (B6C3F1 hybrid), with three exposure concentrations plus untreated controls in groups of 50 animals for 2 years. Both sexes are evaluated to determine if there are differences in outcome caused by gender differences. *Supports ORWH Strategic Plan objectives 1.2, 1.4, and 1.7.*

NIEHS Sister Study

The Sister Study is a landmark research effort created by NIEHS scientists to find causes of breast cancer. More than 50,000 women across the United States and Puerto Rico, who were between ages 35–74 and whose sister had breast cancer, joined this effort between 2004 and 2009. Because of their shared environment, genes, and experiences, studying sisters provides a greater chance of identifying risk factors that may help us find ways to prevent breast cancer and other adverse health outcomes. The Sister Study currently is tracking the health of women in the cohort.

Research in the Sister Study focuses on causes of breast cancer and other health issues in women, as well as on factors that influence the quality of life and outcomes after a breast cancer diagnosis. Results from the Sister Study have been accumulating every year. Several prominent studies appeared in 2015 and 2016. For example, a report published in October 2015 found women who worked with organic solvents prior to their first full-term birth had an increased risk for hormone receptor-positive breast cancer (Ekenga et al., 2015). Increased waist circumference was positively associated with increased risk of breast cancer in

both premenopausal and postmenopausal women participating in the Sister Study, suggesting weight management may be a viable prevention strategy for some cases of breast cancer (White et al., 2015).

A family-based, genome-wide association study of young-onset breast cancer examined single-nucleotide polymorphisms in 1,279 non-Hispanic white cases and their parents or sisters and found three genetic variants associated with the risk of young-onset breast cancer. This was the first study to investigate the prenatal influence of a mother's genome on disease risk of adult daughters (O'Brien et al., 2016). When examining early life exposures of systemic lupus erythematosus cases and controls, researchers found an association between low birthweight and lupus and childhood exposure to pesticides. More frequent use of pesticides in residential dwellings of at least once per month showed a dose response in relation to association with lupus. Prenatal and childhood farm residence was also associated with lupus. Further population-based studies are needed to examine the influence of perinatal/early life exposures on risk of developing lupus (Parks et al., 2016a). *Supports ORWH Strategic Plan objectives 1.1, 1.2, 1.7, 1.8, and 1.9*

Household Air Pollution and Cookstove Research

Chronic exposure to smoke from traditional cooking practices causes a range of health effects including heart disease, stroke, and acute respiratory infections. Most deaths occur in low- and middle-income countries (LMICs), with women and children disproportionately exposed. The NIEHS Household Air Pollution program takes a multi-pronged approach to understanding the global health impact of cookstoves, including research to assess exposures and determine health outcomes, as well as the support of improved cookstove design and intervention trials along with training and capacity building to support these efforts. NIEHS partners with the Fogarty International Center on the **International Hubs of Interdisciplinary Research and Training in**

Global Environmental and Occupational Health (GEOHealth) funding program. GEOHealth supports paired consortia—led by an LMIC institution and a U.S. institution—to develop research, research training, and curriculum development activities that address and inform priority national and regional environmental and occupational health policy issues. GEOHealth Hubs in Bangladesh and Ethiopia support research on household air pollution and disease. The NIEHS-WHO Collaborating Centre for Environmental Health Sciences includes indoor air pollution associated with biomass burning as one of the five focus areas of environmental health concern. Global environmental health, including a focus on cookstoves and indoor air pollution, is identified as a priority research area for NIEHS in the 2012–2017 Strategic Plan. NIEHS is a lead NIH IC in the Global Alliance for Clean Cookstoves, an initiative that is using a specific gender strategy to empower women's role in adopting clean cookstoves and fuels. *Supports ORWH Strategic Plan objectives 4.1, 4.2, 4.4, and 4.6*

NIEHS Inclusion Efforts

NIEHS supports very few clinical trials. However, NIEHS and NTP conduct a great deal of animal research, almost all of which is analyzed by sex. The NIEHS Clinical Research Unit actively recruited women for 27 clinical studies. Researchers are studying the health effects of an herbal supplement taken by some women to treat hot flashes, cramps, or other symptoms in the Black Cohosh Study. To examine whether overweight girls are truly entering puberty before normal weight girls, researchers have recruited girls between the ages of 8–14 to participate in the Body Weight and Puberty Study. The NIEHS-EPA Pilot Study of Exposure to Chemicals in Consumer Products actively recruited healthy, stay-at-home women to improve the way data is gathered for studies that examine chemical exposure from consumer products. The Calorie Restriction, Environment, and Fitness: Reproductive Effects Evaluation Study recruited women participants to understand how nutrition, exercise,

and the environment affect women's reproductive cycles. The Ovarian Health Study recruited women participants for developing assays to measure anti-Müllerian hormone in the urine as a promising biomarker for ovarian health.

NIEHS Science, Technology, Engineering, and Mathematics (STEM) Efforts

NIEHS Scholars Connect

The NIEHS Scholars Connect Program (NSCP) is designed to provide a unique opportunity to highly motivated STEM-focused undergraduate students to solidly connect with NIEHS, and receive frontier-level training in biomedical research. Students in NSCP have an opportunity for hands-on mentored research experiences, as well as professional and personal development. The Program is committed to encouraging students to pursue careers in scientific investigation, both basic and clinical. NSCP also is committed to increasing diversity in environmental health science, and applications from underrepresented populations in STEM are strongly encouraged. In FY 15–16, three African-American women and one Caucasian woman participated in the program.

Female Tenure Track Investigators Program

The NIH Women Scientist Advisors Committee and the Intramural Committee of the NIH Working Group on Women in Biomedical Careers have developed a new program for basic and clinical tenure-track investigators and assistant clinical investigators. NIH program coordinators have agreed to help coordinate and develop a tenure-track investigators program at NIEHS. Female senior scientists serve as mentors for this program. As a result of the initiative, four female tenure-track investigators were hired in FY 15–16. Two additional female tenure-track investigators have been hired in FY 17.

Office of Fellows' Career Development

The Office of Fellows' Career Development has undertaken a project to identify the career outcomes of all trainee alumni who left NIEHS within the past 15 years and to determine whether there are differences in career outcomes based on gender. Determining whether gender-based career outcome differences exist is one of the first steps in evaluating the NIEHS training program to determine what, if any, changes need to be made. To undertake this project, we first identified the pool of NIEHS intramural postdoctoral alumni (N = 891) by analyzing NIEHS records, specifically searching for alumni between January 2000 and December 2014. We conducted searches of publicly available information to determine alumni job titles and employers. This information was categorized into three defined groups (job sector, job type, and job specifics), so that a standard comparison of career outcomes could be made and analyzed with Excel and the open source statistical and visualization computing software, R.

Results: Approximately 49 percent of NIEHS alumni enter into the academic sector after leaving the Institute, while only 30 percent enter into tenure-track positions—figures that mirror those reported in the NIH Biomedical Workforce report (43% and 23%, respectively). Fifteen percent enter into the government sector, and 27 percent enter into for-profit companies.

Job Specifics: Nearly 70 percent of NIEHS alumni enter into research positions while the rest enter into a range of fields, such as science writing, grants management, sales, and technical/customer support.

Gender: The overall composition of [males | females] was [54% | 46%] over the 15-year time period, with a trend towards equal gender composition when binned into 5-year increments. Upon closer examination of career outcomes, we found that 65 percent of tenure-track positions were held by men, while 35 percent were held by women—figures that mirror national statistics on

the gender composition of new investigators. It should be noted, however, that these figures do not take into account the fact that a higher proportion of international fellows also enter into tenure-track positions, and males far outweigh females in this international population. Furthermore, analysis showed that females enter into science writing/communication careers at nearly four times the rate of men.

NIEHS currently is developing creative ways to visualize these data, and is actively in the process of conducting statistical analyses. Thus far, the Institute has accomplished one of the most thorough analyses of postdoctoral alumni career outcomes at a single institution, notably identifying outcomes of 95 percent of all fellows within the past 15 years, as well as factors associated with career outcomes.

Funding Initiatives, Workshops, and Conferences

Funding Initiatives

Administrative Supplements for Research on Sex/Gender Differences

The NIH ORWH developed a program to catalyze exploratory research on sex and gender differences by providing an administrative supplement to ongoing NIH-funded research. NIEHS co-funded research alongside ORWH that investigated the pharmacokinetic properties of flame retardants in rats and found that components of the Firemaster[®] 550 mixture can be transferred to a developing fetus both throughout gestation and during lactation postnatally. This study is one of the first to assess the pharmacokinetic properties of the components of Firemaster[®] 550 and contributes novel and important data regarding this commercial mixture, which can help support human exposure studies and risk assessments (Phillips et al., 2016).

Research co-funded by NIEHS and ORWH has investigated the association between phthalate exposure from personal care products in women

and midlife hot flashes. This work suggests an increased risk of hot flashes in women who were more highly exposed to phthalates, underscoring the need to determine the potential mechanisms whereby phthalates increase the risk of hot flashes (Ziv-Gal et al., 2016). ORWH, alongside the NIH Office of the Director, developed a program to support meritorious research in Women's Health Research through a Trans-NIH High Priority, Short-Term Awards (R56) mechanism. NIEHS has two grantees funded through this mechanism to study phthalates in ovarian toxicity (R01ES025147) and in their effects on inflammatory markers in the breast density of young women (R01ES026177).

The Role of Environmental Exposures in the Development of Autoimmune Disease (R21)

Autoimmune diseases result from an immune response directed against the body's own tissues. There are more than 80 different autoimmune diseases, and though many individual autoimmune diseases are rare, autoimmune diseases collectively afflict approximately 24.5 million Americans, with women disproportionately affected. The cause(s) of autoimmune disorders remain largely unknown. Genetic risk factors have been and continue to be studied and account for a portion of the risk for autoimmune disorders. It is becoming clear from human studies, as well as animal model and *in vitro* research, that the etiology of the autoimmune disease is multifactorial, involving both genetic and environmental influences.

This R21 announcement encourages exploratory research applications aimed at investigating the role environmental exposures play in the development and/or the exacerbation of autoimmune disease. Examples of research addressed in this Funding Opportunity Announcement (FOA) include efforts to understand the interplay between environmental exposures and the hormonal milieu in mediating sex differences in disease incidence, and an examination of the functional consequence of the timing of exposure on disease formation, including characterization of such critical windows in the

timing of specific environmental exposures as during the fetal, perinatal, prepubertal, pubertal, adult, and aged periods in relation to the sensitivity to the development of autoimmune disease.

Environmental Influences During Windows of Susceptibility in Breast Cancer Risk (U01) and Coordinating Center for the Breast Cancer and the Environment Research Program (U01)

The overarching goal of the NIEHS Breast Cancer and the Environment Research Program (BCERP) is to support integrated scientific research to enhance knowledge of environmental and genetic factors underlying breast cancer risk. Projects and the Coordinating Center funded under two complementary FOAs together constitute the BCERP. One funding opportunity supports transdisciplinary research projects to investigate the influence of environmental exposures during specific time windows of susceptibility on breast cancer risk. These transdisciplinary projects should be designed to address one or more potential windows of susceptibility and facilitate the integration of experimental model and human studies to accelerate understanding of the contribution of environmental factors to breast cancer risk, the underlying mechanisms, and the potential for prevention strategies, and must include community-academic partnerships with defined community engagement activities. Collectively, the BCERP will form a consortium of multidisciplinary teams that will work collaboratively to conduct high-quality, transdisciplinary research focused on the impacts of environmental exposures during specific windows of susceptibility on breast cancer risk. The BCERP Consortium also will develop and implement strategies to translate and communicate these research findings to appropriate stakeholders.

Workshops and Conferences

Tribal Ecological Knowledge

Led by the NIH, this [workshop](#) was organized by representatives of seven tribal communities in coordination with NIH, the Indian Health Service,

the Smithsonian, and the Centers for Disease Control and Prevention (CDC)/Agency for Toxic Substances and Disease Registry, and was held in Bethesda, Maryland on December 2–4, 2015. The goals of the workshop were to: (1) explore ways to improve trust in academic-tribal research, (2) identify methods for incorporating community-acquired data and local tribal ecological knowledge (TEK) into environmental health and biomedical research studies, (3) consider ethical approaches for tribal specific data collection, and (4) build capacity to respond to long-term and immediate disaster events. Speakers' tribal affiliations included Mohawk, Blackfeet, Cherokee, Chippewa, Confederated Salish and Kootenai, Cree, Crow, Gros Ventre, Hidatsa, Inupiaq, Mandan, Navajo, Pembina, St. Lawrence Island Yupik, Swinomish, and Taino.

Presentations included talks addressing environmental exposures and reproductive health with the concept of “Woman Is the First Environment.” Outcomes from this workshop include: (1) presentation of the TEK workshop recommendations to the NIH Tribal Consultation Advisory Committee in February 2016, (2) an invited commentary submitted to *Environmental Health Perspectives* in July 2016, (3) a review article in preparation, (4) planning for future workshops in 2017 and beyond to further explore TEK and its potential for biomedical research and to explore the impact of climate change on tribal elderly and other health disparate populations, (5) the inclusion of TEK in the Research to Action FOA to stimulate an increase in tribal projects submitted to NIH, and (6) the provision of emergency response safety training targeted to tribal communities.

Women's Health Awareness Day: Transforming Communities by Enhancing Women's Health

NIEHS sponsored Women's Health Awareness Day on April 11, 2015, and again on April 2, 2016, at North Carolina Central University in Durham, North Carolina. This was a community event that was free to the public, and more than 500 people participated in 2016 alone. The goal of this event was to promote healthier lives through disease prevention, control, and management

by bringing health education and environmental health awareness and literacy to women in the area to ultimately develop healthier families, environmentally safer homes, and communities. Health information was disseminated on cardiovascular disease, diabetes, reducing cancer risk, protecting lung health, human sexuality, breast awareness, and reproductive and maternal health. Breakout sessions included information on women's preventive health care under the Affordable Health Care Act, health care services and challenges for women veterans, and how to make homes environmentally safe. Free health screenings were provided throughout the conference, including mammography, cardiovascular screening, diabetes screening, and lung capacity screening. Plans are underway for the event to be held in 2017.

Transgenerational Inheritance: State of the Science

NIEHS hosted a conference focused on discussing the state-of-the-science in the field of transgenerational inheritance April 21–22, 2016, in Bethesda, Maryland. This conference explored current research on transgenerational inheritance—the inheritance of acquired phenotypes that persist across several generations, even after the inducing factor has been removed. Since this phenomenon was first described in the early 2000s, a number of examples of transgenerational inheritance in animal models have been described by researchers, following exposures to environmental chemicals, nutritional changes, and a variety of other stressors. The goals of the conference were to showcase the breadth of transgenerational inheritance research across the NIH and to chart a course for this emerging field moving forward. Through formal talks and panel discussions, invited speakers provided an overview of the field and examples of transgenerational inheritance resulting from many different types of exposure, discussed unexplored potential mechanisms for transmission of this information across generations, illustrated the use of non-mammalian models in studying this phenomenon, and provided perspective on what these studies might indicate about human health. Sessions included talks on exposures, such as

maternal high fat intake during pregnancy and the association with increased mammary tumorigenesis in F3 generation female mice.

25 Years of Endocrine Disruption Research: Past Lessons and Future Directions

This meeting was part of the NIEHS 50th year celebration and the 25th anniversary of the Wingspread Endocrine Disruption Conference (the seminal endocrine disruptor meeting), and was co-sponsored by the Endocrine Society. The meeting was open to the public and included sessions on the history of endocrine disruption, the current state-of-the-science in endocrine disrupting chemicals (EDCs) research, and how to address data gaps and challenges to move the field forward. Sessions were held on the historical perspective of EDCs, emerging disease endpoints, emerging chemicals, legacy chemicals, new methods for EDC testing, policy/economic implications, and development of the next generation of EDC researchers. This meeting was held September 18–20, 2016, in Bethesda, Maryland, and included talks on “Female Reproduction: Mechanisms and Effects of EDCs” and “The DES Story.”

NIEHS Environmental Health Science FEST (EHS FEST)

As part of its 50th anniversary celebration, NIEHS brought together researchers, trainees, young investigators, community partners, and stakeholders from across the United States to discuss past accomplishments and explore the future of environmental health science in the 21st century. More than 1,200 people registered to attend this first-ever EHS FEST, held December 5–8, 2016, at the Durham Convention Center in Durham, North Carolina. A session was held on “Sex Differences and Environmental Research: Latest Research Advances and Impact of New NIH Policy.” Historically, basic, preclinical, and clinical biomedical research has focused on studies using male humans, animal, models, and cells. However, overwhelming evidence suggests that sex and gender are critical variables in health and disease processes, including cancers and disorders of the endocrine, nervous, and immune systems.

Determining how environmental exposures impact biologic processes differently in males and females is critical for advancing effective intervention and prevention efforts in many diseases and disorders. This session explored the new NIH policy on consideration of sex as a biological variable in research and included presentations highlighting exposure-related research on sex differences in neurodevelopment and the endocrine systems in basic and population studies.

2015 Gulf of Mexico Oil Spill and Ecosystem Science Conference

Researchers from more than 35 states and 20 countries met February 16–19, 2015, in Houston, Texas, to focus on results from oil spill, ecosystem, and public health research 5 years after the Deepwater Horizon Gulf spill. The conference attracted representatives from 140 universities, 80 companies, and 17 government agencies. Altogether, about 1,000 people participated in sharing the results of research and application of findings. Organized by the Gulf of Mexico Research Initiative (GoMRI), the conference included more than 500 oral and poster presentations. One session, titled “Gaps to Gains,” held particular interest for NIEHS staff and grantees, as it addressed two important conference themes—public health and community engagement. Here, NIEHS grantees presented results from the Women and Their Children’s Health Study (WaTCH) and the Transdisciplinary Research Consortium for Gulf Resilience on Women’s Health (GROWH) (*see Section VII*).

HEALTH DISPARITIES

Health Disparities from the 2010 Deepwater Horizon Gulf Spill

The NIEHS-led Deepwater Horizon Research Consortia support community-university partnerships aimed at addressing the health effects stemming from the 2010 Deepwater Horizon Gulf spill to help improve community preparedness and response to disasters and minimize such disaster-related health impacts as stress, exposure to

contaminants, and diet changes. Consortia studies that focus on women and children and involve minority or ethnic populations are being conducted at Louisiana State University and Tulane University:

- **WaTCH (5U01ES021497-04)**. Goal: Determine mid- and long-term physical, behavioral, social, and economic effects on women and children’s well-being.

Two substudies are being conducted on resiliency (the association between resilience, social capital, and emotional health and association between subjects’ exposure and their emotional and physical health) and a Child Impact Study. These studies include women from low-income communities, from Vietnamese subsistence communities, and among Houma Nation (Native American) communities. NIEHS-funded research studied 2,842 women following the Deepwater Horizon Gulf oil spill and found high rates of adverse mental health outcomes, with exposure to the spill being a significant predictor of these outcomes suggesting mental health services are important for mitigating adverse health outcomes resulting from natural disasters (Rung et al., 2016).

- **GROWH**. Goals: Assess mental and reproductive health outcomes and interactions of environmental and social disparities among women who are pregnant or of reproductive age, and characterize women’s exposures to select contaminants.

Two substudies are being conducted on Lifetime Adversity and Reproductive-Aged Women (3U19ES020677-04S1) and Real and Perceived Exposures in Reproductive-Aged Women (3U19ES020677-04S1). These studies also involve low-income communities and ethnic minorities, as noted above. When 742 primarily African-American pregnant and nonpregnant women ages 18–45 residing in southeastern Louisiana were studied, researchers found a link between childhood stressors, menstrual cycle disruption, and adverse effects on fertility, and suggest this effect may be mediated through the hypothalamic-pituitary-adrenal axis (Jacobs et al., 2015). This

research in primarily minority women has indicated that younger age at the time of a natural disaster may impart a protective effect on mental health outcomes postdisaster (Jacobs and Harville, 2015).

Study of Environment, Lifestyle, and Fibroids

NIEHS intramural scientists are studying a variety of diseases that affect women. One epidemiological study, called the Study of Environment, Lifestyle and Fibroids, is being conducted among African-American women ages 23–34, in the Detroit, Michigan area (1ZIAES049013-19). Fibroids are more common in black women than in white women, and fibroids are the leading indication for hysterectomy. The reason for this health disparity is not known. This NIEHS study is a prospective cohort study with an enrollment of women before they are diagnosed with fibroids and with follow-up for at least 5 years to document new fibroid development with ultrasound examinations at intervals of about 20 months. Researchers will examine a wide range of potential risk factors for the condition to evaluate their associations with the appearance of new fibroids and growth of existing fibroids. Initial research from the Sister Study indicated that soy formula exposure in early life was linked to greater risk of fibroids (D'Aloisio et al., 2012). More recent research has indicated that women who were fed soy formula as infants have larger fibroids than women who were not fed soy formula as infants, suggesting early-life exposure to phytoestrogen may have adverse effects on the uterus later in life (Upton et al., 2015).

NIEHS scientists in the National Toxicology Program (NTP) Division have focused on defining the pathogenesis of disorders affecting the uterus and assessing the role of environmental and endogenous hormones and growth factors in these disorders. They have found that both positive and negative regulators of apoptosis are not differentially expressed in uterine fibroids, and that altered apoptosis does not appear to play a significant role in the development of these tumors. Their studies show that cell proliferation

and extracellular matrix production may be the most significant contributors to fibroid growth. In studies addressing the role of growth factors in the pathogenesis of fibroids, receptor tyrosine kinases (RTKs) and their ligands are overexpressed in fibroids during the proliferative phase of the menstrual cycle, and many of the RTKs are activated, suggesting RTK signaling likely plays a role in uterine fibroid pathogenesis.

These studies will help to define some of the basic biological and molecular pathways important in fibroid growth, which can then be applied to developing alternative noninvasive treatment regimens for fibroids. *In vitro* model systems for studying fibroids are limited, but NTP scientists have overcome this obstacle by the development of human telomerase immortalized uterine leiomyoma and myometrial cell lines. These cells are being used to study leiomyoma tumorigenesis in a prospective manner. Additional model systems continue to be explored, including the use of the miniature pig as a model of fibroids in women (Mozzachio et al., 2016). In determining the role of environmental agents in fibroid development, scientists have found that prenatal and neonatal exposures of mice to diethylstilbestrol (DES) results in uterine leiomyomas similar to fibroids observed in women. Other exposures that have been evaluated include the phytoestrogen genistein and the environmental pesticide fenvalerate and metals, such as cadmium, all of which may increase the risk of uterine fibroid development.

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National Institute of General Medical Sciences (NIGMS)

Executive Summary

The National Institute of General Medical Sciences (NIGMS) supports basic research that increases understanding of biological processes and lays the foundation for advances in disease diagnosis, treatment, and prevention. NIGMS-funded scientists investigate how living systems work at a range of levels, from molecules and cells, to tissues, whole organisms, and populations. Investments in such diverse and fundamental areas of biomedical research serve as the foundation for subsequent categorical or disease-specific discoveries and advances. Our ability to effectively treat, diagnose, manage, and ultimately cure diseases increases significantly with an understanding of their underlying mechanisms and biology. The Institute also supports research in certain clinical areas, primarily those that affect multiple organ systems. NIGMS also supports research training, career development, diversity, and capacity-building activities through a variety of programs at the undergraduate, graduate, postdoctoral, and faculty levels. The focus of these programs is to train the next generation of scientists, enhance the diversity of the scientific workforce, and develop research capacities throughout the Nation.

In Fiscal Years (FY) 15–16, NIGMS supported research in a broad range of areas related to women's health and the interests of the Office of Research on Women's Health (ORWH). This includes projects focused on increasing our understanding of biological processes that may lead to improved methods of diagnosing and treating a variety of conditions, including breast cancer, preeclampsia, menopausal symptoms, and brain insults due to disease, injury, and aging. Additionally, NIGMS-supported projects are studying scientific workforce dynamics and barriers for women in biomedical and research careers. These projects align with several goals and objectives in the NIH Strategic Plan for Women's Health Research. For example, several projects align with Goal 2, including one project that has identified a potential candidate biomarker

for breast cancer. Another project aligns with Goal 6 and focuses on understanding the factors that impact promotion and attrition of women in research careers and academia. Other projects align with Goals 1 and 3.

Through the Trans-NIH Coordinating Committee on Women's Health, NIGMS awards supplemental funding to NIH-funded researchers to encourage the consideration of sex/gender factors in their ongoing research. NIGMS staff actively participate in the NIH Working Group on Women in Biomedical Careers, and in 2016, NIGMS and ORWH co-sponsored a workshop on Advancement of Women in Independent Careers.

Accomplishments and Activities

Accomplishments

NIH Strategic Plan for Women's Health Research

Understanding the Function of LBH in Normal Mammary Development and Breast Cancer Pathogenesis

LBH is a protein that is expressed during mammary gland development and is aberrantly overexpressed in aggressive breast cancer. To better understand the physiological functions of LBH, NIGMS-supported scientists investigated the *in vivo* role of LBH in normal breast development in postnatal mice and in normal human and mouse breast cells (Lindley et al., 2015). Study results showed that LBH is a regulatory protein required in adult breast stem cells for their rapid expansion during puberty and pregnancy. In particular, LBH plays an essential role in the expansion and/or maintenance of mammary stem cells, as well as in the specification of breast cell type. Importantly, researchers found that excessive LBH is present in cancer-related dysfunction. This research has important

implications for understanding the role of LBH in breast cancer pathogenesis and will inform efforts to develop novel therapeutic targets. This research supports NIGMS Strategic Plan Goal 1 and Objective 2.7 of the NIH Strategic Plan for Women's Health Research.

Lower Circulating Aspartate Is a Key Feature of Human Breast Cancer

Breast cancer remains one of the most commonly diagnosed cancers and one of the leading causes of cancer deaths among women in the United States. Because long-term survival of women with breast cancer depends on the stage of disease at the time of diagnosis, efforts to reduce breast cancer deaths have focused on early detection and treatment. Although mammography is the most widely used screening method for breast cancer, it lacks the sensitivity and specificity needed to detect tumors smaller than 5 mm in size. Other imaging technologies, such as thermography and magnetic resonance imaging, also lack sensitivity. One promising area of research is focused on finding biomarkers that could be used to detect breast and other cancers through blood tests. NIGMS-supported researchers have found that the blood level of the amino acid aspartate may be a promising biomarker candidate (Xie, et al., 2015). Researchers found significantly higher levels of aspartate in breast cancer tumors than in adjacent nontumor tissues, suggesting that depleted levels of aspartate in the blood of breast cancer patients may be due to increased tumor aspartate utilization. These findings suggest that lower circulating aspartate is a key metabolic feature of human breast cancer and may be utilized as a biomarker for early diagnosis of breast cancer. This research supports the NIGMS Strategic Plan Goal 1 and Objective 3.5 of the NIH Strategic Plan for Women's Health Research.

Developing Safe Glucocorticoid Therapies

Although topical glucocorticoids (GCs) remain the most commonly used anti-inflammatory drugs to treat skin diseases, their use is limited by detrimental side effects that can be severe and partially irreversible, such as skin atrophy. NIGMS-funded researchers are utilizing an integrative bioinformatics approach to elucidate the complex

molecular networks induced by GCs in the skin, as well as the subnetworks related to GCs-induced skin atrophy (Kishibe et al., 2016). Researchers will use this information to identify novel targets (atrophogenes) and establish compounds (anti-atrophogenes) that could be co-administered with GCs to ameliorate skin atrophy while preserving GCs' anti-inflammatory benefits. This highly innovative program has the potential to transform the use of GCs, not only for skin diseases, but also for the wide range of organ diseases/disorders treated with GCs. Importantly, the proposed studies also will incorporate findings to help in the design of gender-specific treatments. This research supports NIGMS Strategic Plan Goal 1 and Objectives 1.2, 1.3, and 1.7 of the NIH Strategic Plan for Women's Health Research.

Phosphodiesterase Type 5 Inhibition May Be an Important Therapeutic Target for Treating Preeclampsia

Preeclampsia, a hypertensive disorder of pregnancy, is a leading cause of maternal morbidity and death worldwide. Additionally, preeclampsia can have long-term effects, placing both mothers and their offspring at increased risk of cardiovascular disease later in life. The mechanisms underlying the pathogenesis of preeclampsia are not yet well understood, and there are currently no effective drug treatments. A recent study using an animal model of preeclampsia tested the effects of inhibiting phosphodiesterase-5, a potential therapeutic target, by the drug sildenafil (Gillis, et al., 2016). Study results showed that sildenafil was effective in ameliorating the effects of preeclampsia for both mothers and offspring. The untreated mothers had a significant rise in blood pressure and a two-fold increase in urinary protein excretion from baseline to late pregnancy; however, sildenafil-treated mothers exhibited drops in blood pressure with no rise in protein excretion. Sildenafil treatment also improved fetal outcomes (survival, weight, and litter size) during late pregnancy. Additionally, various other factors, which are characteristically increased in women with preeclampsia and in experimental models of the disease, were reduced in the treatment group. These data suggest that sildenafil improves the maternal syndrome of preeclampsia and blood

flow to offspring, providing preclinical evidence to support the hypothesis that phosphodiesterase type 5 inhibition may be an important therapeutic target for the treatment of preeclampsia. This research supports NIGMS Strategic Plan Goal 1 and Objective 3.4 of the NIH Strategic Plan for Women's Health Research.

Synthetic Estrogens Offer Neuroprotection Independent of Estrogen Receptors

Although estrogen replacement therapy is effective in alleviating the symptoms of menopause, research also has shown that it provides potent neuroprotective benefits against brain aging and injury, including protecting the brain from the induction of ischemic- and Alzheimer's disease (AD)-like neuropathies. However, the potential increased risk for adverse outcomes related to this hormone therapy (HT) has spurred intense debate as to whether estrogen-containing HT should continue to be administered for treatment of menopausal symptoms and brain aging. Given that approximately half of the aging adult population is female, there is an important medical need to develop novel treatments for the menopausal transition and aging processes with a more acceptable risk-to-benefit ratio. Research has shown that synthetic estrogens provide potent neuroprotective benefits without the negative side effects of traditional estrogen replacement therapy preparations. In a series of studies, scientists have uncovered the mechanism by which synthetic estrogens are neuroprotective (Engler-Chiurazzi et al., 2016). Study results showed that synthetic estrogens do not interact with estrogen receptors, yet still provide neuroprotection. These findings indicate that synthetic hormones are candidates for chronic therapy aimed at preserving the brain from insults sustained by diseases, like AD, or more acute traumas, such as a stroke. However, it is not yet known whether synthetic estrogen will impart the same peripheral benefits of estrogen replacement therapy on the urogenital tract, bone, and cardiovascular tissues. This research supports NIGMS Strategic Plan Goal 1 and Objective 2.2 of the NIH Strategic Plan for Women's Health Research.

NIGMS Science Technology, Engineering, and Mathematics (STEM) Efforts

Using Coauthor Network Metrics to Understand Faculty Advancement and Retention in Academic Medicine

The modern scientific workforce requires teams to solve the most critical intellectual and social problems that confront biomedical research. A network of productive colleagues is among the strongest predictors of research publications, productivity, retention, and advancement of academic faculty. Additionally, differences in the networks of women and minorities explain some of the disparities that exist in these subgroups with respect to research productivity and subsequent career advancement. Co-authorship of a published manuscript is evidence of a connection or collaboration between two or more authors, and collectively, these relationships form a co-author network. Analysis of co-author network data at a major academic medical institution revealed that network reach (the number of first- and second-degree co-authors) was positively associated with promotion and retention (Warner et al., 2015). This association was independent of productivity metrics, such as the number of first-, middle-, and last author publications. Faculty who rated highest in network reach were three times more likely to have been promoted to assistant professor and 17 percent less likely to have left the institution after 4 years, as compared to faculty with the lowest network reach. Additionally, among assistant professors, men and whites had greater network reach than women and underrepresented minorities. The study results highlight the importance of connections and suggest that internal connections should be considered in designing, implementing, and evaluating faculty development programs, and more generally in programs that enhance diversity inclusion, particularly of underrepresented minorities and women. Additionally, this study demonstrates that co-author network metrics can provide useful information for understanding faculty advancement and retention in academic medicine, as well as in other settings. This research supports NIGMS Strategic Plan Goal 2 and Objective 6.3 of the NIH Strategic Plan for Women's Health Research.

Activities

NIGMS actively participates in the “Trans-NIH Coordinating Committee on Women’s Health and is taking part in the Funding Opportunity Announcement (FOA), “Administrative Supplements for Research on Sex/Gender Differences” (PA-16-066). This program provides supplemental funding to NIH-funded researchers to encourage the consideration of sex/gender factors in their ongoing research. Two NIGMS grantees were funded in 2016 under this FOA.

NIGMS actively participates in the NIH Working Group on Women in Biomedical Careers and co-sponsored a workshop with ORWH on Advancing Women in Independent Positions. (The meeting summary is available here.) The Deputy Director, NIGMS, serves as Chair of the Committee on Advancing Women in Independent Positions, which is a part of this working group.

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National Institute of Mental Health (NIMH)

Executive Summary

Sex differences exist in the prevalence and clinical course of several mental disorders. Starting in childhood, girls have higher rates of anxiety disorders and eating disorders than do boys, whereas boys are more likely to suffer from autism spectrum disorder and attention deficit-hyperactivity disorder. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including posttraumatic stress disorder. There also are differences in the course and severity of mental disorders between men and women. Additionally, some women are at increased risk of depression during certain times of reproductive change, such as in the perinatal and perimenopause periods.

The National Institute of Mental Health (NIMH) funds research aimed at increasing scientific understanding of sex differences in mental health and mental illnesses. NIMH funds projects designed to advanced knowledge in the area of specific mental disorders that either affect women exclusively (e.g., perinatal depression), or predominantly (e.g., eating disorders).

Crosscutting NIMH efforts, such as the Women's Mental Health Team, foster interdisciplinary collaboration and research to pave the way for improved diagnosis, treatment, and prevention of mental disorders in women. NIMH prioritizes initiatives in global mental health, mental health disparities, and training of scientists in both of these areas. These efforts lay the groundwork for new interventions to meet the needs of women from diverse socioeconomic, racial and ethnic, and geographic backgrounds in a variety of treatment settings.

This report, from Fiscal Years (FY) 15–16, highlights NIMH offices and groups that are designated to focus on women's mental health, published findings from NIMH-funded research on sex differences and women's mental health, specific workshops and

initiatives to promote research on women's health, and NIMH's efforts on behalf of special populations of women. Research highlights, initiatives, and workshops are organized below according to their alignment with specific objectives of the NIH Strategic Goals for Women's Health and Sex Differences Research.

NIMH Offices and Groups Designated to Focus on Women's Mental Health

The Women's Mental Health Program is located organizationally in the NIMH Office for Research on Disparities and Global Mental Health (ORDGMH). The Women's Mental Health Program was established to ensure coordination of NIMH-funded research on women's mental health and sex differences. Other functions include serving as an organizational point of contact for women's mental health research, liaison with the Office of Research on Women's Health (ORWH), and liaison with governmental and nongovernmental organizations interested in women's issues. To enhance Federal collaboration on women's mental health research, the Women's Mental Health Program Chief serves on a number of NIMH, the National Institutes of Health (NIH), and other Federal working groups and committees.

The Women's Mental Health Program coordinates NIMH's scientific activities related to women's health and sex differences research. Members of the team include representatives from all four extramural research funding divisions (i.e., the Division of Neuroscience and Basic Behavioral Research, the Division of AIDS Research, the Division of Translational Research, and the Division of Services and Implementation Research); the Division of Intramural Research Programs; the Division of Extramural Activities; the Office of Science Policy, Planning and Communications; the Office of Constituency Relations and Public Liaison; and the Office of Clinical Research. Team members

work together across disciplinary boundaries to plan workshops, prepare/review science reports, and develop funding opportunities related to women's mental health.

Accomplishments and Activities

Goal 1: Increase Sex Differences Research in Basic Science Studies

Sex differences in the prevalence of certain mental disorders are demonstrated in population-based epidemiological studies of U.S. adults. For example, adult women experience major depression at almost twice the rate of adult men. Sex differences can be due to a variety of factors, including the effects of sex-linked genes, sex hormones, and differences in environmental stressors that impact brain structure and function. Understanding the mechanisms underlying these sex differences may provide clues as to why men and women are differentially vulnerable to certain mental illnesses. The following examples of NIMH-supported studies illustrate the Institute's efforts in this area.

MicroRNA control of gene expression changes in postpartum state: The postpartum state is associated with changes in mood, including an increased risk of depression. However, it is not known to what extent these changes in mood affect depression. NIMH-funded researchers are examining this question through a study of mice in different reproductive states to identify and understand the myriad of genetic and epigenetic changes in the brain that may underlie changes in postpartum mood state. Large-scale changes in gene expression patterns have been found in brain regions critical for maternal behaviors. In postpartum mice, investigators found altered expression levels of more than 50 microRNAs that targeted more than 1,000 genes. This study highlights the possibility of identifying changes in specific regulatory factors that, if disrupted, could

have large downstream effects on mood during the postpartum period (Saul et al., 2016).

***Objective 1.1** Encourage genetic and epigenetic studies to identify sex differences in gene expression.*

Sex differences in puberty-associated patterns of cell and synapse loss in medial prefrontal cortex:

Adolescence is a critical period of brain maturation that is characterized by the reorganization of interacting neural networks. The prefrontal cortex (PFC), a region of the brain associated with executive function, undergoes synaptic and neuronal pruning during this time in both humans and rats. Sex differences in the timing and distribution of these processes have been observed. However, little is known regarding the timing of these changes in the brain between early adolescence and adulthood. In a set of recent studies, NIMH-funded researchers further delineated the sex-, hormone-, and age-dependence of these processes in the medial PFC (mPFC) of rats. The researchers found a significant decrease of neurons in the mPFC across adolescence only in females and showed that this normal developmental process may depend upon ovarian hormones. Most recently, these scientists reported decreases in mPFC synapses associated with puberty in both females and males. The differences in cell loss in males and females may lead to differential vulnerability to external influences that impact mPFC function during adolescence (Koss et al., 2015; Willing and Juraska, 2015).

***Objective 1.2** Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.*

***Objective 1.7** Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs.*

Sex differences in social behavior related to oxytocin and vasopressin receptors: Sex differences in social behaviors exist, but the underlying neurobiological mechanisms associated with these differences is not well understood. Because oxytocin (OT) and vasopressin (VP) are neuropeptides that play key roles in sex-specific social behaviors, NIMH-sponsored researchers recently explored the roles of OT and VP receptors on a range of social behaviors in both male and female mice. One research team discovered that male rats have significantly more OT receptors in an area of the brain implicated in stress, anxiety, and social behaviors. Another group found that blocking vasopressin 1a receptors increased both social and nonsocial anxiety in male mice, but had no effects on nonsocial anxiety levels in females. OT and VP have been considered as possible therapeutic agents for anxiety and autism spectrum disorders. These results highlight the importance of considering both sex and target selectivity when developing therapeutics for psychiatric disorders (Dumais et al., 2016); (Duque-Wilckens et al., 2016).

***Objective 1.2** Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.*

***Objective 1.7** Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs.*

***Objective 1.8** Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being.*

Possible contributing role for the vaginal microbiome in neurodevelopmental disease risk: The microbial population that inhabits the gut (i.e., gut microbiota), can modulate brain development and behavior. NIMH-funded researchers investigating the long-term effects of early prenatal stress on offspring development hypothesized that stress during pregnancy may disrupt the normal vaginal ecosystem, and that this disruption could

have long-term consequences for the offspring. The investigators conducted a study in pregnant mice, which showed that maternal stress led to alterations in vaginal microbiota. During childbirth, these stress-altered microbiota were transmitted to the neonate's gut, which resulted in their colonization, and likely impacted the availability of metabolites and amino acids that are vital to normal brain development. *Lactobacillus*, the primary microbial population of the vaginal microbiota, was reduced in both the maternal vagina and in the gut of the neonatal offspring that were exposed to early prenatal stress. Depletion of *Lactobacillus* in females corresponded to enrichment of other bacteria (*Clostridium* and *Bacteroides*). Because stress during early neurodevelopment can be a risk factor for neurodevelopmental disorders, and because transmission of the altered maternal vaginal microbiota and the bacterial assembly of the neonatal gut overlap with a critical period of neurodevelopment, the vaginal microbiota appears to be an additional factor by which maternal stress affects the developing brain (Jašarević et al., 2015).

***Objective 1.3** Study sex differences using a systems biology-based approach*

Sex differences in peripheral metabolism of ketamine is responsible for differences in potency of behavioral effects in rodents:

Many important medical advances trace back to basic research. For example, NIMH scientists and collaborators recently uncovered the mechanisms behind the antidepressant effects of ketamine in individuals with treatment-resistant depression. Work in rodent models revealed large sex differences in the potency of antidepressant effects of ketamine, and these were initially assumed to be due to sex differences in brain mechanisms. However, the researchers found that sex differences in potency of ketamine in rodents was due to a significantly higher rate of peripheral metabolism of ketamine in females. This metabolic mechanism may be responsible for sex differences in ketamine's antidepressant effects. Identifying such mechanisms and corresponding sex differences is a crucial step in the drug development process, and highlights

the importance of basic science in getting tailored treatments to patients (Zanos et al., 2016).

Objective 1.3 *Study sex differences using a systems biology-based approach.*

Objective 1.6 *Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases, including HIV/AIDS, urinary tract, and sexually transmitted infections.*

Objective 1.8 *Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being.*

Goal 2: Incorporate Findings of Sex/Gender Differences in the Design and Application of New Technologies, Medical Devices, and Therapeutic Drugs

Improvements in research methodology, instrumentation, and technology have advanced progress in biomedical services. NIMH supports research that utilizes complex modeling to better understand the factors that may promote or inhibit certain behaviors in women and girls. In addition, innovative research design techniques are being developed to improve women's mental health by improving drug delivery systems. Many NIMH-funded published findings focus on technologies and therapeutics aimed at improving treatment for mental illnesses that differentially affect women and girls. The following examples of NIMH-supported studies illustrate the Institute's efforts in this area.

Eating Disorders are associated with adverse mental health outcomes: Eating disorders affect about one in 10 females and most often occur during adolescence. Although eating disorders are associated with increased risk for morbidity and mortality, the relationship between eating disorders and other mental/behavioral conditions is not well understood. NIMH-funded investigators employed advanced multivariate modeling approaches to

analyze data from a longitudinal, population-based cohort. Researchers investigated the prospective association between eating disorders and a range of mental/behavioral conditions (e.g., depression, anxiety, self-harm, binge drinking, and drug use). Adolescents were later assessed on different types of eating disorders and mental/behavioral outcomes. Researchers found that eating disorders were strongly associated with later adverse mental health outcomes, substance use, and self-harm (Micali et al., 2015).

Objective 2.4 *Develop computational models that will utilize multiple levels of analyses to address both qualitative and quantitative outcomes of clinical research related to women.*

Effective use of drug treatment for premenstrual dysphoric disorder is closely linked with timing and dose: For women who live with premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome that can result from a depressive episode associated with hormonal changes due to onset of menses, it may be difficult to know when to take medication for this condition. NIMH-supported clinical researchers set out to determine the efficacy of the selective serotonin reuptake inhibitor sertraline for the treatment of PMDD. The researchers conducted a randomized clinical trial of women with PMDD in which participants were given sertraline or a placebo at the time of symptom onset through the first few days of menses. This was repeated for six menstrual cycles. Compared to placebo, sertraline taken at symptom onset through the first few days of menses resulted in improved outcomes for women with PMDD. However, this effect was moderated by symptom severity. This study demonstrates important potential benefits of sertraline treatment for some women with PMDD (Yonkers et al., 2015).

Objective 2.7 *Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.*

Goal 3: Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women

NIMH-funded research has led to improved biomedical scientific knowledge about the mental health of women and girls, placing a strong emphasis on the importance of translating basic research into clinical applications. NIMH continues to fund research focused on risk factors, etiology, and course of mental illnesses to inform prevention, early detection, and therapeutic interventions for women and girls. Examples of this type of research are highlighted in this section.

Estradiol withdrawal heightens risk of depression for women with a past history of perimenopausal depression: Periodic fluctuations in hormones occur at discrete stages of a woman's life: puberty, pregnancy and menopause. These fluctuations in hormone level can trigger anxiety and/or depression in women. NIMH intramural investigators conducted research to better understand the role of hormonal triggers in mood disorders such as perimenopause-related depression (PMD). In one study, they found that estradiol withdrawal in postmenopausal women precipitates depression, but only in women with a past history of PMD. This finding is important in understanding the role of estrogen level as a moderator of depression in women susceptible to PMD. This study highlights the need for greater awareness of the risk of recurrent depression when hormone therapy is discontinued in later life (Schmidt et al., 2015).

Objective 3.1 Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan.

Childhood adversity and trauma blunts stress response during pregnancy: NIMH and ORWH jointly fund a Specialized Center for Research (SCOR) on Sex Differences that seeks to understand the role of early childhood adversity on adult female psychopathology and stress responses.

The project takes a lifespan developmental approach and focuses on the developmental programming of early life stress and trauma on: (1) brain development and function, (2) physiology during pregnancy and transgenerational effects on offspring, and (3) cognitive function and mood disorders during menopause and aging. SCOR-sponsored projects include translational studies in clinical populations and in model systems. Recent findings from SCOR researchers revealed that, like female mice, women who experienced preadolescent adversity showed a blunted stress response function during pregnancy. These findings indicate that the experience of preadolescent stress influences later stress response during times of hormonal changes, such as pregnancy (Morrison et al., 2016).

Objective 3.1 Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan.

Mindfulness-based cognitive therapy is helpful for perinatal depression: Depression during pregnancy and the postpartum period can have an adverse impact on both mothers and their babies, yet treatment options for depression among pregnant and postpartum women are elusive. NIMH-sponsored researchers conducted a clinical trial comparing the effect of mindfulness-based cognitive therapy (MBCT) to the usual treatment methods for pregnant and postpartum women with a history of depression. Results showed that pregnant women who completed MBCT had significantly improved outcomes, compared with pregnant women who did not receive MBCT. The authors indicate that this intervention may be beneficial for pregnant women with a history of depression (Dimidjian et al., 2016).

Objective 3.1 Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan.

Objective 3.4 *Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.*

Antipsychotic use during pregnancy and risk for congenital malformations: Exposure to antipsychotics during pregnancy has doubled in the last decade, yet there is limited information about the safety of such drugs for a developing fetus. NIMH-sponsored researchers followed 1.3 million pregnant women who were prescribed atypical antipsychotics, typical antipsychotics, or no antipsychotics early in pregnancy. The researchers later identified congenital malformations and cardiac malformations in babies born to these mothers. After adjusting for psychiatric conditions and confounding variables, the researchers determined that the use of antipsychotics early in pregnancy does not meaningfully increase the risk for congenital malformations overall, or cardiac malformations in particular. A small increase in the risk for malformations was observed, however, with one atypical antipsychotic, risperidone. The authors recommend further study on the effects of risperidone on the developing fetus (Huybrechts et al., 2016).

Objective 3.3 *Encourage research on safe and effective interventions for conditions affecting pregnant women.*

Depression and anxiety in women who experience infertility and perinatal loss: Infertility and perinatal loss are common, and can be associated with lower quality of life, marital discord, complicated grief, major depressive disorder, anxiety disorders, and posttraumatic stress disorder. To provide clinicians with recommendations for better detection and management, NIMH-sponsored investigators reviewed recent literature that examined the psychiatric aspects of infertility and perinatal loss. The authors recommend a comprehensive treatment plan that includes proactive clinical monitoring; evidence-based psychotherapy; and discussion of risks, benefits, and alternatives to medication

treatment. This literature review is important for helping clinicians better understand ways to reduce mental health disorders that may be associated with infertility and perinatal loss (Bhat and Byatt, 2016).

Objective 3.4 *Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.*

Differential effects of late-life bereavement in men and women: Late-life bereavement is associated with a higher risk of mortality for the remaining spouse. It is not known to what extent bereavement affects spouses living with comorbid conditions, such as cardiovascular disease and depression. NIMH-sponsored researchers examined bereavement using data from a population-based cohort study of older adults and found that bereavement lowered the risk of mortality in women and increased the risk of mortality in men. The reduced risk of mortality in women was only observed in those living with cardiovascular disease, and the increased risk of mortality in men was only observed in those without cardiovascular disease. Further studies are needed to determine if bereaved women are more likely to be caregivers than bereaved men (Stahl et al., 2016).

Objective 3.6 *Study sex differences in the aging process.*

NIMH staff published an overview on HIV and aging research in women: As more women living with HIV survive into older age, more research is needed to understand how HIV affects this population. Staff from the NIMH Division of AIDS Research authored an article in a special issue on HIV research among aging women highlighting the co-sponsored NIMH Women's Interagency HIV Study. The article also served as an introduction to the other articles in the special issue on HIV infection in older women (Stoff et al., 2016).

Objective 3.8 *Conduct research on aging women with emphasis on prevention of frailty, promotion of health lifestyles, maintenance of independent living, self-management of*

symptoms, preservation of cognitive functions, and health-related quality of life.

Recent intimate partner violence increases the risk of low adherence to HIV prevention treatment:

Intimate partner violence (IPV) is associated with HIV incidence, reduced condom use, and lower adherence to antiretroviral therapy and other medications. For HIV-uninfected women who are in a relationship with a partner who has HIV, an IPV history may reduce her likelihood to take medications, such as HIV pre-exposure prophylaxis (PrEP). NIMH-supported researchers monitored the adherence rates of HIV-uninfected women in HIV serodiscordant couples (i.e., couples in which one member has HIV and one member does not). Women who reported IPV in the past 3 months had lower PrEP adherence. Women taking PrEP who report recent IPV may be at higher risk for HIV infection due to reduced PrEP adherence (Roberts et al., 2016).

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban living, as they influence health, health behaviors, and access to screening and therapeutic interventions.*

An integrated IPV and HIV risk reduction intervention:

IPV has been shown to increase the risk for HIV infection among women by as much as 12–22 percent. Researchers funded by NIMH developed and pilot tested an intervention designed to reduce women’s experiences of IPV and their risk for HIV infection. Data from the pilot study suggest that the intervention can reduce episodes of unprotected sex and promote sexual communication. The intervention also may reduce IPV among women who have a recent history of IPV and who are at risk for HIV infection (Mittal et al., 2016).

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and*

urban living, as they influence health, health behaviors, and access to screening and therapeutic interventions.

Black women have lower risk of depression in later life:

Although depression is more prevalent among women across the lifespan, little is known about the difference in prevalence across racial and ethnic groups. NIMH-sponsored researchers used data from the Nurses’ Health Study to analyze racial variation in depression risk factors and symptom trajectories among older women. Women ages 60 and older were examined to determine if there were racial differences in baseline risk factors for depression and/or changes to symptomatology over time (an average of 12 years). Black women had a lower risk of incident late-life depression, compared to whites. Although differences were noted in some baseline risk factors, findings suggested no significant differences in major contributions of these risk factors to the development of depression in later life and no significant differences in the trajectory of depressive symptoms as a function of race (Chang et al., 2016).

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban living, as they influence health, health behaviors, and access to screening and therapeutic interventions.*

Listening visits improve depression outcomes for low-income, ethnic minority perinatal women:

Compared to perinatal women in general, barriers to treatment for depressive symptoms persist for low-income, ethnic minorities. NIMH-sponsored researchers hypothesized that engagement barriers could be overcome by having listening visits (a reflective listening intervention aimed at collaboratively solving women’s problems) that were provided by someone familiar to the women, who could establish a trusted relationship. As such, researchers conducted a randomized controlled study to assess the effectiveness of the listening visits intervention as a treatment

for depression in pregnant women or mothers of young children. Researchers found that women who participated in the listening visits intervention experienced clinically significant improvements in their depressive outcomes. This study is important because it demonstrates that an intervention where deep listening occurs can provide an accessible, acceptable, and effective first-line treatment option for women who may experience barriers to treatment for depressive symptoms (Segre et al., 2015).

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban living, as they influence health, health behaviors, and access to screening and therapeutic interventions.*

NIMH funding opportunities related to the health sexual and gender minorities: To encourage more research on sexual and gender minority mental health, NIMH is a participating organization under the NIH set of program announcements “The Health of Sexual and Gender Minority (SGM) Populations,” released in 2015. Additional information can be found at—

www.grants.nih.gov/grants/guide/pa-files/PA-15-261.html.

www.grants.nih.gov/grants/guide/pa-files/PA-15-262.html.

www.grants.nih.gov/grants/guide/pa-files/PA-15-263.html.

Several NIH Institutes issued awards in response to these funding announcements. An NIMH-funded project is aimed at developing culturally sensitive evidence-based principles of care for psychological services for transgender individuals living in the Central Great Plains community (R21-MH108897).

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban living, as they influence health, health*

behaviors, and access to screening and therapeutic interventions.

Global mental health initiatives: In FY 15–16, NIMH continued to support the *Healthy Options: Group Psychotherapy for HIV-Positive Depressed Perinatal Women* project in Tanzania, awarded to a Grand Challenges funding recipient. The project is a cluster randomized controlled trial to test the effectiveness of a combination of evidence-based approaches for treating depression among HIV positive women receiving services to prevent maternal-to-child transmission (R01-MH100338).

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban living, as they influence health, health behaviors, and access to screening and therapeutic interventions.*

Understanding and addressing the multi-level influences on uptake and adherence to HIV prevention strategies among adolescent girls and young women in Sub-Saharan Africa: These funding announcements called for research to enhance our understanding of the multilevel factors that influence HIV prevention strategy use among adolescent girls and young women in Sub-Saharan Africa by developing and testing novel interventions to address these factors and enhance the uptake and adherence to HIV prevention strategies. This funding announcement is a joint effort with the *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD) and Fogarty International Center (RFA-MH-17-550, RFA-MH-17-555, RFA-MH-17-560).

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban living, as they influence health, health behaviors, and access to screening and therapeutic interventions.*

Interventions for health promotion and disease prevention in Native American populations

(PAR-14-260): This program announcement supports applications for research on mental health among Native Americans, including developing culturally appropriate interventions to increase engagement in mental health services and expansion of science-based interventions that preempt or prevent mental disorders, including suicide. Several applications from this program announcement have been funded, including one NIMH-sponsored project aimed at developing caring text messages for a suicide prevention trial in Native American communities **(R01-MH106419)**.

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban living, as they influence health, health behaviors, and access to screening and therapeutic interventions.*

Administrative supplements for minority health and mental health disparities research

(PAR-14-238): NIMH awarded administrative supplements to enable NIMH-sponsored researchers to address mental health disparities among racial and ethnic groups in the United States. In FY 15, four administrative supplements were funded in response to this funding announcement. One NIMH-funded study utilizes a randomized controlled trial designed to assess whether person-centered care planning can promote maintenance of service engagement among minority women and men who successfully re-engage with the mental health system **(R01-MH099012)**.

***Objective 3.9** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban living, as they influence health, health behaviors, and access to screening and therapeutic interventions.*

Goal 4: Create Strategic Alliances and Partnerships to Maximize the Domestic and Global Impact of Women's Health Research

NIMH strives to create and maintain alliances with the NIH, the U.S. Department of Health and Human Services (HHS), other U.S. governmental agencies, and women's health stakeholders to advance mental health research focusing on women and girls. Initiatives undertaken in FY 15–16 allow integration of knowledge gained by research in women's health and parallel research in global mental health, HIV/AIDS, and mental health disparities. Maternal and child health research also is relevant to each of these areas. NIMH outreach and collaborations that pertain to these research areas are described below.

Activities related to the health of sexual and gender minorities:

NIMH staff participated in the NIH Sexual and Gender Minority Research Coordinating Committee. NIMH staff also participated in the National Action Alliance for Suicide Prevention's Lesbian, Gay, Bisexual, and Transgender Populations Task Force.

***Objective 4.2** Establish new ventures and initiatives with a wide cross-section of partners, including NIH Institutes, Centers, and Offices; academia; other Federal agencies; international organizations; private foundations; and industry.*

Collaboration and committees: In an effort to contribute to NIH/HHS Federal coordination of women's mental health research issues and related policy, the ORDGMH Women's Program Chief worked with several trans-HHS committees, including the National Action Alliance for Suicide Prevention's Research Task Force, the NIH Sexual and Gender Minority Research Coordinating Committee, and the White House Working Group on the Intersection of HIV/AIDS, Violence Against Women, and Gender-Related Health Disparities. The Women's Program Chief also contributed to the NIH

Coordinating Committee on Research on Women's Health, the Women and Trauma Federal Partners' Committee, the NIMH Steering Committee, and the NIMH Diversity and Re-entry Supplements Committee.

Objective 4.2 *Establish new ventures and initiatives with a wide cross-section of partners, including NIH Institutes, Centers, and Offices; academia; other Federal agencies; international organizations; private foundations; and industry.*

Outreach to advocacy groups: The Office of Constituency Relations and Public Liaison, in the NIMH Office of the Director, maintains a robust outreach effort to mental health advocacy groups. This includes outreach to a number of women's health-related groups that participate in the annual NIMH Alliance for Research Progress meetings. Women's health groups that are members of the NIMH Alliance and have participated in FY 15–16 include Postpartum Support International, the Society for Women's Health Research, the Eating Disorders Coalition for Research, Policy and Action, the National Eating Disorders Association, and Families Empowered and Supporting Treatment of Eating Disorders.

Objective 4.4 *Create solid partnerships by engaging in scientific briefings and ad hoc meetings with policymakers, elected officials, and advocacy groups.*

Global research hubs: During FY 15–16, NIMH continued to fund the Collaborative Hubs for International Research on Mental Health, a set of five hubs in South Asia, Sub-Saharan Africa, and Latin America. Guided by ORDGMH, the aim of these hubs is to reduce the mental health treatment gap in low and middle-income countries (LMICs). The hubs conduct research on task sharing for the delivery of mental health services in LMICs, support mental health research capacity-building in countries in their regions, and will utilize the network they form to answer mental health service questions across different health systems

environments. The [South Asian Hub for Advocacy, Research, and Education \(SHARE\)](#) has developed an innovative approach for the delivery of an established psychological treatment that reduces the burden of depression in mothers in South Asia. A second Hub, the [Africa Focus on Intervention Research for Mental Health \(AFFIRM\)](#), tested the effectiveness of a task-sharing model to provide counseling for depressed pregnant women by non-specialist health workers in a primary care setting in South Africa.

Objective 4.6: *Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries.*

Goal 5: Develop and Implement New Communication and Social Networking Technologies to Increase Understanding and Appreciation of Women's Health and Wellness Research

NIMH responded to numerous requests for expert information from NIH, HHS, and Congress, as well as more than 100 annual requests from potential investigators, currently funded investigators, and the broader research community on women's health research opportunities. In addition to responding to these requests, NIMH utilized new media technologies (e.g., Twitter, Facebook, YouTube, RSS feeds) to disseminate research findings and cultivate relationships with advocacy groups.

NIMH Twitter chats: In FY 15–16, NIMH utilized social media to host several "Twitter Chats" on topics related to women's and girl's mental health:

- [NIMH Twitter Chat on Disruptive Mood Dysregulation Disorder and Severe Irritability](#)
- [NIMH Twitter Chat on Mind and Body Approaches to Stress Management with NCCIH](#)
- [NIMH Twitter Chat on Perimenopausal Depression](#)
- [NIMH Twitter Chat on Binge Eating Disorder](#)

Objective 5.1 *Serve as a key informational resource for Federal and state agencies, elected representatives, the media, health and advocacy organizations, and the public on women's health research issues.*

Webinars on women's mental health: To engage global audiences on NIMH-funded research efforts that contribute to reducing mental health disparities, ORDGMH coordinates a webinar series on a variety of mental health topics. In FY 15–16, NIMH grantees presented on topics, which included Building Resilience to Reduce Suicide in Arctic Communities, Translational Research in Women's Mental Health, the NIMH Strategic Plan, Grants Management for LMIC Investigators, and Implementation Science.

Objective 5.1 *Serve as a key informational resource for Federal and state agencies, elected representatives, the media, health and advocacy organizations, and the public on women's health research issues.*

Educational outreach efforts: In FY 15, the NIMH Office of Constituency Relations and Public Liaison and ORDGMH, together with NICHHD, entered into a 2-year collaboration with Delta Sigma Theta Sorority, Inc. called the [Mental Health Across the Lifespan Initiative](#). The educational outreach initiative seeks to raise awareness about certain mental health conditions affecting women and their families, including postpartum depression (PPD) and bullying, as well as about successful aging later in life. The Initiative harnesses the power of the organization's membership network to extend the reach of NIH's research-based information directly into the communities served by more than 1,000 Delta Sigma Theta chapters in the United States and abroad. The collaboration could expand and intensify NIH's efforts to increase awareness about the diagnosis, treatment, and latest research in the area of PPD. Expansion of efforts to increase support, education, and research related to PPD was a key provision of the Affordable Care Act.

Objective 5.3 *Expand strategic alliances and partnerships with key national and international organizations to maximize the communication and impact of women's health research.*

Goal 6: Employ Innovative Strategies to Build a Well-Trained, Diverse, and Vigorous Health Research Workforce

STEM training efforts: NIMH continued funding diversity and re-entry supplements, expanded efforts to provide additional training to early-stage investigators who have received diversity supplements, and conducted outreach to potential and early-stage researchers in global mental health. A number of these grantees and students are pursuing research interests in topics of interest in women's health, such as perimenopausal depression.

Objective 6.1 *Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH.*

Ongoing initiatives: In FY 15–16, NIMH reissued Biobehavioral Research Awards for Innovative New Scientists (RFA-MH-15-600). This program is intended to support the research and research career development of outstanding scientists who are in the early formative stages of their careers and who plan to make a long-term career commitment to research in specific mission areas of NIMH. In FY 15–16, 26 awards were issued in response to this funding announcement, a number of which went to female scientists.

Objective 6.1 *Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH.*

Training of global researchers: ORDGMH continued to host the Global Mental Health Careers Listserv to build an ever-growing community of new investigators. The listserv serves as a vehicle for the dissemination of training news, upcoming global meetings, and funding opportunity announcements. A number of the grantees and students that have participated on this listserv are pursuing research topics of interest to women's mental health.

***Objective 6.1** Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH.*

Research supplements: NIMH continues to co-sponsor the Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (PA-16-289). This program supports individuals with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances.

***Objective 6.3** Address the organizational, institutional, and systemic factors that impede recruitment, retention, and advancement of women in science, and modify practices that impede the careers of biomedical scientists.*

Inclusion Efforts

NIMH follows several steps to ensure compliance with inclusion guidelines for both extramural and intramural research. Applications are evaluated for the appropriateness of sex and gender, racial, and ethnic minority enrollment goals; recruitment plans that demonstrate how the investigator will meet these goals; and for Phase III studies, plans to conduct analyses to detect significant differences in intervention effects among sex/gender, racial, and ethnic groups. For extramural research, the NIMH Office of Clinical Research prepares aggregate reports for ORWH. For intramural research, the

Office of Protocol Services, in collaboration with the Department of Clinical Research Informatics, submits inclusion data to ORWH. During FY 15–16, there were no large (Phase III) clinical trials that published a separate analysis by sex.

Funding Initiatives, Workshops, and Conferences

Mechanisms underlying suicide risk: Integrating Research Domain Criteria (RDoC) to inform novel and personalized intervention research (June 2–3, 2016). NIMH hosted a workshop to review current themes in suicide research and to consider how approaches consistent with the RDoC framework could provide new insights on the underlying mechanisms of suicide risk. Discussion topics included gender differences and the timing of early life stress as strong influences in the trajectory of suicide risk over the life course.

Health Disparities

Addressing inequities in mental health is a major focus of ORDGMH. Some racial and ethnic groups bear a greater burden of certain mental health issues, such as suicide. In addition, there often are barriers to mental health care for certain populations of women that may be related to racial and ethnic differences, geographic location, socioeconomic status, or the presence of serious mental illness. In addition to research findings described elsewhere in this report, NIMH has sponsored or participated in several efforts in this area.

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National Institute on Minority Health and Health Disparities (NIMHD)

Executive Summary

The National Institute on Minority Health and Health Disparities (NIMHD) leads scientific research to improve minority health and reduce health disparities. To fulfill its mission, NIMHD uses a comprehensive strategy to plan, coordinate, review, and evaluate NIH minority health and health disparities research and activities; conduct and support research in minority health and health disparities; promote and support the training of a diverse research workforce; translate and disseminate research information; and foster innovative collaborations and partnerships.

The work of NIMHD covers a broad range of issues, diseases, and conditions impacting specific populations that experience differences in health outcomes. Although NIMHD's mission, programs, and activities align most closely with objective 3.9 of the NIH Strategic Plan for Women's Health Research and Sex Differences, "Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions," NIMHD's research and activities support the implementation of the plan in other areas as well. NIMHD's research studies and activities are consistent with objective 1.6: "Increase basic and translational research on sex and gender differences in the pathobiology, prevention, and treatment of diseases, including HIV and AIDS, urinary tract infections, and sexually transmitted infections;" objective 1.8: "Further understanding of sex and gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being;" and objective 3.4: "Expand research on pregnancy-related conditions such as preeclampsia, diabetes,

and hypertension on the subsequent health of women and their offspring."

Within the context of health disparities, this report highlights various research projects related to women's health that cut across different diseases and conditions, including HIV and AIDS, obesity, type 2 diabetes, breast cancer, lymphedema, and chronic pain. Among the issues addressed are physical activity, substance use, oral health care, pregnancy, postpartum weight management, emotional abuse of older women, and early initiation of sexual activity. Obesity is a risk factor for developing other diseases and conditions, such as breast cancer, type 2 diabetes, and heart disease. Studies in this report examine different strategies to engage African-American and Latina women in regular physical activity and lifestyle modification programs to better manage body weight and improve health. A study was conducted in beauty salons and barbershops with African-American women to assess the association between physical activity and social support networks. Participants completed a survey and wore an accelerometer to monitor actual physical activity. This study may offer insights into effective health promotion interventions to address cardiometabolic risk in African-American women. Another study is testing the feasibility of developing a smartphone app for Latinas using the location-based services (LBS) feature to identify walking social support networks within geographic proximity and to promote increased physical activity. To better understand the pathway of type 2 diabetes among Latina and Asian women who have had gestational diabetes, the Women's Health Intervention Study has adapted an effective telephone counseling intervention in conjunction with theory-based health communication strategies to deliver health information and emotional support to the women. The study can potentially advance the knowledge base about Latina and Asian women's risk

perception for diabetes and offer information on prevention strategies.

Accomplishments and Activities

¡Caminamos!: A Smartphone App to Promote Walking Among Latinas

One NIMHD-funded study, *¡Caminamos!*, is using technology to impact health disparities among Latinas by increasing physical activity to help manage the user's weight. This project is developing a smartphone app using the LBS feature to link users together. The goal is to create a walking social support network for Latinas within a user's neighborhood. Community partners will provide input into the development of the app, which will be pilot tested using a national sample of Latinas. Participants will test the usability and functionality of the app, including accuracy in locating other users and connecting to the social support network, as well as satisfaction with the app. The data from this study will help to develop a full-fledged app to use in a randomized clinical trial and subsequently market the app to Latina consumers. [1R43MD009652]

Determining Lifestyle Modification Strategies for African-American Breast Cancer Survivors

African-American women have the highest rate of death due to breast cancer among all racial and ethnic populations and are just as likely to be diagnosed with breast cancer as white women (DeSantis et al., 2016). This disparity may be due to several factors, including lack of access to health insurance, late stage diagnosis, and delay in seeking timely breast cancer screening. Obesity is a risk factor for breast cancer, and the effects of lifestyle modification programs among obese African-American women breast cancer survivors are not well understood. This research is working to define lifestyle modification strategies and examine the influence of psychosocial factors in

African-American women's participation in these strategies after breast cancer diagnosis and during treatment. There were 240 women ages 18 years and older who participated in the study, in which a culturally appropriate assessment tool was developed and administered to identify lifestyle modification practices and determine quality of life. These data are used to assess the impact of lifestyle modification practices, weight history after breast cancer diagnosis, and breast cancer treatment history on the quality of life of African-American breast cancer survivors. The study highlights that weight management is an important factor for African-American breast cancer survivors. [5P20MD006881]

E-Diaries to Assess Health Effects of Microaggressions in Bisexual Women

There are limited data on the health status, behaviors, and health outcomes of sexual and gender minorities (SGM). SGM individuals face many types of stressors related to identity, and the burden of health disparities is more profound among bisexual women than heterosexual and lesbian women (Fredriksen-Goldsen et al., 2010). Bisexual women may experience microaggressions, which are daily intentional and unintentional insults and discriminatory actions, more often than lesbian women. This study used electronic diaries to assess the effect of microaggressions on bisexual women's mental health. These e-diaries were used to better understand the frequency and source of sexual orientation microaggressions (SMAs) and the effect on mental health among a racially diverse group of bisexual women. The research also characterized the microaggression experiences of bisexual women and identified lifetime stressors, such as childhood or adult sexual or physical abuse, which may influence associations between SMAs, lifetime depression, and daily health. These findings may increase knowledge about the risk factors linked to mental health disparities among racially diverse bisexual women and identify

potential preventive strategies and areas for future research. [1R21MD009585]

Preventing HIV Exposure in Middle School Age African-American Girls

The Teamwork in Research and Intervention to Alleviate Disparities (TRIAD-2) Center of Excellence in Health Disparities Research is working to develop community approaches to reduce HIV/AIDS and other diseases with health disparities among underserved populations. Research has shown that early initiation of sexual activity among African-American girls increases the risk of exposure to HIV. Factors that influence early sexual activity include lack of knowledge of HIV transmission, poor self-esteem, perception of mother's monitoring, and intention to refuse sex. The Girls Empowered Through Mind and Mission is a 12-week community-based intervention involving middle school girls and their mothers, designed to improve mother and daughter relationships, inspire racial and ethnic pride in girls, build self-esteem and assertiveness, and empower girls to safeguard themselves against HIV. Pilot testing showed success in decreasing the number of risky sexual encounters among girls who already were sexually active and delaying initiation of sexual activity among girls who were not yet sexually active. If the intervention proves successful, TRIAD-2 intends to prepare a toolkit for adaptation and dissemination by churches, afterschool programs, and other community settings for delivery to young women from diverse racial and ethnic groups. [5P20MD002289]

Expanding Research to Understand African-American Women's Health

In Fiscal Year (FY) 2015 and FY 16, NIMHD provided a supplement to a Center of Excellence at a historically black college to expand and improve its women's health research, with particular emphasis on diseases that disproportionately impact women of color. The program is supporting pilot projects on diabetic gastroparesis, vitamin D deficiency, and uterine fibroids in African-American

women and the role of gene polymorphisms and vitamin D deficiency in preterm birth, as well as supporting the development of investigators who can contribute to the diversity of the biomedical workforce. [P20MD006881]

Role of Family Members in Emotional Abuse Among Latinas

The Center for Substance Use and HIV/AIDS Research on Latinos in the United States has been investigating the role that emotional abuse plays as a risk factor for substance use in Latinas. Emotional abuse is the most common form of violence experienced by Latinas, and emotional abuse can have negative physical, social, emotional, and sexual implications for an individual's overall health and well-being. This research included a 5-year study of more than 200 Latina mothers and daughters to examine whether drugs and alcohol contributed to emotional abuse. In addition, this study was the first of its kind to investigate whether Latina women suffer emotional abuse from people other than their partners. Among participants who reported emotional abuse, other family members (e.g., daughters, sons, and mothers) perpetuated much of the abuse, and women who used illicit substances were more likely to experience emotional abuse. These findings suggest a need for interventions focused on family members, not just intimate partners, as well as the role that substance abuse may play in exacerbating risk for emotional abuse in Latinas. [P20MD002288]

Sisters Healthy and Physically Empowered (SHAPE) Program Uses Social Networks to Create Physical Activity Intervention for African-American Women

African-American women have a higher prevalence of coronary heart disease, hypertension, and obesity than white women. Although physical activity may impact these risk factors, there are few effective interventions for African-American women to increase levels of physical activity and,

in fact, more than 50 percent of African-American women do not participate in any regular physical activity. The SHAPE project is working to develop a culturally tailored intervention that capitalizes on strong social networks in African-American communities. Currently, 200 African-American women have been surveyed about their physical activity in beauty salons and barbershops, and 25 women completed a physical activity social network interview and wore an accelerometer for 7 days. The findings of this community-based study may help develop culturally effective health promotion interventions to reduce cardiometabolic risk for African-American women. [5P20MD006737]

Tribal Collaboration on the Prevention of Alcohol-Exposed Pregnancies

In collaboration with tribes in the Northern Plains who have an interest in developing an alcohol-exposed pregnancies (AEP) prevention program, this community-based project is investigating how to prevent AEP and fetal alcohol spectrum disorders (FASD) in American Indian communities. Tribal Community Advisory Boards recommended the implementation of AEP prevention pilot projects at three large Indian Health Service hospital sites: Pine Ridge IHS Hospital, Sioux San IHS Hospital, and the Rosebud Comprehensive IHS Hospital. A focus on preventing FASD and AEP before a woman becomes pregnant would overcome a critical barrier in the field of FASD prevention. The short-term goal of this study is to implement AEP prevention programs with nonpregnant American Indian women, focusing on evaluating such programs for effectiveness in decreasing risky behaviors related to AEP. The long-term goal of the study is to prevent any and all pregnancies from having alcohol exposure utilizing community-based participatory research principles to foster sustainable efforts to prevent AEP. [R24MD008087]

Web and Mobile Intervention to Manage Chronic Pain Related to Lymphedema

Lymphedema, a swelling beneath the skin that consists of high-protein fluid, is a health problem that affects thousands of breast cancer survivors. Lymphedema can lead to daily pain and symptoms that negatively impact survivors' quality of life. Research from the Center for Study of Asian American Health on lymphedema has developed a Web- and mobile-based system for managing chronic pain and symptoms related to lymphedema. The application features a set of exercises that are easy to integrate into a daily routine to promote lymph flow and drainage, as well as guidance to maintain an optimal body mass index. The system is being tested in a clinical trial, which will be completed during FY 17. Other research from the Center for Study of Asian American Health also has identified obesity as a risk factor for lymphedema and preliminarily identified gene variants that may contribute to lymphedema. [P60MD000538]

NIH Strategic Plan for Women's Health Research

1. NIH Strategic Plan Mapping to IC Research or Other Programmatic Activities Highlights

Global HIV Epidemiology and Prevention Research for Transwomen

Transwomen across the globe experience disparities in health, including increased risk of mental health disorders and an undue burden of HIV. The impact of gender transition on different diseases and conditions is understudied. This study is examining HIV prevention strategies for an international sample of transwomen. A longitudinal study of 1,100 HIV-negative participants is being established in San Francisco, California, and São Paulo, Brazil, to collect data on health risks and the impact of social, biological, and medical influences on gender transition and contracting HIV. To facilitate

recruitment and retention of participants into the study, respondent-driven sampling, social media, mobile, and Web technologies will be used. In addition, culturally appropriate survey measures are being designed. Future cross-sectional surveys in Nanjing, China, and Windhoek, Namibia, are planned, with the intention of establishing a collaborative international HIV prevention research program and the infrastructure for studies on the health of transwomen. [IR01MD010678] (Goal 1, Objective 1.6)

Oral Health Care: A Potential Risk Factor for Preterm Labor in Hawaiian Women

The Bioscience Research Infrastructure Development for Grant Enhancement and Success program has established an interdisciplinary network across Hawaii to address health disparities among underserved populations. Poor dental health in pregnant women has been shown to be a potential risk factor for preterm labor, but it is not well-studied. In Hawaii, lack of access to dental care and lack of water fluoridation may contribute to these risk factors. This study examined utilization of oral health services and preterm labor in a sample of pregnant women living in Hawaii and found a decline in women's use of preventive dental services as they transitioned from pregnancy to postpartum status. Prior to pregnancy, nearly 50 percent of women received dental cleanings. During pregnancy, 40 percent received cleanings, while only 26 percent of women had dental cleanings within 1 year after delivery. Significant associations were found between preterm labor and race, age, education, insurance, the use of prescription drugs preceding pregnancy, smoking, and alcohol use. This study adds to the limited literature on the association between oral health care and preterm labor in Hawaiian women and highlights the need for new interventions and research to help reduce health disparities arising from pregnant Hawaiian women's oral health. In 2017, researchers will begin examining placental tissue samples from women in Hawaii who experienced preterm labor for the presence and type of oral bacteria.

[G12MD007601 (2015); 5U54MD007584 (2016)]
(Goal 3, Objective 3.4)

Telephone Support Program to Prevent Type 2 Diabetes in Minority Women with Recent Gestational Diabetes

Women are at increased risk of developing type 2 diabetes after having had gestational diabetes. Little is known about the diabetes knowledge, risk perceptions, or preferences related to telephone-based counseling interventions of Latina and Asian women, particularly those born outside the United States. The Women's Health Intervention Study has adapted an existing telephone counseling intervention that has been shown to improve diabetes control in low socioeconomic status (SES) women from racial and ethnic minority populations who already have diabetes. The new adaptation, called STAR MAMA, uses theory-based health communication strategies to provide health information and emotional support in English and Spanish for women who experienced gestational diabetes for 9 months after giving birth. A community-based participatory research framework was used to collect input from Latina women and their health care providers to ensure that the preventive health behaviors used in STAR MAMA were congruent with Latina health beliefs and communication preferences. [4P60MD006902] (Goal 3, Objective 3.4)

2. Other IC activities that support the implementation of the NIH Strategic Plan for Women's Health Research

NIMHD has no other activities to report.

3. Specific Position, Office, Branch, or Component Designated for Research on Women's Health

Although there is no office or branch specifically designated to address research on women's health issues, women's health is an integral part of the NIMHD health disparities scientific research

portfolio, which is administered through NIMHD extramural grants, co-funding with other Institutes, Centers, and Offices, and collaborations with other Federal agencies.

Inclusion

Partnering with the Women, Infants, and Children Program to Address Postpartum Weight Loss

Women in racial and ethnic minority groups and women of low SES are at increased risk for weight-related health disparities. The postpartum period is critical to maintaining a healthy weight for many women. On average, women retain an estimated 3 kg (6.6 lbs.) weight gain per pregnancy 10 years after giving birth, with racial and ethnic minorities at greater risk of postpartum weight retention. Weight loss in the postpartum period thus is key to the long-term health of young women of disadvantaged backgrounds. The Fresh Start project has established a partnership with the Women, Infants, and Children (WIC) program to provide culturally appropriate weight loss strategies to low-income women. This clinical trial has adapted an innovative, narrative-based group intervention to support women's weight loss into a format that is relevant, acceptable, and effective for low SES women. Using a real-world setting, the intervention aims to improve participant self-efficacy through storytelling, group discussions, print materials, and access to exercise facilities. Women 6 weeks to 6 months after childbirth were eligible to participate. The storytelling section allowed women to share stories of their experience with postpartum weight loss through face-to-face sessions and video-recorded interviews. Initial analysis found that women lost an average of 2.1 kg (4.62 lbs.) after 4 months. The study will continue monitoring women for a total of 12 months. Development of effective interventions for low SES women has the potential to reduce health disparities for many communities and the creation of a sustainable weight-management program with WIC could reach women across the United States. [5P60MD006912]

IC STEM Efforts

None to report.

Funding Initiatives, Workshops and Conferences

Because NIMHD funding announcements are inclusive of sex and gender, as well as racial and ethnic diversity, NIMHD did not issue any funding announcements during FY 15 or FY 16 that were specific to women's health or the influence of sex on health and disease.

In FY 16, NIMHD supported the "Our Health Matters: Achieving Maternal and Child Health Equity" conference held in Florida from September 30 to October 1, 2016. This conference discussed strategies to address the inequity in maternal child health for the black community, priorities for eliminating health disparities, and culturally responsive mechanisms that could be used by health care providers to ensure maternal child health equity. [R13MD011260]

Health Disparities

All of the accomplishments and activities listed under Accomplishments and Activities, NIH Strategic Plan for Women's Health Research, and Inclusion pertain to health disparities among women.

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Accomplishments & Activities

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[¡Caminamos!: A Smartphone App to Promote Walking among Latinas](#)

Myers VH. (n.d.). Caminamos: A Location-Based Smartphone App for Latinas to Connect with Nearby Walking Partners (Grant No. R43MD009652). NIMHD grant. Klein Buendel, Inc., Golden, CO; and Stanford University, Palo Alto, CA.

Determining Lifestyle Modification Strategies for African-American Breast Cancer Survivors

Braithwaite RL. (n.d.). Reducing Health Disparities in Vulnerable African-American Families and Communities (Grant No. P20MD006881). NIMHD grant. Morehouse School of Medicine, Atlanta, GA.

[E-Diaries to Assess Health Effects of Microaggressions in Bisexual Women](#)

Bostwick W. (n.d.). E-Diaries to Assess Health Effects of Microaggressions (Grant No. R21MD009585). NIMHD grant. Northern Illinois University, DeKalb, Illinois; University at Buffalo, Buffalo, New York; and University of Illinois at Chicago, Chicago, IL.

[Preventing HIV Exposure in Middle School Age African-American Girls](#)

Wallace DC. (n.d.). TRIAD Center for Health Disparities (Grant No. P20MD002289). NIMHD grant. University of North Carolina, Greensboro, NC.

[Expanding Research to Understand African-American Women's Health](#)

Braithwaite R. (n.d.). Reducing Health Disparities in Vulnerable African American Families and Communities (Grant No. P20MD006881). NIMHD grant. Morehouse School of Medicine, Atlanta, GA.

[Role of Family Members in Emotional Abuse Among Latinas](#)

De La Rosa M. (n.d.). Center for Substance Use and HIV/AIDS Research on Latinos in the United States (Grant No. P20MD002288). NIMHD grant. Florida International University, Miami, FL.

Related Publication:

Kanamori M, De La Rosa M, Weissman J, Rojas P, Villar ME, Trepka MJ, and Jaramillo M. (2015). Associations between drug/alcohol use and emotional abuse: who perpetrates emotional abuse against Latina women? *Journal of Epidemiological Research*, 2(1), 95.

Sisters Healthy and Physically Empowered (SHAPE) Program Uses Social Networks to Create Physical Activity Intervention for African-American Women

Thomas SB, and Quinn SC. (n.d.). Center of Excellence on Race, Ethnicity, and Health Disparities Research (Grant No. 5P20MD006737). NIMHD grant. University of Maryland, College Park, MD.

[Tribal Collaboration on the Prevention of Alcohol-Exposed Pregnancies](#)

Hanson JD. (n.d.). Tribal Collaborative in the Preventive or Alcohol-Exposed Pregnancies (Grant No. R24MD008087). NIMHD grant. Sanford Research/USD, Sioux Falls, SD.

Related Publication:

Hanson JD, and Jensen JL. (2016). Epidemiology of substance-exposed pregnancies at one Great Lakes hospital that serves a large number of American Indians. *American Indian and Alaska Native Mental Health Research (Online)*, 23(4), 44. PMID:27536897

[Web and Mobile Intervention to Manage Chronic Pain Related to Lymphedema](#)

Rey M. (n.d.) NYU Center for the Study of Asian American Health -Research Center of Excellence (Grant No. P60MD000538). NIMHD grant. New York University, New York, NY.

Related Publications:

Fu MR, Axelrod D, Guth A, et al. (2016). A web-and mobile-based intervention for women treated for breast cancer to manage chronic pain and symptoms related to lymphedema: randomized clinical trial rationale and protocol. *JMIR Research Protocols*, 5(1). PMID:26795447

Fu MR, Axelrod D, Guth AA, et al. (2015). Patterns of obesity and lymph fluid level during the first year of breast cancer treatment: A prospective study. *Journal of Personalized Medicine*, 5(3), 326–40. PMID:26404383

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Global HIV Epidemiology and Prevention Research for Transwomen

McFarland W. (n.d.). The Transnational Cohort: Global HIV Epidemiology and Prevention Research for Transwomen (Grant No. R01MD010678). NIMHD grant. Public Health Foundation Enterprises, San Francisco, CA.

Oral Health Care: A Potential Risk Factor for Preterm Labor in Hawaiian Women

Berry M. (n.d.). Bioscience Research Infrastructure Development for Grant Enhancement and Success(G12MD007601). NIMHD grant. University of Hawaii at Mānoa, Honolulu, HI.

Related Publications:

Hedges JR, and Mokuau N. (n.d.). RCMI Multidisciplinary and Translational Research Infrastructure EXpansion (Grant No. U54MD007584). NIMHD grant. University of Hawaii at Mānoa, Honolulu, HI.

Mattheus D, Shannon M, Lim E, and Gandhi K. (2016). The association between socio-demographic factors, dental problems, and preterm labor for pregnant women residing in Hawai'i. *Hawai'i Journal of Medicine & Public Health*, 75(8), 219. PMID:27563498

Telephone Support Program to Prevent Type 2 Diabetes in Minority Women with Recent Gestational Diabetes

Bibbins-Domingo K. (n.d.). Addressing Disparities in Chronic Disease with a Teen and Young Adult Focus (Grant No. P60MD006902). NIMHD grant. University of California, San Francisco, CA.

Related Publication:

Handley MA, Harleman E, Gonzalez-Mendez E, et al. (2016). Applying the COM-B model to creation of an IT-enabled health coaching and resource linkage program for low-income Latina moms with recent gestational diabetes: the STAR MAMA program. *Implementation Science*, 11(1), 73. PMID:27193580

Inclusion

Partnering with the Women, Infants, and Children Program to Address Postpartum Weight Loss

Allison JJ. (n.d.). UMass Center for Health Equity Intervention Research (Grant No. P60MD006912). NIMHD grant. University of Massachusetts Medical School, Worcester, MA.

Related Publication:

Rosal MC, Haughton CF, Estabrook BB, et al. (2016). Fresh Start, a postpartum weight loss intervention for diverse low-income women: design and methods for a randomized clinical trial. *BMC Public Health*, 16(1), 953. PMID:27612615

Funding Initiatives, Workshops, and Conferences

Our Health Matters: Achieving Maternal and Child Health Equity

Brown Speight J. (n.d.). Our Health Matters: Achieving Maternal and Child Health Equity (Grant No. R13MD011260). NIMHD grant. Florida State University, Tallahassee, FL.

National Institute of Neurological Disorders and Stroke (NINDS)

Executive Summary

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. This burden is borne by every age group, every segment of society, and people all over the world. Most disorders of the nervous system affect men and women equally, but certain disorders, such as epilepsy, Rett syndrome (RTT), stroke, traumatic brain injury (TBI), multiple sclerosis (MS), chronic pain, and migraines disproportionately affect women, or have specific health implications for women. NINDS supports basic, translational, and clinical research on these disorders, as well as targeted research to understand sex-based differences in normal development and function of the nervous system, behavior, cognition, and perception.

Epilepsy affects 1 in 26 people during their lifetime, and currently, there are an estimated 2.5 to 3 million individuals with epilepsy in the United States. Although several effective treatments are available, about 30 percent of individuals do not benefit from them. Women with epilepsy face special problems during phases of the menstrual cycle, and those who take certain antiepileptic drugs during pregnancy face higher than normal rates of birth defects in their children. Of importance for the development of future treatments is the need to understand the varying roles of steroid hormones in epilepsy for both males and females.

RTT is a childhood neurological disease most often caused by mutations in the gene that encodes methyl-CpG binding protein 2 (MeCP2), a transcriptional regulatory protein. The disorder is almost exclusive to females, affecting about

1 in 10,000, and is characterized by behavior and movement features similar to those found in autism, Parkinson's disease, and dystonia. Research has shown that some features are probably due to dysfunction of neurons and supporting cells, rather than to neural degeneration. Symptoms found to be reversible in mouse models could lead to the development of promising new therapies.

Stroke is caused by a rapid disruption in the blood supply to part of the brain as a result of either blood vessel blockage (ischemic stroke) or blood vessel rupture (hemorrhagic stroke). A stroke can result in sudden numbness or weakness; confusion; trouble with vision, speech, or coordination; or a sudden, severe headache. Although women in general have a lower risk of stroke than men, because of their longer life expectancy, women account for 60 percent of stroke fatalities in the United States.

MS, a chronic and often disabling disease of the central nervous system, is two to three times more common in women than in men. The progress, severity, and specific symptoms of MS are unpredictable and vary from one person to the next. MS affects more than 2 million people worldwide; its cause is still not known. Ongoing research indicates that a combination of several factors may be involved, including immunology and genetics.

Chronic pain is caused by the improper function of neuronal pain circuits and results in abnormal pain that persists for weeks, months, or even years. Certain chronic pain conditions, such as migraine headaches, temporomandibular joint disorders, endometriosis, and fibromyalgia are diagnosed more often or exclusively in women, and women often have more than one of these conditions. Current research is examining the genes involved in familial forms of migraine, as well as the influence of the sex hormones estrogen and testosterone.

Accomplishments and Activities

Research Findings

Epilepsy

Sex Differences in Potential Therapeutic Targets for Epilepsy Intervention. Investigators have continued to explore intrinsic sex differences in molecular regulation of the endocannabinoid system in the rat hippocampus, which controls excitation in this brain region. Researchers observed that the female hormone estradiol stimulated higher levels of several intracellular mediators of signal transduction in females than it did in males, which resulted in an increased release of the endogenous cannabinoid molecule, anandamide. These studies demonstrate sex differences in both estrogen-dependent and estrogen-independent regulation of the brain's cannabinoid system and suggest that manipulation of these endogenous cannabinoids could affect physiological and behavioral responses differently in each sex. This result is suggestive of mechanisms through which epilepsy therapeutics could affect the sexes differently. (Tabatadze et al., 2015)

Understanding Differences in Cellular Excitability. Global functional and behavioral responses in males and females may be the same. Some research, however, indicates that sexually dimorphic latent differences in brain mechanisms may mediate these global similarities. Investigators have, indeed, identified a latent sex difference in molecular regulation of excitatory synapses in the hippocampus. The sex steroid 17β -estradiol is known to acutely potentiate glutamatergic synaptic transmission in both sexes. This occurs through a combination of increased presynaptic glutamate release probability and increased postsynaptic sensitivity to glutamate in both sexes, but this study has revealed that distinct estrogen receptor subtypes underlie each aspect of potentiation in each sex. These results indicate that therapeutics targeting a specific estrogen receptor subtype or its downstream signaling cascades could

affect synaptic transmission differently in the hippocampus of each sex. (Oberlander and Woolley, 2016)

Stroke

Contribution of Age-Dependent Factors in Stroke. Stroke is among the most common causes of death and disability in the United States, and ranks as the third leading cause of death in women. There is a marked age-dependent sex difference in the incidence of stroke, with younger women being less likely to experience a stroke but older women being at higher risk of stroke. Females, however, generally have poorer outcomes after a stroke than males. Recent studies have attempted to parse whether estrogen or chromosomal factors contribute to this difference. Research has found that in younger female mice, the hormone estrogen is responsible for exerting protective effects regardless of the sex chromosome complement. However, in aged mice that lack hormonal influences, the presence of two X chromosomes results in larger brain lesions after stroke. The greater brain damage after stroke in aged female mice appears to be due to exacerbated inflammatory responses to the brain injury mediated by brain microglial cells. Further studies will be needed to determine the exact immune factors and/or genes responsible for the interaction of age and sex in stroke-induced brain damage, but there appear to be distinct mechanisms involved in aged females, compared to younger females with ample sex hormone levels (McCullough et al., 2016; Manwani et al., 2015).

Mechanism Contributing to Female Resistance to Brain Injury During Neurodevelopment. Brain injury following neonatal hypoxia-ischemia leads to lifelong morbidities, such as cerebral palsy and learning disabilities, which are among the most common childhood neurological disorders. Clinical and preclinical data point to males being at greater susceptibility for the most severe consequences of perinatal hypoxic-ischemic injury, compared to females. The factors responsible for protecting young female infants, however, is not clear because

estrogen is not abundantly present in early life. A recent study revealed that the expression of the estrogen receptor alpha is significantly up-regulated in the female, but not male, brain following perinatal brain injury. Furthermore, the increased levels of estrogen receptor alpha in the female brain after hypoxia-ischemia are more effective in activation of an important brain growth factor receptor, TrkB, as well as other important receptor kinases. By increasing TrkB activation, brain cell death can be reduced and brain function protected following perinatal hypoxic-ischemic brain damage in the female brain, and may account for the enhanced vulnerability of males to neurodevelopmental brain insults (Cikla et al., 2016).

Differential Drug Responses in Cerebral

Aneurysm. Brain aneurysms are more common in women than in men, and inflammatory mechanisms are central elements in the pathogenesis of aneurysm formation. In a recent large epidemiological study of unruptured intracranial aneurysms, the prototypic anti-inflammatory drug aspirin was found to reduce the risk of aneurysm rupture and subsequent subarachnoid hemorrhage. Re-analysis of the data from this study showed that men taking aspirin had a lower risk of aneurysm rupture. However, in women, aspirin failed to exert any protective effect. To investigate mechanisms associated with this sex difference, studies in mice were performed. Following aneurysm induction, male and female mice were placed on an aspirin treatment regimen at doses proportional to those used in humans, and it was found that only male mice were protected from cerebral aneurysm rupture. At the molecular level, substances linked to aneurysm formation and rupture were higher in females. When a specific inhibitor of 15-hydroxyprostaglandin dehydrogenase was added to the treatment cocktail, female mice and male mice had identical, and lower, risks of cerebral aneurysm rupture, with both groups showing reductions in genes associated with aneurysm formation and rupture. These findings suggest that aspirin may be valuable in reducing the risk of aneurysm rupture in males and that raising

levels of protective prostaglandins in females in conjunction with more general anti-inflammatory drugs may confer an equal level of protection from cerebral aneurysm rupture. Aspirin is a ubiquitously used medication, and this study points to a new use of an old drug for prevention of aneurysmal subarachnoid hemorrhage in both men and women (Chalouhi et al., 2016).

RTT

Identification of an Intervention to Improve Cognition in Females Affected by RTT.

Deep brain stimulation (DBS) has improved the prospects for many individuals with diseases affecting motor control, and recently it also has shown promise for improving cognitive function. Several studies in individuals with Alzheimer's disease and in amnesic rats have demonstrated that DBS targeted to specific neural pathways regulating hippocampal activity can improve deficits in hippocampus-dependent memory. Despite these promising results, DBS has not been tested for its ability to improve cognition in any childhood intellectual disability disorder. Investigators studied the effects of DBS in a well-characterized mouse model of RTT, which is a leading cause of intellectual disability in females. Caused by mutations that impair the function of the methyl-CpG-binding protein 2 gene, RTT appears by the second year of life in humans, causing profound impairment in cognitive, motor, and social skills, along with an array of neurological features. RTT mice, which reproduce the broad phenotype of this disorder, also show profound deficits in hippocampus-dependent learning and memory and hippocampal synaptic plasticity. When DBS was applied to RTT mice, it improved hippocampal-dependent memory. At the cellular and molecular levels, DBS normalized hippocampal long-term potentiation and hippocampal neurogenesis. These results indicate that DBS might mitigate cognitive dysfunction in patients with RTT syndrome (Hao et al., 2015).

Loss- and gain-of-function mutations in MeCP2 underlie two distinct neurological syndromes with strikingly similar features, but the synaptic

and circuit-level changes mediating these shared features are undefined. Researchers report three novel signs of neural circuit dysfunction in three mouse models of MeCP2 disorders (constitutive MeCP2 null, mosaic MeCP2(+/-), and MeCP2 duplication): (1) abnormally elevated synchrony in the firing activity of hippocampal CA1 pyramidal neurons, (2) an impaired homeostatic response to perturbations of excitatory-inhibitory balance, and (3) decreased excitatory synaptic response in inhibitory neurons. Conditional mutagenesis studies revealed that MeCP2 dysfunction in excitatory neurons was responsible for elevated synchrony at baseline, while MeCP2 dysfunction in inhibitory neurons increased susceptibility to hypersynchronization in response to perturbations. Chronic DBS improved all three features of hippocampal circuit dysfunction in these mice, further defining the electrophysiological mechanisms by which DBS may improve memory in female patients with RTT (Lu et al., 2016).

Fundamental Brain Mechanisms Disrupted by RTT. RTT is a neurodevelopmental disorder that results from mutations in the X-linked gene for MeCP2. The underlying cellular mechanism for the sensory deficits in patients with RTT is largely unknown. This study used a mouse model of RTT to investigate changes in the neurocircuitry underlying the sensory deficits observed in MeCP2-null mice. Electrophysiological results showed an imbalance in the relationship between excitatory and inhibitory neurotransmission with a bias toward inhibition, due to an increase in efficacy of postsynaptic inhibitory receptors, rather than presynaptic release properties. Enhanced inhibition impaired the transmission of tonic signals throughout the sensory neurocircuitry. Previous morphological studies also showed an increase in brain excitatory glutamate receptors in the neocortex of both RTT patients and MeCP2-null mice at early ages. Although glutamate receptor-mediated excitatory synaptic transmission was not altered in some parts of the sensory cortex of MeCP2-null mice, extrasynaptic glutamate receptor-mediated responses increased markedly. These responses were blocked by a glutamate receptor

blocker, suggesting that extrasynaptic glutamate receptors play an important role in the pathogenesis of RTT. The results suggest that enhancement of both postsynaptic inhibitory and extrasynaptic excitatory glutamate receptor-mediated responses may underlie impaired somatosensation and that pharmacological blockade of extrasynaptic glutamate receptors may have therapeutic value for RTT (Lo et al., 2016).

MS

Hormone Modulation of Neuroinflammatory Mechanisms. There is high variability in the presentation of MS and there are few effective treatment options for women with this disorder. In preclinical models of MS, investigators found a neuroprotective effect of the hormone estrogen. In a more thorough study, investigators examined the effects of estrogen on specific neuroinflammatory cells, notably regulatory B cells and resident brain microglia, which are key elements in MS pathogenesis. The studies revealed that estrogen in these two important cell populations could induce an anti-inflammatory phenotype and turn on a number of genes associated with anti-inflammatory mechanisms, which may be responsible for the improved phenotypic response. This study suggests estrogen may be useful therapeutically for the treatment of MS in some female patients (Benedek et al., 2016).

New or Ongoing Research

Chronic Pain

Sex-Specific Mechanisms in Chronic Pain. The goal of this project is to elucidate the cellular and molecular mechanisms involved in vascular pain in female and male rats to understand the marked sexual dimorphism that exists for many chronic pain syndromes (e.g., migraine, endometriosis, and microvascular [syndrome X]). The studies evaluated the sexual dimorphism that leads to chronic pain and suggested novel approaches for the development of a specialized class of drugs to treat chronic pain in women. The investigators found that priming male rats with interleukin-6,

tumor necrosis alpha, and nerve growth factor would lead to long-term hypersensitivity to subsequent nonpainful stimuli. They also found that these compounds did not prime pain receptors in female rats. Further studies showed that the female rats were very sensitive to activation of a novel ryanodine receptor and activated calcium-calmodulin kinase II. These findings suggest treatments targeting this receptor and enzyme may be selectively effective in females with chronic pain (Levine, n.d.).

Spinal Cord Injury (SCI)

Understanding Sex Differences in SCI

Mediators. This grant seeks to understand the role of variations in inflammatory cell types and activation states on recovery after SCI. SCI traditionally has been most prevalent in young males, due in part to risk-taking lifestyle and choices. There is a changing demographic, however, with an increasing age of injury and increasing prevalence of women as an older, active population experiences injuries from falls. Some studies suggest that women have better recovery than men with similar injuries, and this may be due to estrogen or nonestrogen-dependent mechanisms. In this study, the interaction of sex (males and females), age, and treatment on the inflammatory response and recovery in rats following SCI will be directly tested. The results will help understanding of the mechanisms that may underlie differences in responses of men and women following spinal cord trauma (Gensel, n.d.).

Stroke

Sex Differences in Moyamoya Syndrome

(MMS). MMS is an unexplained change in the cerebrovasculature that leads to the formation of aberrant new blood vessels and subsequent stroke. The female-to-male ratio of MMS prevalence is about 2:1. In this study, investigators will utilize innovative brain imaging methods to test fundamental hypotheses about the relationship between parenchymal function, hemodynamic compensation mechanisms, and stroke incidence to

improve our understanding of the pathophysiology of MMS (Donahue, n.d.).

Alzheimer's Disease (AD)

Interaction of Sex and Genotype in AD. AD, a neurodegenerative disorder and the most common cause of dementia, represents a rapidly growing epidemic in the United States for which there is no cure. Currently, 5.3 million Americans have AD, representing a serious economic and social burden worldwide. Aging is the greatest risk factor for AD, and the E4 allele of the apolipoprotein E (APOE4) gene is the greatest genetic risk factor. The APOE gene provides instructions for making a protein called apolipoprotein E. This protein combines with fats (lipids) in the body to form molecules responsible for packaging cholesterol and other fats and carrying them through the bloodstream. APOE4 is associated with accelerated A β accumulation, both as amyloid and soluble oligomeric forms. Importantly, female APOE4 carriers have a greater lifetime risk for developing AD, an increased rate of cognitive decline, and accelerated accumulation of A β , compared to male carriers. The link between APOE4 and AD risk is likely multifactorial but remains poorly understood, while the increased risk for APOE4 females remains virtually unexplored. As sporadic AD represents about 98 percent of cases with age as the key risk factor, investigators will use a novel preclinical mouse model to investigate the interactive effects of aging, APOE genotype, and sex on AD progression, establishing the foundation for testing mechanistic-based therapeutic interventions (Vavilala, n.d.).

TBI

Studying Sex-Dependent Factors in Pediatric

TBI. There is increasing interest in understanding the effects of concussions and brain injury in adolescents. Currently, there is very limited information on differential responses to brain injuries in boys and girls and how those injuries may be detected. This study will provide new information as to whether and how vasoactive agents affect the neurovascular unit, cerebral hemodynamics, and cerebral perfusion

characteristics in a pediatric TBI cohort parsed by age and sex. Given the importance of cerebral perfusion to TBI recovery, understanding neurovascular reactivity is critical to diagnosing and treating adolescent TBI (LaDu, n.d.).

Sex Differences in Female and Male Athletes.

A mounting body of evidence now suggests that the incidence of and recovery rate from concussion differs between men and women. For example, in soccer, it is believed that women are at risk for having more frequent and severe physical and cognitive symptoms both following concussion and from the accumulation of hitting the ball with their heads (headers). NINDS is funding a study to characterize sex differences following soccer-related concussion and the accumulation of headers in amateur adult soccer players. Beyond comparison of the sexes, this study will investigate whether hormonal variation contributes to differences in cognitive functional changes, and potentially in post-concussive symptoms for those suffering concussion. This study also intends to investigate sex differences in the brain's white matter integrity as it relates to exposure to head impacts throughout 28 days of the season and/or 28 days following concussive injury. Results will provide insight into sex as a mediator of the response to accumulation of head impacts and concussion. Moreover, this study also will provide information regarding the influence of menstrual cycle hormonal fluctuations on symptom reporting, recovery, and brain physiology (Lipton, n.d.).

Gaining a Better Understanding of TBI Across Clinical Populations. The role of sex differences in response to moderate and severe TBI is being investigated in two large comparative effectiveness clinical trials. The first is a pediatric observational trial in severe TBI. The Multiple Medical Therapies for Pediatric TBI; Comparative Effectiveness Approach trial is studying the effectiveness of first-line therapies for treatment of severe TBI in children, including intracranial hypertension strategies, secondary injury detection, and metabolic support (Bell and Wisniewski, n.d.).

The second trial—Transforming Research and Clinical Knowledge in Traumatic Brain Injury—is an observational TBI trial focused on patients across the TBI severity spectrum that present at the emergency room. This trial is enrolling 3,000 consecutive patients and will compare differences in outcomes across the severity range and between sexes. The results of these trials will help to inform both current clinical care and future clinical trials (Manley et al., n.d.).

NIH Strategic Plan for Women's Health Research

Highlights

This highlight addresses Goal 3.1 of the NIH Strategic Plan for Women's Health Research (research to understand the role of reproductive transitions on conditions affecting women and girls across the lifespan). Although women with MS are known to experience an elevated risk of relapse after giving birth, the impact of exclusive breastfeeding on this postpartum risk has been unclear. In this study, 201 pregnant women with relapsing-remitting MS who participated in a German MS and pregnancy registry were followed for 1 year postpartum. Women who breastfed exclusively experienced a lower rate of MS symptom relapse in the first 6 months postpartum, compared to those who supplemented or did not breastfeed. The time to first postpartum relapse after the introduction of supplemental feedings did not differ significantly between women who previously breastfed exclusively and those who did not. The findings suggest that exclusive breastfeeding is a modestly effective MS treatment during a vulnerable time (Hellwig et al., 2015).

Goals 3.1 and 3.3 of the NIH Strategic Plan for Women's Health Research are addressed in this study. In contrast to the postpartum experience, relapses of MS decrease during pregnancy, a time when levels of the hormone estriol are increased. To study whether estriol treatment could reduce relapses in women who are not pregnant, a

randomized, double-blind, placebo-controlled Phase II trial studied 164 patients. Estriol add-on therapy was compared to patients receiving glatiramer acetate only. The primary endpoint was annualized relapse rates after 24 months. Unfortunately, no statistically significant outcome was achieved, indicating that this estrogen-related hormone offers little value in reducing MS symptoms in nonpregnant women (Voskuhl et al., 2016).

Goals 1.5 and 1.8 are addressed in a study of women with myalgic encephalomyelitis/chronic fatigue syndrome (CFS/ME). Poor sleep quality has been linked to inflammatory processes and worse disease outcomes in the context of many chronic illnesses, but less is known in such conditions as CFS/ME. This study examined the relationships between sleep quality, pro-inflammatory cytokines, and CFS/ME symptoms. Women diagnosed with CFS/ME were assessed using the Pittsburgh Sleep Quality Index (PSQI), Fatigue Symptom Inventory, and Centers for Disease Control and Prevention (CDC)-based CFS/ME symptom questionnaires, and circulating plasma pro-inflammatory cytokine levels. Poor sleep quality (PSQI global score) was associated with greater pro-inflammatory cytokine levels of interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor-alpha (TNF- α). Worse sleep quality was found to be related to greater fatigue severity and fatigue-related interference with daily activities, and more severe and frequent CDC-defined core CFS/ME symptoms. These results underscore the importance of managing sleep-related difficulties in this population. Further research is needed to identify the etiology of sleep disruptions in CFS/ME and mechanistic factors linking sleep quality to symptom severity and inflammatory processes (Milrad et al., 2017).

The following highlight also addresses Goal 1.8 of the NIH Strategic Plan for Women's Health Research. CFS/ME symptoms have been shown to be exacerbated by stress and ameliorated by group-based psychosocial interventions, such as cognitive behavioral stress management (CBSM). Still, individuals with CFS/ME may have difficulty attending face-to-face groups. This study compared

the effects of a telephone-delivered (T-CBSM) versus a live (L-CBSM) group on perceived stress and symptomology in adults with CFS. Intervention data from 100 individuals with CFS (mean age 50 years; 90% female) participating in T-CBSM or L-CBSM in previously conducted randomized clinical trials were obtained. Perceived Stress Scale (PSS) was compared with repeated measures analyses of variance in adjusted and unadjusted analyses. Participants across groups showed no differences in most demographic and illness variables at study entry and had similar session attendance. Both group sessions significantly reduced PSS scores, with L-CBSM showing a large effect and T-CBSM a medium effect. For CFS symptom frequency and severity scores, L-CBSM reported large effect size improvements, while T-CBSM showed no significant changes over time. Two different formats for delivering group-based CBSM—live and telephone—showed reductions in perceived stress among patients with CFS. However, only the live format was associated with physical symptom improvements, with specific effects on post-exertional malaise, chills, fever, and restful sleep. The results provide important implications for future technology-facilitated group interventions in this population (Hall et al., 2017).

Inclusion

NINDS uses several processes to address inclusion of women in clinical research. During the peer review process for grant applications, the inclusion plan for clinical research is examined. Phase III clinical trials are required to have inclusion analysis plans to inform enrollment targets. Peer reviewers assess the inclusion plans, and prior to each council meeting, program directors examine the reviewers' comments on unacceptable inclusion goals and resolve issues in writing with the investigators. Program directors also review enrollment data submitted in the annual progress reports and determine whether the enrollment targets for gender inclusion are scientifically appropriate. The NIH Inclusion Monitoring System allows access to Institute records and cumulative reports, enabling

program staff to track enrollment data. At NINDS, the Division of Clinical Research assists program staff and grants management on issues of tracking exemptions and making any necessary changes to the tracking codes in the population tracking database.

Science, Technology, Engineering, and Mathematics (STEM) Efforts

NINDS has actively participated in several outreach activities to foster interest in neuroscience among girls and underrepresented individuals. During the National Week at the Labs (February 29–March 4, 2016), an effort coordinated by the White House Council on Women and Girls and the My Brother's Keeper Task Force, NINDS scientific and program staff met with students during engaging experiments and STEM mentoring sessions to encourage further interest in brain sciences. In addition, NINDS staff have been visiting local elementary schools to share the wonders of the brain and to stimulate students' curiosity about neuroscience in the hopes of attracting more diverse individuals to the field of neuroscience.

Research Supplements to Promote Diversity in Health-Related Research (Admin Supp.)

PA-NS-16-288. NINDS' ability to help ensure that the Nation remains a global leader in scientific discovery and innovation is dependent upon a pool of highly talented scientists from diverse backgrounds, particularly those from underrepresented groups, who will help to further the Institute's mission. Research shows that diverse teams working together and capitalizing on innovative ideas and distinct perspectives outperform homogenous teams. These research grant supplements are available to support underrepresented populations among high school students through junior faculty members. It should be noted that women from diverse groups face particular challenges at the graduate level and beyond in neuroscience. Most NIH Institutes and Centers participate in this program.

Funding Initiatives, Workshops, and Conferences

Funding Initiatives

The BRAIN® Initiative (U01, R21, UH2/UG3) RFA-15-003, RFA-NS-15-004, RFA-NS-15-005, RFA-NS-15-006, RFA-15-008, RFA-NS-16-006, RFA-NS-16-007, RFA-NS-16-008, RFA-NS-16-008, RFA-NS-16-009, RFA-NS-16-010, RFA-NS-16-011.

The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN®) Initiative is aimed at revolutionizing our understanding of the human brain. By accelerating the development and application of innovative technologies, researchers will be able to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space. Long desired by researchers seeking new ways to treat, cure, and even prevent brain disorders, this picture will fill major gaps in our current knowledge and provide unprecedented opportunities for exploring exactly how the brain enables the human body to record, process, utilize, store, and retrieve vast quantities of information, all at the speed of thought. The BRAIN® Initiative is a research activity that involves NINDS and the National Institute of Mental Health, the National Institute of Biomedical Imaging and Bioengineering, the National Eye Institute, the National Institute on Drug Abuse, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Aging (NIA), the National Institute on Deafness and Other Communication Disorders, and the National Center for Complementary and Integrative Health.

The Research Program Award (R35) RFA-NS-16-001. The Research Program Award (R35) or RPA, is intended for outstanding investigators with track records of conducting high-impact, high-quality research in neuroscience for at least the past 5 years. An RPA is a single long-term grant for up to \$750,000 in direct costs per year for

8 years, and is designed to fund an investigator's research program, rather than a specific research project. The award will encompass the entirety of an investigator's funding from NINDS and is intended to allow her or him to spend more time engaging in creative, potentially longer term projects and enhancing student mentoring. In exchange for the long-term stability and flexibility provided by the RPA, recipients must commit at least 6 calendar months of effort to the grant annually and consolidate all of their NINDS support under this umbrella. NINDS awarded 30 RPA grants in 2016.

Alzheimer's Disease-Related Dementias (ADRD) Research Challenges and Opportunities, (U24, UH2/UH3) RFA-NS-16-019, RFA-NS-16-020, RFA-NS-16-021, RFA-NS-16-022, RFA-16-023. The Alzheimer's Disease-Related Dementias Research Challenges and Opportunities was a suite of funding opportunities that enabled investigators to address unmet research needs in the broad area of dementia research. With the increasing age of the U.S. population, there is an increasing demand to understand brain mechanisms contributing to neurological disorders and dementia in individuals of advanced age. Such disorders as frontotemporal degeneration, Lewy body dementia, vascular contributions to cognitive impairment and dementia, and mixed dementias are becoming increasingly prevalent in the U.S. population. These funding opportunities address the critical need for clear mechanistic understanding and improved clinical detection of ADRD in our aging population, as well as more knowledge about the presence and significance of comorbid brain pathologies in individuals diagnosed with AD. Clarification will emerge from multiple sources: pathological findings; clinical characterization; biomarkers that differentiate among dementia syndromes; disease mechanisms, including targets and justifications for intervention; and, ultimately, therapeutic approaches that leverage these advances to stop, delay, or even reverse disease pathogenesis and dementia burden. Because women frequently outlive men, these research opportunities may be of high impact for women.

Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (PA-NS-16-289). These research grant supplements support individuals with high potential to re-enter an active research career after interruption for family responsibilities or other qualifying circumstances. This program is sponsored by the Office of Research on Women's Health and many NIH Institutes and Centers.

Workshops and Conferences

Translational Stroke Research: Vision and Opportunities Workshop. Although stroke risk and mortality have steadily been decreasing over the past two decades, thanks to improved prevention strategies and improved access to reperfusion therapies, the attempts to develop new pharmacological treatments for acute stroke have been unsuccessful overall. The principal goal of the 2016 Translational Stroke Research: Vision and Opportunities workshop was to bring together key stakeholders to identify the steps needed to improve drug development in stroke. Discussions focused on animal modeling, experimental design, existing infrastructure and bridging between preclinical and clinical studies, and establishing a vision for the field. Among the recommendations of the Workshop was the need for expanded consideration of such factors as sex, age, and comorbid conditions when attempting to develop novel agents as stroke therapies and how these factors affect response outcomes.

Alzheimer's Disease-Related Dementias. The second ADRD Summit was held in 2016. The incidence of ADRD is increasing dramatically in U.S. populations due to the increasing age of the population and poorly controlled risk factors, including hypertension. It is clear that in the near future, these disorders could represent a major public health crisis. Epidemiological studies also indicate that underrepresented individuals and women are particularly susceptible to developing AD or related dementias due to common vascular risk factors. A main focus of the Summit was to address the health disparities in AD and

related dementias. The full complement of recommendations from the ADRD Summit can be found at www.aspe.hhs.gov/adrd-summit-2016-report-national-advisory-neurological-disorders-and-stroke-council.

TBI Workshop. Little is known about the differential outcomes following TBI in males and females. To address this knowledge gap, NINDS, along with other federal partners and several other NIH Institutes and Centers, is planning a state-of-the-science conference focused on understanding the challenges and opportunities to better understand sex differences in TBI.

Health Disparities

Initiatives

Health Disparities and Alzheimer's Disease (R01) PAR-15-039. NINDS partnered with NIA and the National Institute on Minority Health and Health Disparities to solicit applications proposing to study health disparities in AD and related disorders. Health disparities research related to AD will include the study of biological, behavioral, sociocultural, and environmental factors that influence population-level health differences. Specific research approaches may include improving recruitment and retention of populations underrepresented in AD research; identifying priority factors or locating pathways and mechanisms that create and sustain AD health disparities; addressing the challenges faced by informal/family caregivers from diverse racial, ethnic, and socioeconomic backgrounds that are associated with the growing population of individuals with AD; and understanding the disparities in access to and utilization of formal long-term supports and services for those with dementia.

Research Findings

Sex Disparities in Ischemic Stroke Care. Significant sex differences in the age of onset of stroke and stroke outcomes have been reported.

This study sought to determine whether there were differences in the type and quality of stroke care received between men and women in a registry program using Get With the Guidelines stroke metrics in Florida and Puerto Rico hospitals. The care of more than 50,000 patients was considered in this study. Women were found to receive comparable stroke care to men in this registry, as measured by prespecified Get With The Guidelines metrics. Women were less likely, however, to receive thrombolysis and were less likely to have door-to-needle time of less than 1 hour, an observation that calls for the implementation of interventions to reduce sex disparity in these measures (Asdaghi et al., 2016).

Identifying Strategies to Enhance Diversity in Clinical Research.

Poor recruitment and retention of minority populations in clinical research, and clinical trials in particular, continues to be a significant barrier in the reduction of health disparities, although there are a few best-practice guidelines that have systematically outlined successful strategies to promote and sustain successful recruitment and retention of minority populations. Researcher-identified best practices included using standardized project management procedures and protocols (e.g., realistic budgeting to support challenges in recruitment, such as travel/parking reimbursement for participants), research staff cultural competency and communication training, and developing and fostering community partnerships that guide the research process. These strategies may provide mechanisms to improve retention of underrepresented groups, including women, in clinical research studies and trials (Boden-Albala et al., 2015).

Funded Project

Stroke Risk Identification Using the REGARDS Study. There is a disproportionate burden of stroke among African-Americans and individuals in the Southeastern United States. The NINDS-funded Reasons for Geographic and Racial Differences in Stroke (REGARDS) is an observational study of more than 30,000 participants, of whom 59 percent

are women, which attempts to further understand the reasons for this disparity. In this newly funded project, investigators will utilize sophisticated biochemical approaches to analyze biospecimens from REGARDS participants with the goal of identifying predictors of cerebrovascular disease in this population (Kimberley, n.d.).

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National Institute of Nursing Research (NINR)

Executive Summary of Women’s Health and Sex Differences Research

The mission of the National Institute of Nursing Research (NINR) is to promote and improve the health of individuals, families, and communities. To achieve this mission, NINR supports clinical and basic research and research training on health and illness that spans and integrates the behavioral and biological sciences. In addition, the Institute works to develop the scientific basis for clinical practice. NINR’s vision of health research is based on a patient-provider partnership paradigm that is person-centered, rather than disease-oriented, focuses on preventing the development of chronic conditions, and features the person as an active participant in his or her own health. From premature infants, to adolescents living with diabetes, to elderly cancer survivors coping with pain, nursing research develops the science to help people strengthen the quality of their lives. Nursing science reaches out beyond the boundaries of disease and disciplines to better develop personalized approaches that maximize health and well-being for individuals at all stages of life, across populations and settings. Across all scientific programs, NINR’s research addresses disease prevention, elimination of health disparities, and promotion of health equity.

NINR’s research portfolio explores some of the most important challenges affecting the health of women, including:

- Growth of an aging female population faced with chronic conditions requiring complex self and symptom management strategies.
- The need to better understand the symptoms of chronic conditions, such as irritable bowel syndrome (IBS), diabetes, and cancer treatment-related symptoms.

- Growth in the number of women with diverse racial and ethnic backgrounds and the associated issues of health disparities in underserved populations.
- An increase in the number of women acting as caregivers for their parents, partners, and children with chronic and life-limiting illnesses.
- The need to support the growth of the next generation of scientists in women’s health research.

NINR funds and co-funds programs of research with specific attention to issues surrounding pregnancy, aging and menopause, chronic conditions, health disparities, and the promotion of women in research. Central to the themes within its latest strategic plan, NINR seeks to strengthen research specific to women, whether as patients, caregivers, or community members. The Institute actively ensures that research it supports includes a diversity of women and that health disparities experienced by women in urban, minority, rural, and other underserved communities are addressed. Findings during Fiscal Years (FY) 15 and 16 have furthered understanding of issues uniquely relevant to women’s health, including:

- Chronic and life-limiting conditions.
- Promotion of healthy physical and dietary lifestyles to prevent obesity and heart disease.
- Menopause and aging.
- Pregnancy, the perinatal period, and preterm birth.
- HIV and sexually transmitted infection (STI) prevention in adolescent girls and young women.

Today’s challenges in the field of women’s health present opportunities for NINR to continue to support innovative studies in areas highlighted in its newest strategic plan, and results from these studies will inform future strategies that will advance women’s health in the future.

NINR and Women's Health

NINR is committed to supporting research on women's health through a wide range of research initiatives and investigator-initiated research. The Institute's research portfolio on women's health spans a range of topics that affect women in particular, and may affect women differently from men. The portfolio consists of grants given to individuals, collaborative groups, multisite projects, and training grants that help to develop the clinical evidence base for treating women's symptoms, conditions, and diseases.

Accomplishments and Achievements

NINR's research portfolio focuses on developing the clinical evidence base for women's health; the portfolio supports projects that range across the lifespan, from the perinatal period to the end of life. The following listing serves as evidence for the success of this focus from 2015 and 2016.

Chronic and Life-Limiting Conditions

An NINR-supported study identified mobility disabilities in ovarian cancer survivors and associated symptoms: Symptom-related mobility disabilities (defined by self-reported difficulty walking) were identified in a majority (60%) of ovarian cancer patients and survivors. Related symptoms included abdominal bloating, fatigue, lack of appetite, numbness/tingling, and pain. Research has shown that these symptoms can be mitigated through treatment and recovery processes. The identification of symptoms that are associated with impaired mobility among ovarian cancer patients and survivors is an important step in the development of effective symptom management strategies that can help patients and survivors improve their quality of life (Campbell et al., 2016).

Resourcefulness training is effective for reducing stress, depressive cognitions, and negative emotions in women dementia caregivers: In the United States, nearly 10 million women are caregivers for elders with dementia; this role often causes stress and adverse health effects for these women. Resourcefulness training (RT) incorporates eight skills constituting personal and social resourcefulness, including such self-help strategies as organizing daily activities, using positive self-statements, positive reframing, exploring new ideas, and changing from one's usual reaction. In a pilot study of female dementia caregivers, RT was delivered by trained interventionists. The study found that RT helped to reduce stress, depressive conditions, and negative emotions, providing preliminary evidence for the effectiveness of this strategy for improving quality of life for these caregivers (Zauszniewski et al., 2016).

Practicing Tai Chi may help reduce cardiovascular risk biomarkers and increase well-being: In an 8-week randomized controlled trial co-funded by NINR, practicing Tai Chi was found to be associated with down-regulation of proinflammatory cytokines associated with cardiovascular disease risk, and increased mental well-being, as measured by changes in mindfulness, spiritual thoughts and behaviors, and self-compassion. The study sought to understand the unique psychoneuroimmunology of cardiovascular disease, focusing on modifiable risk factors related to stress, and inflammatory processes associated with the development of cardiovascular disease in women. The trial also found that the practice of Tai Chi improved fatigue immediately after the intervention, and led the women to develop new understandings of the impact of stress on their lives. The trial also was found to decrease depressive symptoms in the participants (Robins et al., 2016).

Women with recurrent ovarian cancer develop individualized symptom management goals and strategies for cancer-related fatigue (CRF):

One of the most common symptoms of women with recurrent ovarian cancer is CRF. In a NINR-supported study, women with recurrent ovarian cancer were encouraged to develop individualized symptom management goals and strategies in a Web-based symptom management trial, the WRITE (Written Representational Intervention to Ease Symptoms) study. Four general themes were revealed among the women's symptom management goals: enjoying time with friends and family, doing the things each woman enjoyed, having energy to be physically active, and keeping up with what needs to be done. The women individualized their symptom management strategies to develop effective means of attaining their symptom management goals (Hagan et al., 2016).

Patients with recurrent ovarian cancer and their clinicians identify symptoms differently:

In this study, patients with recurrent ovarian cancer were asked to identify their symptoms and to prioritize them according to their experiences. Clinicians also documented patients' symptoms, and ordered treatment for those they thought to be of the highest priority. However, there was considerable discord between the priority symptoms identified by patients and those recorded by their clinicians. Of the 150 symptoms identified by the patients, 53 percent of them were neither clinically documented nor treated. The study indicates a clear need to improve communication between patients with recurrent ovarian cancer and their clinicians (Hay et al., 2016).

NINR intramural scientists identify the genetic basis of fibromyalgia: Researchers at NINR's Division of Intramural Research at the NIH Clinical Center examined the expression of genes in women with fibromyalgia and compared them to healthy controls. The team discovered 12 genes that were differentially expressed in women with fibromyalgia; the genes are associated with immune response. The discovery of the genetic basis for fibromyalgia is an important step in understanding

the mechanisms under this condition, and a step towards the development of better testing and therapeutic advances (Lukkahatai et al., 2015).

Aging and Menopause

Women who begin the menopausal transition at younger age experience symptoms for a longer period of time than those who begin at an older age:

In a multisite, multiethnic longitudinal study of the menstrual transition, researchers supported by the NIH, including NINR, examined the duration, symptomology, and physiological changes associated with menopause. In a recently published study, researchers determined that the age of onset of menopause had an impact on the duration of the transition, and identified differences in behavior and ethnicity associated with different lengths of the transition. Cigarette smoking was found to be associated with younger onset of menopause. African-Americans were found to experience longer transitions. Higher weight women experienced later menopausal transition. Understanding these differences in age at onset and duration of transition are key to helping develop better screening processes for menopause, improve symptom management during menopausal transition, and improve screening for bone loss and cardiovascular risks associated with menopause (Paramsothy et al., 2016).

Pregnancy, Childbirth, and Perinatal Health

A trial of a mobile app to track early breastfeeding offers insights into some groups of women's experiences, especially for married women with higher levels of education:

In a feasibility trial of a mobile app, first-time mothers were asked to record their experiences of breastfeeding their young infants (0–2 months old). Although the app was used by the majority of the study participants, some women reported that keeping track of their breastfeeding experiences to be too time-consuming or anxiety-provoking. The app was more feasible for recording early breastfeeding in women who had higher levels of education, were married, and had not used

formula in the hospital. Further research is needed to develop more user-centered methods for recording breastfeeding activities and experiences (Demirci et al., 2016).

An NIH-supported study of women who experience preterm birth revealed that placental infections and inflammation may cause this dangerous condition: Chorioamnionitis, or a placental infection, is associated with risk of preterm birth. The infection causes inflammation, which may be the source of alterations in the placental microbiome. The study examined the placentas of preterm birth infants, and identified bacteria that generally are associated with the oral and urogenital microbiomes in subjects with chorioamnionitis, as well as alterations in microbial metabolic pathways. The identification of the types of bacteria associated with preterm birth forms a strong basis for investigation of the mechanisms that cause placental infection, inflammation, and preterm birth, and may lead to therapeutic targets for the prevention of these infections and preterm birth (Prince et al., 2016).

Women who experience racial discrimination during their pregnancies have lower levels of social support and psychological well-being: In a study of pregnant African-American women, researchers explored their experiences of racial discrimination and psychological distress. The women who reported the highest levels of discrimination and distress also reported lower levels of social support; experiences of racial discrimination were highest among women with higher levels of education. Women who experienced discrimination also had higher cytokine levels in their blood, indicating systemic inflammation that could compromise immune function. Identifying pregnant women who experience racial discrimination and perceived stress is key to developing new ways to help the psychological well-being of these women and their families (Giurgescu et al., 2016).

NINR-supported researchers discover key differences in the cervicovaginal metabolome: Metabolomics, the study of metabolites necessary for the structure and function of an organism at the cellular level, can reveal key differences between women who experience preterm or full-term birth. In a recent study, key differences were found in the biochemical compounds found in the cervicovaginal metabolome of these two groups of women. Changes in the metabolome can be detected weeks, if not months, before clinical symptoms of risk for preterm birth, and may lead to important ways to identify and treat women at risk of preterm birth (Ghartey et al., 2015).

A telenursing program successfully delivers psychological support for pregnant rural women: Rural women often face challenges in accessing health care because of their residence and lack of medical resources in their communities. Many of these women are vulnerable to health disparities because of these conditions. A group of nurse scientists developed the Baby Behavioral Educational Enhancement of Pregnancy (Baby BEEP) program to provide for weekly conversations between pregnant rural women and nurses to help answer questions and provide counseling to these expectant mothers. The retention rate was high during the intervention, and effective therapeutic relationships were established between patients and nurses. The intervention provides a good example of a well-received psychosocial program to access underserved and vulnerable populations (Evans et al., 2017).

Social support from family and friends is the biggest driver in increasing pregnant Latinas' fruit and vegetable intake: A group of pregnant Latinas were interviewed about their dietary habits as a preliminary step in developing an intervention to increase prenatal fruit and vegetable intake. The study identified 10 factors that influence fruit and vegetable intake, including social support, family structure, access, preferences, and health

knowledge about fruit and vegetable intake; self-efficacy; planning strategies for dietary intake; and maternal health status. The study identified social support from friends and family as the key factor in influencing prenatal dietary intake; this information will be a key factor in developing the planned intervention (Hromi-Fiedler et al., 2016).

In addition to these advances, NINR supported the following grants in this topic area during FY 15–16:

- F31NR015400—Activation and Perinatal Outcomes in African-American Women
- F31NR015725—Is Spontaneous Preterm Delivery Associated with Inflammation?
- F31NR015961—Intergenerational Attachment and Executive Functioning and the Development of Young Children of Adolescent Mothers
- F31NR01382—Acculturation and Reproductive Health Disparities in Mexican-Origin Adolescents
- K23NR015810—Biological Underpinnings of Maternal Attachment in High-Risk Populations
- R00NR013187—Sleep-Related Determinants of Gestational Diabetes
- R01NR013661—Maternal Stress, Obesity, and Influenza Immunogenicity in Pregnancy
- R01NR013662—The Effectiveness of Non-Pharmacological Treatment for Perinatal Insomnia
- R01NR014245—Informing Evidence-Based Maternal Weight Gain Guidelines for Twin Pregnancies

Obesity, Physical Activity, and Disease Prevention

Research identifies the cardiovascular risk levels of sedentary, urban community-living, midlife women who participated in a lifestyle physical activity program: NINR-supported scientists recruited inactive, urban, midlife African-American women to test a physical activity intervention, which consisted of group meetings and follow-up motivational telephone calls. The women in

the study had a higher number of cardiovascular disease risks than national averages, including obesity, hypertension, and hypercholesterolemia (Braun et al., 2016). Women who participated in the intervention showed a significant increase in their physical activity 24 weeks after first receiving the intervention, and maintained this increase at 48 weeks, whether or not they received follow-up telephone calls. The study demonstrated a successful model for a face-to-face intervention with strong adherence to promote physical activity in an at-risk minority population (Wilbur et al., 2016).

Women’s childhood and adult socioeconomic status associated with odds of having metabolic syndrome (MeS) in adulthood:

More than 20 percent of U.S. adults have MeS, which is a cluster of cardiometabolic risk factors for such chronic diseases as cardiovascular disease and diabetes. A better understanding of the development of MeS can lead to improved prevention and improve the health of older adults. Researchers examined the impact of childhood and adult socioeconomic status (SES) on the development of MeS among pre- and postmenopausal women. Women who experienced adverse childhood SES, and those with a high school credential, had higher chances of having MeS, while women raised in better SES situations, or who were college-educated, had lower risks of MeS. The study also found that this relationship reflected SES-related differences in exercise and alcohol consumption (Montez et al., 2016).

A mail-delivered physical activity intervention increased physical activity among Latinas:

Physical inactivity, which can lead to a number of chronic health conditions, remains a problem among Latinas. NINR-supported researchers developed a mail-delivered intervention to increase physical activity. The intervention effectively increased physical activity, and was found to be a cost-effective strategy for disseminating individually tailored health information. Overall, the intervention participants increased the time that they engaged in physical activity by an average of 72 minutes/week at 6 months after the intervention,

and 94 minutes/week at 12 months after the intervention (Larsen et al., 2016).

In addition to these advances, NINR supported the following grants in this topic area during FY 15–16:

- F31NR015690—Intervention to Increase Exercise Among Breast Cancer Survivors
- F31NR014960—Mother-Daughter Relationship Influences on Daughter’s Dietary Practices
- K23NR014661—Understanding Social Networks and Obesity Risk Factors Among Black Women
- R15NR015620—Modeling Postmenopausal Chemotherapy-Associated Weight Gain

Inclusion: Sex/Gender Analysis at NINR

NINR supports research that examines the differences between men and women with regard to signs and symptoms, response to treatments, and chronic conditions. This research reveals gender differences as an important focus that helps to improve men and women’s health, and ensures that women are fully integrated in clinical research and clinical trials. The Institute is dedicated to supporting research that incorporates gender differences across the lifespan and across all conditions and illnesses, and includes research that examines behavioral and biological differences. Examples of research that incorporates sex/gender analysis that the Institute has supported include the following advances and grants.

Caregiving tasks, depressive symptoms, and life changes vary by gender, race, and relationship differences: A study of caregivers of stroke victims revealed that women caregivers experience more difficulty with life tasks and suffer higher rates of depressive symptoms than their male counterparts. Differences also vary by race, with non-African-American caregivers more likely to experience task difficulty and experience depressive symptoms, and vary by relationship type. This information is useful in developing interventions to improve and maintain the health and quality of life of caregivers (Jessup et al., 2015).

Symptom clusters vary in acute coronary syndrome by sex, age, and discharge

diagnosis: Researchers examined symptom clusters experienced by patients with possible acute coronary syndrome (ACS) in the emergency department and identified four separate clusters. Women tended to present with symptoms of one cluster more than the other three clusters; this cluster was titled Heavy Symptom Burden and included non-chest pain, shortness of breath, weakness, and fatigue. The other clusters were named Chest Symptoms and Shortness of Breath, Chest Symptoms Only, and Weary. Younger patients were more likely to exhibit Heavy Symptom Burden, while patients who were diagnosed with ACS tended to have symptoms categorized in the Chest Symptoms and Shortness of Breath or Shortness of Breath clusters. This information can be useful in assessing patients for potential ACS (Rosenfeld et al., 2015).

Initiatives in Women’s Health Research

Maternal Nutrition and Prepregnancy Obesity: Effects on Mothers, Infants, and Children:

In conjunction with the Office of Dietary Supplements, NINR co-sponsored this request for interdisciplinary research on maternal nutrition and prepregnancy obesity in mothers and their children. The funding opportunity encourages applications to improve health outcomes for women, infants, and children. Maternal prepregnancy obesity is a contributing factor in the etiology of such poor maternal outcomes as gestational diabetes, pregnancy-induced hypertension, risk of pre-term birth, pre-eclampsia and eclampsia, venous thromboembolism, and fetal macrosomia. [PA-15-100]

Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations

(Admin. Supp.): NINR co-sponsors an initiative to support administrative supplements to expand existing research to focus on SGM health. SGM populations include, but are not limited to, lesbian, gay, bisexual, and transgender people,

and individuals with differences or disorders of sexual development (sometimes referred to as “intersex” or as specific diagnoses). This trans-NIH effort is intended to encourage investigation in this underrepresented, but growing, field of research and includes studies on increased disease risk; mental, behavioral and social health; approaches to personalized medicine; access to care; reproductive and sexual development; neurological and cognitive development; and resilience. [PA-17-098]

Women’s Health and Health Disparities Research at NINR

Health Disparities

Among NINR’s research priorities, understanding and overcoming health disparities has long been a goal for the Institute. The research portfolio has deep ties with researchers who have worked to challenge disparities with strong evidence-based interventions and related research. As evidenced by the advances featured here from 2015 to 2016, NINR continues the advance of science in understanding and overcoming health disparities in a diverse set of vulnerable, underserved, and at-risk communities.

A Primary Prevention Trial to Strengthen Child Attachment in a Native Community: Research has shown that attachment security in infancy and early childhood promotes resilience in children who grow up under stressful circumstances. In FY 15, the University of Washington Partnerships for Native Health, in collaboration with the Fort Peck Tribes in northeastern Montana, made progress in adapting the Promoting First Relationships (PFR) program to ensure cultural appropriateness. Once completed, researchers will use this program to test the effectiveness of PFR in promoting sensitive caregiving and child attachment (Booth-Laforce, 2013–2017).

Research examined breast cancer literacy in participants in a community health worker program to increase cancer screening: Research shows that individuals from medically underserved populations are more likely to be diagnosed with

late-stage diseases that might have been treated more effectively or cured if diagnosed earlier. NINR-supported scientists developed the Kin Keeper model to increase breast and cervical cancer screening in minorities. The program used individuals known as “Kin Keepers,” from community-based health networks, who brought together female family members to learn about and share knowledge and experiences through a program to improve breast and cervical cancer education and health literacy, and to increase screening among minority women. Data collected during a study of the Kin Keeper intervention demonstrated that functional breast cancer literacy, as well as motivation, were associated with breast cancer screening, indicating that these two factors are important to consider when developing new interventions to improve rates of screening (Talley et al., 2016).

A physical activity intervention increased physical activity among Latinas, an improvement that was sustained after the end of the intervention: Obesity is associated with poor cardiovascular health, and increasing physical activity is essential to reducing rates of obesity. Latinas report high rates of inactivity and related health conditions, including obesity and diabetes. A randomized control trial of an individually, linguistically, and culturally tailored physical activity intervention was developed for a group of Latinas, which included mailed materials sent for 6 months at regular intervals. Six months after the intervention ended (12 months from the start of the intervention), participants were contacted again, and reported significantly higher levels of moderate to vigorous physical activity. The effectiveness of this intervention in promoting physical activity in Latinas suggests a potential for broad impact in improving health outcomes for a minority population (Marcus et al., 2015).

In addition to these advances, NINR supported the following grants in this topic area during FY 15–16:

- F31NR016624—Black Women’s Perspectives About Sexually Transmitted Infection Risk: A Grounded Theory Study

- K23NR015810—Biological Underpinnings of Maternal Attachment in High-Risk Populations
- R01NR014851—A Novel Pregnancy Prevention Intervention for Latina Middle School Girls
- R03NR014329—Development and Evaluation of a Physical Activity Intervention for Latina Girls

HIV/AIDS and Sexual Health

NINR supports a number of grants that are focused on developing improved interventions for women who are at risk of HIV/AIDS infection and sexual health problems. These studies are generally focused on prevention of HIV and STIs, as well as improving the understanding of how to best treat women's sexual health. Advances and grants in this area include both domestic and global research.

A human papillomavirus (HPV) screening program increased awareness of the threat of cervical cancer among women with HIV:

Women living with HIV experience a higher risk of cervical cancer, but screening rates among these women remain low. A randomized controlled trial of an HPV and cervical cancer education program was developed to increase screening rates in this vulnerable population. The study found that self-sampling for HPV testing was feasible, but found no difference in screening rates between the intervention and control groups. The study also found that participants in the intervention who tested positive for HPV perceived a more accurate and higher risk of cervical cancer (Murphy et al., 2016).

A sample of adolescent and young women who have pelvic inflammatory disease (PID) often are diagnosed with STIs and forgo treatment: In a study of urban adolescent and young adult women who were diagnosed with PID, 39 percent also were diagnosed with an STI. Of those who tested positive for an STI, only about half received treatment. Participants anecdotally reported barriers to treatment, such as schedule conflicts and a lack of knowledge about the need for STI treatment. The study indicates a continuing need for better

strategies to improve treatment adherence for urban youth diagnosed with an STI (Butz et al., 2016).

In addition to these advances, NINR supported the following grants focused on HIV-positive women and gynecological health during 2015–2016:

- F31NR01510—Determinants of Infant Feeding Practice Among HIV-Positive Mothers in Ethiopia
- K01NR01435—Tailoring a HIV Prevention Intervention for College-Aged Black Women
- K23NR014107—Self- and Family-Management Intervention in HIV-Positive Chinese Mothers
- R01NR013507—Technology-Enhanced Community Health Nursing to Reduce Recurrent STIs After PID

Training in Health Disparities and Women's Health

NINR supports a number of institutional training grants (T32) that focus on health disparities and include women's health and special populations of women, including minorities, rural women, women of lower SES, urban women, and other special populations of women.

- T32NR007968—Interdisciplinary Training in Health Disparities
- T32NR007969—Reducing Health Disparities Through Informatics
- T32NR007077—Vulnerable Populations/Health Disparities
- T32NR012718—Transdisciplinary Training in Health Disparities Research

NINR Science, Technology, Engineering, and Mathematics (STEM) Efforts: Career Development and Women's Health

NINR has a long tradition and commitment to supporting training programs to build the next generation of nurse scientists and strongly

supports research and training in women's health. The Institute funds both pre- and postdoctoral trainees, mentored career development awardees, and institutional training programs in a range of scientific areas from basic, to clinical, to translational research. Through the Ruth L. Kirchstein National Research Service awards (F31 and F32), NINR supports pre- and postdoctoral students to undertake their own research programs and learn research skills that will support their future work as nurse scientists. Mentored career development awards (K awards) allow early-stage and mid-career scientists to enhance their research skills and expand their theoretical and methodological repertoires. In addition, one of NINR's institutional grants focuses particularly on women's health (Research on Vulnerable Women, Children and Families, T32NR007100). This emphasis on training will lead to an expanded body of highly skilled nursing scientists that will help to lead science towards better, more advanced, more personalized, and enhanced health care for women.

In addition to the training programs supported by NINR, the Institute also co-funded systematic research conducted from 2009 to 2012 on women in STEM doctorate programs, who often do not enter into academic careers. The research team published findings in 2016 that help to explain this phenomenon; they identified conditions that lead to unfair treatment and persistent gender biases in academic science. The researchers identified specific strategies that the female doctoral students used to navigate in circumstances where bias and unfair treatment were most evident and explicit. Understanding the barriers that women scientists continue to face is imperative for the development of interventions and more supportive environments to encourage women scientists to pursue an academic career (Remich et al., 2016).

Strategic Plan for Women's Health Research and NINR

NINR's training and research programs, as well as the Intramural program at the NIH Clinical Center, are strongly invested in women's health.

In particular, the training programs and symptom science portfolios meet the goals and objectives of the NIH Strategic Plan for Women's Health Research.

Goal 6: Employ innovative strategies to build a well-trained diverse women's health workforce.

As mentioned above, NINR is strongly invested in training the next generation of nurse scientists through a variety of individual, institutional, and mentored career grants. The large majority of nurse scientists are women; therefore, by providing training support to nurse scientists, NINR has assisted hundreds of women scientists in advancing their training and careers, building a strong base of basic and clinical female scientists.

In addition to the extramural training grants that the Institute supports, the NINR Division of Intramural Research provides opportunities for nurse scientists to train at the NIH Clinical Center through pre- and postdoctoral fellowships, career transition grants, and the Graduate Partnership program. NINR also provides short-term courses for training, including the Symptom Methodologies Boot Camp and the Summer Genetics Institute. These training programs provide nurse scientists with opportunities to develop new research skills to integrate newly developing methodologies, such as symptom science, precision medicine, and big data. Many of the scientists trained in the NINR intramural training programs subsequently return to the extramural community as university faculty in nursing programs throughout the country. These researchers are improving the research capacity of schools of nursing, serving as mentors and models to their students and peers.

Objectives met by this activity:

6.1—Connect and empower scientists by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH.

6.2—Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training program; encourage evaluation of mentoring practices.

6.3—Address organization, institutional, and systematic factors that impede recruitment, retention, and advancement of women in science, and modify practices that impede the careers of biomedical science.

Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women.

NINR supports work in its intramural and extramural programs on symptom science in women's health, and is dedicated to developing ways to better identify and manage adverse symptoms of chronic disease and conditions, as well as identifying the underlying pathways that cause symptoms. As lifespans increase, the possibility of developing conditions and diseases that adversely impact the quality of life increases. Science too must reach further to develop ways to improve symptom and self-management. Symptom science focuses on personalized strategies to treat and prevent symptoms of diseases and conditions that interfere with activities of daily life and the quality of life. In the intramural research program at NINR, scientists are studying pain and fatigue associated with fibromyalgia, which typically affects women more than men, as well as symptoms related to chronic fatigue syndrome and depressive symptoms.

In the extramural community, NINR has supported a number of studies identifying symptom clusters, biomarkers of symptoms, and improved symptom management strategies. Recently funded grants are examining the mechanisms underlying dyspnea, fatigue, and sleep disturbance in pulmonary arterial hypertension, the relationship between certain biomarkers and the microbiome in irritable bowel syndrome, and the sleep-related determinants of gestational diabetes. Recent advances in symptom science and women's health include understanding mobility disabilities in women with recurrent

ovarian cancer, identifying differences between symptoms reported by women with cancer and those reported by their clinicians, facilitating women in the development of strategies to manage their symptoms, and methods to reduce women's depressive symptoms through physical activity.

Objectives met by this research area:

3.8 Conduct research on aging with emphasis on prevention of fragility, promotion of healthy lifestyles, maintenance of independent women, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

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Fogarty International Center (FIC)

Executive Summary

The Fogarty International Center (FIC) seeks to advance the mission of the National Institutes of Health (NIH) by supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the United States and abroad, and training the next generation of scientists to address global health needs. The Office of Research on Women's Health (ORWH) is among the many NIH Institutes and Centers (ICs) that collaborate with FIC to support this mission. Although FIC does not have any programs that are designed to specifically address women's health issues, several FIC efforts support research and research training related to conditions that disproportionately or exclusively affect women or girls. FIC programs also enhance understanding of sex as a biological variable and gender differences. Scientific areas of focus include violence against women, mental health—including postpartum depression and post-traumatic stress disorder—cervical cancer, HIV/AIDS, pregnancy, and other reproductive health/contraception issues.

FIC accomplishments and activities particularly relevant to women's health and highlighted in this report include the following:

- The Trauma and Injury Research Training (TRAUMA) program funds research training in the diagnosis, prevention, and/or treatment of injury and trauma in low- and middle-income countries (LMICs).
- The International Research Scientist Development Award (IRSDA) supports early-career U.S. scientists to pursue independent research careers in global health.
- The Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries (mHealth) Program funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology.
- The Chronic, Non-Communicable Diseases and Disorders Across the Lifespan (NCD Lifespan) program is a collaborative research training program that supports training of scientists to conduct research on chronic, non-communicable disease and disorders in LMIC contexts.
- The Global Health Program for Fellows and Scholars supports 1-year mentored clinical research experiences for postdoctorates, medical students, or graduate students in the health sciences at 27 LMIC research sites.
- The International Tobacco and Health Research and Capacity Building (TOBAC) program provides opportunities for scientists to engage in locally relevant observational, intervention, and policy research and build research capacity related to tobacco consumption in LMICs.
- The Fogarty HIV Research Training Program—a consolidation of the AIDS International Training and Research Program (AITRP) and International Clinical, Operations and Health Services Research Training Award for AIDS TB program—strengthens the human capacity to contribute to the ability of institutions in LMICs to conduct research on the evolving HIV-related epidemics in their country to provide training in infrastructure development in support of the research programs and maintenance of grants and to compete independently for research funding.
- The Global Brain and Nervous System Disorders Research Across the Lifespan program supports collaborative research and capacity-building projects relevant to LMICs on brain and nervous system disorders throughout life.

- The Fogarty Emerging Global Leader Award provides research support and protected time for career development activities to a research scientist from an LMIC who holds an academic junior faculty position or research scientist appointment at an LMIC academic or research institution.
- In the NIH-PEPFAR (President’s Emergency Plan for AIDS Relief) PMTCT Implementation Science Alliance, FIC collaborates with the Office of the U.S. Global AIDS Coordinator (OGAC) to bring together researchers, program implementers, and policymakers from the United States and sub-Saharan Africa who are pursuing interventions to prevent mother-to-child transmission (PMTCT) of HIV, to tackle intractable barriers to implementation of proven interventions, and ultimately contribute to translation of effective PMTCT interventions into community- and population-level services, programs, and strategies at scale.
- FIC—in partnership with other NIH ICs, key Federal agencies, and the Global Alliance for Clean Cookstoves—has launched the Clean Cooking Implementation Science Network (ISN) to advance the science of uptake and scale-up of clean cooking technology in the developing world.
- The Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA) aims to enhance the effective use of evidence and help overcome implementation challenges related to prevention, screening, and treatment of HIV among adolescents (ages 15 to 24) in sub-Saharan Africa by catalyzing collaboration and communication among implementation scientists, program implementers, and policymakers.

Accomplishments and Activities

The FIC portfolio includes a variety of programs and projects related to research that disproportionately or exclusively affects women

and/or girls. Several of these are in areas of expressed Congressional interest, including neuroscience, cardiovascular disease and stroke, inclusion of women in clinical research, and sex differences in basic, applied, and clinical research. FIC’s programs fall under several of ORWH’s strategic goals, primarily Goal 4, “Create strategic alliances and partnerships to maximize the domestic and global impact of women’s health research,” and Goal 6, “Employ innovative strategies to build a well-trained, diverse, and vigorous health research workforce.” Highlights of these programs and projects are provided below.

Trauma and Injury Research Training Program

FIC’s TRAUMA program supports research training in diagnosis, prevention, and/or treatment related to injury and trauma in LMICs, including such scientific areas of focus as treatment at the scene, emergency medical facilities and services, diagnosis imaging, post-acute care, and long-term care, including rehabilitation. A number of TRAUMA-funded projects address gender-relevant research training, including violence against women with an emphasis on intimate partner violence during pregnancy, the impact of trauma on South African women in abusive HIV-serodiscordant relationships, and sexual violence against Zimbabwean refugees in South Africa.

The University of California, Los Angeles/South African Trauma Training Research (Phodiso) Program, with support from the TRAUMA program, prepares future investigators to conduct research on trauma exposure and injury prevention in the context of South Africa’s high levels of intimate partner violence (IPV) and intentional injuries. Trained researchers from the Phodiso program have demonstrated how violence during pregnancy contributes to low birth weight and detrimental health effects in South African infants. Pregnant subjects presenting at two antenatal clinics in a low-income, semirural region outside of Cape Town participated in the study. Researchers trained by the TRAUMA-supported program

administered the Childhood Trauma Questionnaire, a survey tool specifically tailored to study IPV in this context, in conjunction with the World Health Organization's IPV Questionnaire. After controlling for study site, maternal height, ethnicity, socioeconomic status, substance use, and childhood trauma, the study confirmed that exposure to IPV resulted in the delivery of an infant with a low birth weight (Koen et al., 2014).

International Research Scientist Development Award (IRSDA)

IRSDA supports U.S. postdoctoral biomedical, epidemiologic, clinical, social, and behavioral scientists in the formative stages of their careers in pursuing careers in research on global health and preparing them for independent research by engaging in a mentored career development experience. Current IRSDA investigators are studying PMTCT of HIV in Malawi, reducing barriers to a cervical cancer screening program in rural Senegal, family smoking cessation starting with pregnant women in Romania, prevention of intimate partner violence in India, and mental and sexual health in pregnant Liberian women.

With support from IRSDA, Dr. Jodi Rae Lori examined the impact of maternal waiting homes (MWH) and traditional midwives on labor and delivery outcomes in rural Liberia. The aim of her research was to understand whether MWHs improve the use of skilled birth attendants at rural primary health clinics, to assess whether traditional midwives can work collaboratively with them, and to understand whether maternal and child mortality and morbidity were reduced in these circumstances. Through a randomized control trial, Dr. Lori found that MWH had lower rates of maternal and perinatal death (Lori et al., 2013). In addition, communities with MWHs experienced a significant increase in team births, more integration of traditional midwives, and lower rates of maternal and perinatal death than the communities without MWHs.

Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries

The mHealth program funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology. The overall goal of the program is to contribute to the evidence base for the use of mobile technology to improve clinical outcomes and public health. mHealth researchers are developing and testing mobile phone interventions that could enhance conception safety for HIV-serodiscordant couples in Kenya and improve maternal and child health home visits by community health workers in Mali.

In response to the low level of HIV testing and care among pregnant women in Nigeria, one mHealth grantee is developing and testing a Web-based database and medical decision model that builds on the Healthy Beginning Initiative (HBI), a congregation-based intervention that engages pregnant women at prayer sessions, baby showers, and receptions. HBI participants will have their encrypted data stored on a "smart card" that can be accessed by the health care provider using a mobile phone application. Previous research has shown that clinicians with access to these maternal records at the point-of-delivery are more likely to initiate antiretroviral prophylaxis for HIV-exposed infants. The mHealth study will develop this technology and establish its usability and sustainability for early identification and management of infants at risk for HIV.

Chronic, Non-Communicable Diseases and Disorders Across the Lifespan (NCD-Lifespan)

NCD-Lifespan is a collaborative research training program that pairs high-income and LMIC institutions to train LMIC scientists to conduct research on chronic, non-communicable diseases and disorders with the goal of implementing evidence-based interventions relevant to their

countries. This program covers areas of particular Congressional interest, including cardiovascular disease and stroke.

One current NCD-Lifespan award with the University of Ibadan in Nigeria trains scientists at various career levels using an interdisciplinary approach where trainees receive added research training in an additional health-related discipline that is consistent with the needs expressed by the country collaborators. One area of study selected was to identify the unique molecular and genetic profiles of breast cancer in Nigerian women and relate these risk factors to a patient's response to chemotherapy. The study of certain microbiomes in Nigerian breast cancer tissues using DNA extracted from breast tissues will give insight into the involvement of microbes in breast cancer etiology among Nigerians. The grantee anticipates training more than 400 African researchers through the grant.

Global Health Fellows and Scholars

The Fogarty Global Health Program for Fellows and Scholars, in partnership with 17 NIH ICs, including ORWH, supports 1-year mentored clinical research experiences for postdoctorates, medical students, or graduate students in the health sciences at 27 LMIC sites. The most recent gender-based clinical research topics include developing multidisciplinary approaches for targeted prevention and screening strategies for breast cancer in Thailand, identifying educational determinants for early pregnancy in the Peruvian Amazon, and assessing the physical and mental health of women with HIV and the impact of social support networks.

One Fogarty Fellow is currently collecting data in an underserved and recent conflict-affected setting in Northeastern Uganda to understand contemporary human rights issues and gender-based violence in the context of communities that have experienced armed conflict (Mootz, 2015). Dr. Jennifer Mootz is using her fellowship to establish the prevalence of various forms of gender-based violence, determine correlations between experiencing gender-based violence and

mental health outcomes, and explore gender-based violence survivors' conceptualizations of their mental health experiences.

International Tobacco and Health Research and Capacity Building Program (TOBAC)

With support from TOBAC, scientists engage in locally relevant observational, intervention, and policy research and build capacity in epidemiologic and behavioral research, prevention, treatment, communications, health services, and policy research related to tobacco consumption in LMICs. This program supports the expansion of a network for tobacco control among women in Parana, Brazil, to conduct community-based participatory research on gender-relevant tobacco control issues, such as light smoking. The goals of the network are to reduce tobacco use and exposure to environmental tobacco smoke among women in the community and develop a cadre of well-trained researchers who will continue to address comprehensive tobacco control strategies at multiple levels.

Fogarty HIV Research Training Program and AIDS International Training and Research Program

AITRP began in 1988 as part of a then-new generation of research training programs sponsored by FIC. AITRP provided training for scientists in LMICs through partnerships between high-income and LMIC research institutions. The primary goal of this program was to build multidisciplinary biomedical, behavioral, and social science research capacity for the prevention, care, and treatment of HIV/AIDS and HIV-related conditions for those adults and children affected by HIV/AIDS in the collaborating LMIC country.

In 2013, FIC consolidated AITRP with other FIC HIV investments to create the HIV Research Training Program. The Fogarty HIV Research Training Program seeks to strengthen the capacity of LMIC investigators and their institutions to conduct HIV-related research on the evolving HIV-

related epidemics in their countries and to compete independently for research funding. Mentored research training projects conducted under this program include addressing AIDS-related cervical cancer (screening, exploring disease mechanisms, and identifying treatment strategies) and the PMTCT of HIV.

One HIV Research Training Program grantee is building capacity around implementation science focused on HIV, women, and adolescents to inform health care practice and service delivery in Kenya. The project will first train medical doctors in implementation science at the University of Washington; they will then return to Kenya to work with the Kenya Medical Research Institute (KEMRI) for 9 months to conduct implementation science research projects focused on HIV treatment and prevention for women with guidance from U.S. and in-country partners. As part of the project, faculty also will conduct 1-week workshops on implementation science, grant writing, and manuscript preparation for KEMRI staff and 1-day workshops for county medical directors to promote engagement of local care, treatment, and prevention leaders in areas where women are hardest hit by the HIV epidemic.

Global Brain and Nervous System Disorders Research Across the Lifespan Program

The Brain program supports collaborative research and capacity-building projects that are relevant to LMICs on brain and nervous system disorders throughout life. Grantees have developed innovative, collaborative research programs that contribute to the long-term goal of building sustainable research capacity in nervous system function and nervous system impairment. Scientific areas of focus include violence against women, mental health—including postpartum depression and post-traumatic stress disorder—and HIV/AIDS-related stigma and research to enhance understanding of sex as a biological variable and gender differences in these and other neurological diseases, disorders, and neuro-health issues.

In addition, the impact of the environment and infectious diseases on maternal and prenatal child health and development is being investigated.

A group of researchers, with funding from the Brain program, is assessing mother-to-child transmission of chikungunya virus in Grenadian pregnant mothers. They will compare the neurodevelopment of 2-year-olds who have been exposed at different trimesters *in utero* to chikungunya virus to that of unexposed children and assess the burden of confounding factors. Working with a local university, the group will build local capacity for arboviral and neurodevelopmental testing.

Fogarty Emerging Global Leader Award

The purpose of the Fogarty Emerging Global Leader Award is to provide 3 to 5 years of research support and protected time for career development activities to an early-career research scientist from an LMIC who holds a junior faculty position at an LMIC academic or research institution. Along with other NIH ICs and ORWH, FIC expects this intensive, mentored research career development experience to lead to an independently funded research career at an LMIC institution.

ORWH and the Office of the Director co-funded an FIC grantee who will improve care, screening, and outcomes for Kenyan women with a history of gestational diabetes mellitus (GDM) and hypertensive disease in pregnancy (HPD) by focusing on metabolic syndrome, a direct predictor of cardiovascular disease. Over the course of 5 years, the grantee will work with mentors from the University of Nairobi and the University of Washington to conduct a prospective cohort study to estimate the burden and characteristics of metabolic syndrome in Kenya following GDM and HPD. The study findings will inform use of high attendance of maternal health clinics in sub-Saharan Africa and may inform maternal health and primary care linkages and development of screening and monitoring strategies of women with HDP, GDM, and metabolic syndrome in resource-constrained settings.

Clean Cooking Implementation Science Network (Clean Cooking ISN)

In collaboration with other NIH ICs, key Federal agencies, and the Global Alliance for Clean Cookstoves, FIC launched the Clean Cooking ISN, which aims to advance collaborative efforts and understanding among researchers and implementers to accelerate successful adoption and use of clean cooking technologies, with the goal of scaling up appropriate use. Half of the world's population relies on elemental stoves for cooking or heating. Those using cookstoves usually burn dung, wood, soft coal, or rice husks, all of which produce toxic carbon emissions. In many cultures, women traditionally do the majority of the cooking and, therefore, are disproportionately impacted by this exposure. The resulting indoor air pollution is estimated to take 1.9 million lives each year due to increased risks of acute pneumonia in children younger than 5 years of age and chronic obstructive pulmonary disease and lung cancer in women.

The primary goal of the ISN is to develop an implementation science platform to advance the understanding of how to improve the uptake and appropriate use of evidence-based clean cooking interventions to maximize their benefits on the health and longevity of populations in LMICs. To that end, the ISN supports four research projects on active clean cooking research and implementation programs that will advance generalizable learning. One such project is implementing a conditional cash transfer program focusing on newly married and newly pregnant women in the northern Pune district of Maharashtra, India. To encourage the use of improved, liquefied petroleum gas stoves, a specially modified stove use monitor (SUM) will be installed to track the stove's use. When a pregnant woman brings the SUM to her antenatal health visits, she will receive a small cash payment for each meal prepared using the stove. The effect of the program on stove use will be evaluated using SUMs tracking on improved stoves and traditional stoves, air pollution monitoring, and time-activity tracking.

Preventing Mother-to-Child Transmission of HIV

FIC collaborated with the OGAC to host the NIH-PEPFAR PMTCT Implementation Science Alliance (the Alliance). Launched in March 2013, this novel platform brought together PMTCT researchers, program implementers, and policymakers from the United States and sub-Saharan Africa, as well as representatives from multilateral organizations. The Alliance improved communication among these stakeholders and catalyzed collaboration to enhance the evidence base for translating effective PMTCT interventions into community- and population-level services, programs, and strategies at scale.

The Alliance successfully enabled cross-fertilization of ideas, insights, and experiences as the research progressed and was able to bridge the gap between PMTCT research and program/policy through dialogue among scientists, program implementers, and policymakers. Ultimately, the Alliance was able to (1) enable PMTCT research to be better informed by challenges identified by the implementer community and locally driven priorities, (2) stimulate new implementation research questions and collaborations, (3) catalyze a spinoff country-specific and country-led HIV implementation science network, (4) enable researchers to better understand how to effectively engage implementers and policymakers throughout the research process, and (5) encourage use of implementation science evidence to revise policies and delivery interventions. Several publications resulted from this project, including a 15-paper supplement in the *Journal of Acquired Immune Deficiency Syndromes*, "Advancing Implementation Science in Prevention of Maternal-Child HIV Transmission" (2016). The collective findings of the Alliance indicate that advancing implementation science will require, among other important investments, novel approaches to facilitate collaboration, communication, and relationship building among researchers, implementers, and policymakers.

Adolescent HIV Prevention and Treatment

The Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA) aims to enhance the effective use of evidence and help overcome implementation challenges related to prevention, screening, and treatment of HIV among adolescents (ages 15 to 24) in sub-Saharan Africa by catalyzing collaboration and communication among implementation scientists, program implementers, and policymakers. Launched in September 2016, AHISA is a collaboration with OGAC, the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), other NIH ICs, and multilaterals that will (1) provide a platform for cross-fertilization and exchange of ideas and information among implementation scientists and other stakeholders focusing on different aspects of HIV in adolescents, (2) enable the research to be better informed by programmatic challenges and questions, (3) inform policymakers of promising evidence and encourage use of the data in decision making, and (4) extend the reach and impact of implementation science related to adolescent HIV prevention and treatment.

NIH Strategic Plan for Women's Health Research

FIC's work maps closely to ORWH/NIH Strategic Plan Goal 4, "Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research," and Goal 6, "Employ innovative strategies to build a well-trained, diverse, and vigorous health research workforce."

As mentioned above in Accomplishments and Activities, ORWH supports the Fogarty Emerging Global Leader Award and reviews applications for their ability to directly fulfill Goals 4 and 6. In the first round of reviews, ORWH co-funded one award. FIC participation in ISN supports ORWH/NIH Goal 4, primarily Objective 4.6, "Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the

world, particularly in developing countries," and, secondarily, Objective 4.4, "Create solid partnerships by engaging in scientific briefings and ad hoc meetings with policymakers, elected officials, and advocacy groups." FIC's research training portfolio generally addresses Goal 6 by supporting scientists' career development. Many grants involve a significant mentorship component. In addition, FIC's Medical Education Partnership Initiative (MEPI) and Global Health Program for Scholars and Fellows both address Goal 6, primarily, Objective 6.1, "Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH," and, secondarily, Objective 6.2, "Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs, and encourage evaluation of mentoring practices."

MEPI funds foreign institutions in sub-Saharan African countries that receive PEPFAR support and their partners to develop or expand and enhance models of medical education and clinical research training. MEPI supports African institutions in a dozen countries, forming a network including more than 30 regional partners, country health and education ministries, and more than 20 U.S. and foreign collaborators. The recent Limited Competition: Research Training for Career Development of Junior Faculty in MEPI Institutions states, "Support for increased engagement of female junior faculty and mentors in research activities in any relevant health area is also highly desired." FIC also promotes the careers of emerging young global health leaders through the Global Health Program for Scholars and Fellows. Following their year abroad, many female scholars and fellows successfully compete for a FIC IRSDA career development award (see Accomplishments and Activities) and acquire a faculty position at an academic institution.

In addition, as mentioned above, AHISA and the PMTCT Alliance both are collaborations of researchers, program implementers, and

policymakers in the United States and sub-Saharan Africa, as well as representatives from multilateral organizations, that aim to improve communication among these stakeholders. These projects seek to catalyze partnerships to enhance the evidence base for translating effective interventions into community- and population-level services, programs, and strategies at scale. The PMTCT Alliance published a supplement in the *Journal of Acquired Immune Deficiency Syndromes* that calls for increasing implementation science to inform understanding of key implementation barriers and successful adaptation of scientifically proven interventions to the local environment.

Inclusion

FIC has incorporated the following language in its research training announcements to encourage research training activities related to sex and gender differences: “Where appropriate, the design of training-related research projects should take into account potential sex and gender differences that may affect the questions asked and the analyses performed. These might include different responses to and impacts of health interventions, differences in physiology, and different behavioral bases for disease prevention strategies.”

Science, Technology, Engineering, and Mathematics Efforts

The Fogarty Global Health Program for Fellows and Scholars is a 1-year mentored clinical research experience in 27 LMIC sites for postdoctorates, medical students, or graduate students in the health sciences. The most recent gender-based clinical research topics include maternal and child health, knowledge and attitude toward contraception methods, and progestin-only injectable contraceptives to determine increased risk of HIV infection. Over the last 2 years, 242 fellows and scholars have participated. Of the 179 who reported gender information, 110 were women.

Funding Initiatives, Workshops, and Conferences

Several funding initiatives are relevant to women’s health or the influence of sex on disease in this reporting period. The Fogarty Emerging Leader Award provides research support and protected time for career development activities to an LMIC research scientist from an LMIC academic or research institution. The mHealth program funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology. The NCD Lifespan program is a collaborative research training program that pairs high-income and LMIC institutions to train LMIC scientists to conduct research on chronic, non-communicable diseases and disorders with the goal of implementing evidence-based interventions relevant to their countries.

The annual Fogarty Global Health Program for Fellows and Scholars supports 1-year mentored clinical research experiences for postdoctorates, medical students, or graduate students in the health sciences at 27 LMIC sites. The Fogarty HIV Research Training Program seeks to strengthen the collaborations in the LMIC with U.S. partners and local researchers to increase capacity to conduct HIV-related research on the evolving HIV-related epidemics in their countries; to obtain the technical expertise, administration and financial management skills to support research grants; and to compete independently for research funding.

The Brain program supports collaborative research and capacity-building projects that are relevant to LMICs on brain and nervous system disorders throughout life.

In addition to funding initiatives, several FIC-sponsored workshops and conferences have been relevant to women’s health or the influence of sex on disease. An estimated 3 billion people rely on basic cookstoves and/or open fires fueled by coal or solid biomass to cook and to heat their homes.

Limited research has been conducted to isolate and define the household air pollution risks caused by basic cookstoves and open fires, understand the health impacts of an improved cookstove, and identify low-cost stoves and interventions. In response to this need, FIC held a 3-day training course in 2012 for scientists from the United States and LMICs interested in developing research projects on the health effects of traditional and improved cookstoves. In follow-up to this training, FIC launched the Clean Cooking ISN in 2015 to advance the science of uptake and scale-up of clean cooking technology in the developing world. The Clean Cooking ISN currently supports four projects that aim to use implementation science to more effectively understand adoption and use of clean cooking technologies.

FIC is collaborating with OGAC to host the PMTCT Implementation Science Alliance. This novel platform brings together PMTCT researchers, program implementers, and policymakers in the United States and sub-Saharan Africa, as well as representatives from multilateral organizations. The Alliance aims to improve communication among these stakeholders and catalyze collaboration to enhance the evidence base for translating effective PMTCT interventions into community- and population-level services, programs, and strategies at scale. Coordinators in this initiative published a supplement in the *Journal of Acquired Immune Deficiency Syndromes* in 2016 that calls for increasing implementation science to inform understanding of key implementation barriers and successful adaptation of scientifically proven interventions to the local environment. Elsewhere, the authors state that advancing implementation science will require deliberate and strategic efforts to facilitate collaboration, communication, and relationship building among researchers, implementers, and policymakers (Sturke et al.,

2014). In the reporting period, the Alliance held two meetings, the first in January 2015 and the second in May 2015.

Health Disparities

Health disparities work is embedded in a variety of FIC programs and projects. For example, the study mentioned within the TRAUMA program that demonstrated how IPV during pregnancy contributes to low birth weight in South African infants speaks to an exposure that disproportionately affects women, resulting in negative health outcomes for their children. In the study, exposure to IPV was shown to result in the delivery of an infant with a low birth weight (Koen et al., 2014).

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National Center for Advancing Translational Sciences (NCATS)

Executive Summary

The National Center for Advancing Translational Sciences (NCATS) was established to catalyze a transformation in the way health interventions are developed and to bring more treatments to more patients more quickly. Translation is the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public. Translational science is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process. Understanding of the translational process creates a basis for more science-driven, predictive, and effective intervention development for the prevention and treatment of all diseases. Translational science analyzes the scientific and operational relationships among the traditional scientific fields, builds bridges, and creates networks to more effectively develop and deliver interventions that benefit the health of the public. It encourages and organizes modern scientific practices, such as team science, collaboration development, and patient engagement.

Accomplishments and Activities

NCATS' tissue chip program is an extramural program that demonstrates the promise of translational science. Tissue chip devices are designed as accurate models of the structure and function of human organs and can provide researchers with scientifically valid alternatives for predicting treatment effectiveness and safety. Too often, laboratory and animal tests used by scientists in the early phases of research fail to predict a therapy's effectiveness or potential side effects in humans. Use of inaccurate models can result in

many years and millions of dollars being wasted while patients wait for effective treatments. By creating organs-on-a-chip, researchers can test the varied effects of potential drugs before any testing in humans and can check chemicals for toxicity.

Tissue chips raise the exciting possibility to model both genders, as well as gender-specific genetic variations, in the coming years. Their utility for precision medicine efforts and moving toward clinical trials-on-chips could be transformative for the effective modeling of female populations that are currently underrepresented. In 2016, NCATS issued a series of funding opportunities around tissue chip initiatives and projects, including the Tissue Chips for Disease Modeling and Efficacy Testing initiative (Tissue Chips 2.0 RFA) designed to support development of models of human disease and pathology. The Request for Applications contains specific language to encourage the study of sex differences in disease onset, progression, and response to therapy, as well as the use of primary cells or induced pluripotent stem cells representative of gender, genetic variations, and demographics. ORWH signed on as a participating organization for these exciting opportunities, and awards are expected to be made in 2017.

Ex vivo Female Reproductive Tract Integration in a 3-D Microphysiologic System

The female reproductive tract is an integrated set of organs that supports women's overall endocrine health, fertility, and fetal development. Each organ within the tract is composed of different cells that interact with each other. Studying the tissues as individual units limits scientists' ability to learn how these organs work as a system. A team of scientists from Northwestern University, Charles Stark Draper Laboratory, and the University of

Illinois at Chicago is assembling an integrated model of the human female reproductive system within a functioning circulatory system. EVATAR™ is a miniaturized three-dimensional representation of the female reproductive tract and liver on a handheld, interconnected platform. The team is designing the model for use in drug testing and for studying the basic biology of female reproduction.

The EVATAR™ device will facilitate consideration of sex as a biological variable in preclinical testing, because it enables female reproductive tissues to interact over periods of a month or longer, much like they do in the human body. The hormone fluctuations and behavior of the cells are designed to mimic a woman's 28-day reproductive cycle. This advance solved a major technical challenge in the field: enabling organ models to communicate with one another via secreted factors, including hormones, to more closely resemble how they work together in the body. The integrated model will allow further study of female reproductive physiology, the effects of endocrine disruptors, and the toxicology and effectiveness of new drugs before their first use in women.

Zika Virus Repurposing Screening

In response to the current global health emergency posed by the Zika virus outbreak and its link to microcephaly and other neurological conditions in babies born to infected women, researchers developed two rapid tests to find drugs that will help patients. They screened a library of approximately 6,000 compounds, including approved drugs, clinical trial drug candidates, and other pharmacologically active compounds for activity against Zika virus infection. So far, the scientists have identified two categories of compounds for further evaluation: those that protect against Zika virus-induced cell death (neuroprotective) and those that suppress Zika virus replication (antiviral). The overall findings and the tools should significantly advance current Zika virus research and have an immediate effect on the development of anti-Zika virus therapeutics.

Bioprinting of an Omentum Model for Modeling Ovarian Cancer Metastasis

Metastasis is the process of spreading of tumor cells to different parts of the body and, in most cases, it is the pathology that leads to ultimate death in cancer. The omentum is a fold of tissue in the abdominal cavity that lies near the ovaries and can be an early site of metastasis in ovarian cancer. A three-dimensional model that recreated the human omentum using cells from ovarian cancer patients undergoing surgery was successfully used to discover compounds that would prevent attachment of tumor cells to the omentum. Researchers currently are using tissue bioprinting techniques to increase the relevance of the metastasis modeling by introducing additional cell types that are important for the tumor interaction in the omentum metastatic site, including blood vessels, fat cells, and immune cells. Once a native omentum model is recreated, the scientists will study the growth of cancer cells and screen for pharmacological agents that prevent tumor metastasis.

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- NCATS also has several intramural projects that bring the benefits of translational science to women's health research.

National Center for Complementary and Integrative Health (NCCIH)

Executive Summary

The National Center for Complementary and Integrative Health (NCCIH) is the lead Federal agency for scientific research on the usefulness and safety of complementary and integrative health practices. Complementary and integrative health approaches include modalities and products with a history of use or origins outside of conventional medicine. Examples include mind-body interventions—such as massage, acupuncture, yoga, and meditation—and natural products, such as dietary supplements and probiotics. To address the need for objective evidence regarding the safety and efficacy of many of these approaches, NCCIH supports rigorous scientific investigation to better understand how these interventions work, for whom, and the optimal method of practice and delivery.

Many individuals seek complementary and integrative approaches to improve their health and well-being or to manage symptoms associated with chronic diseases or conditions. Results from the 2012 National Health Interview Survey, conducted by the Centers for Disease Control and Prevention with support from NCCIH, indicate that more than one-third of the population uses complementary and integrative health approaches.¹ Natural products—such as non-vitamin, non-mineral dietary supplements—are the most commonly used complementary health approaches, followed by deep-breathing exercises and yoga.

NCCIH supports a wide variety of research to examine the use of complementary and integrative health approaches to treat the symptoms associated with menopause. With funding from NCCIH, the National Cancer Institute, and the National Institutes of Health's Office of Dietary

Supplements (grants.nih.gov/grants/guide/rfa-files/RFA-OD-09-001.html), the Botanical Estrogen Research Center at the University of Illinois at Urbana-Champaign recently reported developing estrogen-like compounds that show promise of conferring metabolic and vascular protection for menopausal women, while minimizing the risk of developing breast or uterine cancer. Investigators at the Purdue University Center for Age-Related Disorders have shown that soy isoflavones can provide some protection against postmenopausal bone loss. Research conducted at the Wake Forest School of Medicine and Duke University indicated that acupuncture may reduce the frequency and severity of hot flashes and night sweats associated with menopause; however, the extent to which nonspecific effects and the expectation of benefit influenced the outcome could not be determined in this particular pragmatic study.

Pain is an important factor in many conditions affecting women of all ages and is a common reason for individuals to turn to complementary and integrative health approaches. Investigators at the University of Michigan used magnetic resonance imaging of the brain to show that opioid treatment for fibromyalgia-associated pain may not be effective. Another research group at the University of Michigan, working with colleagues at Massachusetts General Hospital, recently reported that pelvic pain caused by endometriosis is linked to known pain-processing regions of the brain.

Research Accomplishments

Pain

Fibromyalgia is a common disorder that involves widespread pain, tenderness, fatigue, and other

¹ Clarke T. C., Black L. I., Stussman B. J., Barnes P. M., and Nahin, R. L. (2015) Trends in the use of complementary health approaches among adults: United States, 2002–2012. *National Health Statistics Reports* No. 79. Hyattsville, MD: National Center for Health Statistics.

symptoms and can interfere with a person's ability to perform everyday activities. An estimated 5 million American adults have fibromyalgia, and 80 to 90 percent of them are women. Endogenous opioid system dysfunction potentially contributes to chronic pain in fibromyalgia, but it is unknown if this dysfunction is related to established neurobiological markers of hyperalgesia (increased sensitivity to pain). Previous research has shown that μ -opioid receptor (MOR) availability is reduced in several pain-processing regions in the brains of patients with fibromyalgia, as compared with the brains of healthy controls. A recent study compared pain-evoked functional magnetic resonance imaging with endogenous MOR binding and clinical pain ratings in female opioid-naive patients with fibromyalgia (n=18) using whole-brain analyses. Results showed that reduced MOR availability was associated with decreased pain-evoked neural activity within antinociceptive brain regions. Pain-evoked brain activity and MOR binding potential also were associated with clinical affective pain ratings. These findings may therefore contribute to the mechanistic understanding of experimental pain sensitivity and clinical pain reports in fibromyalgia. The data suggest that dysregulation of the endogenous opioid system in fibromyalgia could lead to less excitation in antinociceptive brain regions by incoming noxious stimulation, resulting in the hyperalgesia and allodynia (experience of pain from a non-painful stimulation of skin, such as light touch) commonly observed in this population. Importantly, these results suggest that opioids are unlikely to be an effective treatment for fibromyalgia because of the already reduced numbers of MORs or receptor affinity, and they support a plausible mechanism by which long-term opioid use could worsen pain outcomes by exacerbating an existing vulnerability in the endogenous opioid system.

- **ORWH Objective 2.6:** Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery. (NOTE: Study only

included women and thus cannot address sex differences.)

Endometriosis is a disease in which tissue that normally grows inside the uterus begins to grow outside it, most often on the ovaries, fallopian tubes, and surrounding tissues. The main symptoms are pelvic pain and infertility. In contrast to women with relatively asymptomatic endometriosis, women with endometriosis-associated chronic pelvic pain exhibit nonpelvic hyperalgesia and decreased gray matter volume in key neural pain-processing regions. Although these findings suggest central pain amplification in endometriosis-associated chronic pelvic pain, the underlying changes in brain chemistry and function associated with central pain amplification remain unknown. A study recently performed proton spectroscopy and seed-based resting functional connectivity magnetic resonance imaging to determine whether women with endometriosis with chronic pelvic pain (n=17) and without chronic pelvic pain (n=13) display differences in insula excitatory neurotransmitter concentrations or intrinsic brain connectivity to other pain-related brain regions, as compared to age-matched healthy controls (n=24). Relative to age-matched pain-free controls, women with endometriosis-associated chronic pelvic pain displayed both increased levels of the excitatory neurotransmitter glutamate within the anterior insula and greater anterior insula connectivity to the medial prefrontal cortex. Increased connectivity between these regions was positively correlated with the excitatory neurotransmitter concentration and pain intensity. No significant differences were found in neurotransmitter levels or resting-state connectivity in endometriosis patients without chronic pain versus controls. These results support that, like other chronic pain conditions, endometriosis-associated pelvic pain is associated with altered brain chemistry and function in pain-processing regions. These findings support central pain amplification as a mechanism of chronic pelvic pain, independent of endometriosis, and clinicians could consider the use of adjunctive therapies that target central pain dysfunction in these women.

- **ORWH Objective 2.6:** Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas, such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery. (Note: This study only included women because endometriosis is a female-specific disease.)

Cardiovascular Disease

Estrogens regulate many essential physiological processes and are needed for the functional maintenance of numerous adult target tissues within and outside of the reproductive system. They can, however, have deleterious actions in promoting breast and uterine cancers. There is great medical need for estrogens with favorable pharmacological profiles that support desirable activities for menopausal women, such as metabolic and vascular protection, but that lack stimulatory activities on the breast and uterus. A study recently reported the development of structurally novel estrogens that preferentially activate a subset of estrogen receptor signaling pathways and result in favorable target tissue-selective activity. Through a process of structural alteration of estrogenic ligands that was designed to preserve their essential chemical and physical features while greatly reducing their binding affinity for estrogen receptors, the authors obtained “pathway preferential estrogens.” These chemicals elicited a pattern of gene regulation and cellular and biological processes that did not stimulate reproductive and mammary tissues or breast cancer cells. Furthermore, in ovariectomized mice, pathway preferential estrogens triggered beneficial responses both in metabolic tissues (adipose tissue and liver), reducing body weight gain and fat accumulation, and in the vasculature, accelerating repair of endothelial damage. This process of designed ligand structure alteration represents a novel approach to developing ligands that shift the balance in estrogen receptor-mediated extranuclear and nuclear pathways to obtain tissue-selective, non-nuclear pathway preferential estrogens, which may be beneficial for postmenopausal hormone replacement. The

approach also may have broad applicability for other members of the nuclear hormone receptor superfamily.

- **ORWH Objective 1.7:** Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs. Apply this knowledge to sex differences in disease prevalence, symptoms, management, and outcomes in conditions, such as lupus and cardiovascular diseases, and to such predominantly sex-specific diseases as breast cancer and uterine fibroids.

Inclusion of Women in Clinical Research

Menopause

Vasomotor symptoms (e.g., hot flashes, night sweats) are the most common and troubling symptoms associated with menopause. Although hormone therapy is the most effective treatment of these symptoms, it is associated with many side effects, thus many women seek alternative therapies. A recent study evaluated the short- and longer term effects of acupuncture on vasomotor symptoms among 209 perimenopausal and postmenopausal women ages 45 to 60 years. Participants were experiencing four or more vasomotor symptoms per day and were randomized to acupuncture for 6 months (up to 20 treatments) or wait-list control. The frequency of acupuncture treatments was determined by the licensed study acupuncturist and participant. Primary outcomes were frequency and severity of vasomotor symptoms, as assessed by daily diaries. Vasomotor symptom frequency and severity declined and was significantly improved in the acupuncture group versus the wait-list control group at 6 months, and the reduction in symptoms in the acupuncture group was largely maintained at the 12-month follow-up. Statistically significant clinical improvement was observed after three acupuncture treatments, and maximal clinical effects occurred after a median of eight treatments.

Because this study was designed as a pragmatic clinical trial, the lack of a time-and-attention control group precludes knowing to what extent nonspecific effects and the expectation of benefit may have influenced results. Future research can explore mechanisms of action. This study provides evidence that acupuncture can reduce vasomotor symptom frequency and severity.

- **ORWH Objective 3.8:** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

Osteoporosis

Postmenopausal estrogen depletion is a major contributing factor to bone loss. Adverse events related to hormone replacement therapy have prompted many to consider complementary and alternative treatments to reduce the risk of osteoporosis. Although some studies have shown evidence that soy isoflavones may prevent postmenopausal bone loss, the evidence has been mixed. It is possible that the specific isoflavone content or the capacity of individuals to convert isoflavones to equol (selective for estrogen receptors associated with the bone response) contribute to variable effects. A recent study sought to determine the effect of the equol-producing capability on bone calcium retention in postmenopausal women given various isoflavin mixtures using a double-blinded, randomized, cross-over design. Participants (n=24) were healthy women more than 4 years postmenopausal who all were screened at baseline for equol-producing capability. Five soy isoflavone interventions were administered in a randomized order for 50 days, followed by a 50-day washout between treatments. The main outcome variable was percentage of bone calcium retention. Results showed that equol-producing status did not influence bone calcium retention across any intervention. All five isoflavone treatments demonstrated improved bone calcium retention

with moderate effectiveness, and mixed isoflavones in their natural ratios were the most effective. The results show that soy isoflavones are an effective anti-absorptive therapy for postmenopausal women with minimal side effects and can be used long term for some protection against postmenopausal bone loss.

- **ORWH Objective 3.8:** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

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National Human Genome Research Institute (NHGRI)

Executive Summary

The National Human Genome Research Institute (NHGRI) dates back to 1989, when its preceding organizational entity, the National Center for Human Genome Research, was created to lead National Institutes of Health (NIH) efforts in the Human Genome Project (HGP). Since the 2003 completion of the HGP, NHGRI has funded and pursued genomics research to advance basic knowledge about how genomes function, discover the genomic underpinnings of health and disease, and facilitate the application of genomics to clinical care.

NHGRI pioneers the development and dissemination of new genomic technologies, which have consistently catapulted the field forward and dramatically increased the accessibility of genomic approaches in biomedical research. NHGRI's focus on technology development has had a positive effect not only on the immediate field of genomics, but also on the many disease-specific research efforts inside and outside of NIH, including those specific to women.

NHGRI also funds research that positively affects women in a more targeted manner, and NHGRI-funded research in fiscal years 15–16 has led to advances in disease areas specific to women's health (such as endometrial cancers) and issues affecting maternal and child health (such as prenatal genetic testing). Women represent more than half of the participants in NHGRI-funded human subjects research.

Women often are at the center of health-related decisionmaking in families and bear disproportionate psychosocial burdens associated with genetic testing and participation in genomics research. NHGRI has funded research and conducted outreach activities on the ethical and psychosocial aspects of participating in genomics

research through activities in NHGRI's Ethical, Legal, and Social Implications (ELSI) Research program and the intramural Social and Behavioral Research Branch.

Finally, NHGRI is committed to supporting the most qualified trainees and ensuring that our training programs are accessible to all. Approximately one-half of NHGRI's intramural and extramural trainees are women.

Intramural Research

Intramural researchers at NHGRI are studying the genomics of reproductive cancers, including endometrial cancer and breast cancer. One group recently found hypermethylation of the ZNF154 CpG island in 15 solid tumor types from 13 tissues and validated the signature in lung, stomach, colon, breast, and endometrium tumors. These findings indicate that the marker has potential as a pan-cancer indicator, which could be useful for screening through blood-based testing of circulating tumor DNA. Additional characterization of the utility of the marker is under way (Margolin et al., 2016).

NHGRI researchers also have participated in social and behavioral research with women. One study explored how providing family health history-based obesity risk feedback to 147 mothers with overweight children affected their levels of guilt. Those receiving this feedback felt more guilt than mothers who received more general information about behavioral risks. However, guilt was lower when mothers demonstrated healthy feeding behaviors in a virtual reality environment (Persky et al., 2015).

Population Architecture Using Genomics and Epidemiology (PAGE) Consortium

Genome-wide association studies, mostly in European populations, have identified many genetic variants related to disease, highlighting the need to further explore initial findings in non-European populations. PAGE is a consortium of U.S. studies that focuses on analyzing the relationship between genetic variants and a range of common diseases and traits. PAGE draws from as many as 100,000 study participants, including those from non-European ancestry groups, and examines replication, generalization, and variant discovery in non-European individuals. Beginning in 2011, PAGE focused on studying findings in non-European (African-American, Hispanic/Latino, Asian, and Native Hawaiian) populations. PAGE was renewed for a second round in 2013 to develop a new genotyping method that is tailored to non-European populations and to conduct new analyses spanning a broad range of diseases and characteristics.

Exonic variants and their relation to complex traits in minorities of the Women's Health Initiative (WHI)

This PAGE study (*U01 HG007376*) is using more than 40,000 samples from African-Americans, Hispanics, and Native Americans in the WHI to investigate the genetic basis of such common complex traits as cardiovascular disease, cancer, body composition, blood lipids, glucose, and insulin. They will use the newly developed ExomeChip genotyping platform tailored to non-European populations.

Ethical, Legal, and Social Implications (ELSI) Research Program

NHGRI's ELSI Research program was established in 1990 as an integral part of the HGP. The program's primary mission is to foster basic and applied research on the ethical, legal, and social implications of genomic research and medicine

for individuals, families, and communities. NHGRI dedicates at least 5 percent of its annual extramural research budget to support research focused on these issues, including ELSI issues related to the health of women. NHGRI currently is funding a number of projects that focus on ELSI issues related to noninvasive prenatal testing (NIPT), in which a maternal blood sample is used to screen DNA from the mother and fetus for chromosomal abnormalities, and prenatal testing in general.

Utah Center of Excellence in ELSI Research (UCEER)

The University of Utah Center for Excellence in ELSI Research (UCEER) (*P20 HG007249*) began in spring 2016 and focuses on population screening for genetic conditions in the health care of women and children, specifically prenatal genetic screening and newborn screening. Among its goals are to identify how aneuploidy screening information and choices are communicated to couples by providers and to use the Utah Population Database to describe rates of prenatal screening in the population of pregnant women in Utah.

Preparing for Emerging Applications of NIPT

This study (*R21 HG008511*) anticipates widespread adoption of NIPT in the near future and aims to ensure that informed consent practices and counseling are structured to meet the needs of expectant parents for the decisionmaking process. The study will describe the components of an effective informed consent process from the perspectives of pregnant women and partners. It also seeks to determine obstetric and genetic health care providers' perspectives on approaches and barriers to effect informed consent in this setting.

Goals and Practices for Next Generation Prenatal Testing

This study (*R01 HG008805*) also anticipates broader use of next-generation prenatal tests and is bringing together experts to draft analyses and recommendations for clinicians, researchers, and

policymakers, among others, on the ethical and effective use of these tests. The questions they address will include when and how next-generation prenatal tests should be employed, what policy needs exist in the field, and what empirical research needs to be performed.

Adoption of NIPT in Diverse Populations: A Multilevel Approach

The investigators on this project (*R21 HG009567*) aim to understand the use of NIPT among populations by socioeconomic status, race and ethnicity, and insurance coverage. They will use a health care database that covers all Massachusetts residents ages 18–64 and includes information on the entire spectrum of maternity care. The project will use its findings to identify the factors associated with uptake of NIPT to inform policymakers and other stakeholders of the inequities that may be arising with its use.

Education

NHGRI's Education and Community Involvement Branch (ECIB) encourages genomic careers and science exploration in young adults through a variety of science, technology, engineering, and mathematics (STEM) programming and pipeline enhancement activities. Many of these activities focus on encouraging young women and girls to explore opportunities in the sciences. For example, in 2015, ECIB hosted two female high school students from Ohio for a weeklong internship designed to explore genomic careers, public policy, and lab experiences. In 2016, ECIB hosted 10 middle school students from the *Every Girl Can Learn Institute* and 20 middle school students from the *Techbridge* program; these two organizations work with girls from underserved communities and provide experiences in possible STEM careers. For these visits, ECIB staff designed days that provided hands-on activities, lab tours, and introductions to genomic careers.

NHGRI Awards Receiving ORWH Administrative Supplements on Sex/Gender Influences

Two ongoing NHGRI awards have received supplemental funding to add analysis of sex as a biological variable to their funded projects. One of these projects, Drug Combination Signatures for Prediction and Mitigation of Toxicity (*U54 HG008098*), is part of the Common Fund Library of Network-Based Cellular Signatures program and is developing computational methods to predict adverse drug reactions and signatures of drug interactions. The supplement will allow the research team to model these interactions separately by sex to better predict sex-specific effects. The other, the NoVa Project (*R01 HG008133*), supports computational methods to integrate data sets related to gene and variant function to predict which variants cause differences in disease risk or other traits and to assess experimentally the accuracy of these predictions. In the course of this work, it was observed that a given RNA sequence can fold differently in male and female cells. Given this finding, the researchers were granted a supplement to characterize sex-specific differences in the transcriptome by profiling 50 multiethnic cell lines derived by the 1,000 Genomes Project.

CSER

NHGRI, with co-funding from the National Cancer Institute (NCI), began the Clinical Sequencing Exploratory Research (CSER) initiative to (1) leverage NHGRI's longstanding experience in genomic sequencing and analysis to ease the adoption of these methods into clinical care, (2) guide the development and dissemination of best practices for the integration of clinical sequencing into clinical care, and (3) research the ethical, legal, and psychosocial implications of bringing broad genomic data into clinical decisionmaking, including, for example, evaluation of the risks and potential benefits associated with the return of incidental findings or information on variants of uncertain effect. In line with these goals, CSER funds the

following ongoing project on clinical implementation of next-generation sequencing for carrier testing.

Clinical Implementation of Carrier Testing Using WGS

This project (*UM1 HG007292*) investigates the clinical implementation of carrier testing using whole genome sequencing (WGS) to aid reproductive decisionmaking in adults. The study population includes women and their partners requesting preconception testing for cystic fibrosis carrier status, as well as other conditions. The group is working on a variety of projects that address the outcomes associated with carrier testing using WGS, which variants should be reported to doctors and patients, and the ethical and psychosocial implications of expanded carrier screening. So far, the research team has created a taxonomy for patients to help women and their partners make decisions about the categories of disease they would like to learn about for reproductive decisionmaking. The research team validated this taxonomy tool by surveying 1,500 adult females who were Kaiser Permanente Northwest members and had received preconception genetic testing in the 3 years prior to this study (Leo et al., 2016).

Newborn Sequencing In Genomic medicine and public Health (NSIGHT)

Newborn screening programs currently screen more than 4 million U.S. infants per year, making that the most common form of genetic testing performed in the United States. Traditionally, DNA-based testing has not been a primary newborn screening methodology, but has been used for second-tier confirmation of the diagnosis for many newborn screening disorders for which molecular testing is available (e.g., cystic fibrosis). Genomic technologies have advanced dramatically over the past decade, however, to the point where the prospect of incorporating individuals' whole genome sequence information into their medical care is under serious discussion and careful study. The NSIGHT program, which began in 2013 and is jointly funded by NHGRI and the *Eunice Kennedy Shriver* National

Institute of Child Health and Human Development, features pilot research projects investigating the implications, challenges, and opportunities associated with the possible use of genomic sequence information in the newborn period. The intent of funding such projects is to further the understanding of disorders that appear during the newborn period and to improve treatments for these diseases.

NSIGHT currently funds four U19 cooperative agreement awards: (1) Genome Sequence-Based Screening for Childhood Risk and Newborn Illness (*U19 HD077671*, known as BabySeq), (2) Clinical and Social Implications of 2-Day Genome Results in Acutely Ill Newborns (*U19 HD077693*, known as Stat-seq), (3) Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening (*U19 HD077627*, known as NBSeq), and (4) NC NEXUS, North Carolina Newborn Exome Sequencing for Universal Screening (*U19 HD07763*). These groups are in the process of recruiting participants and conducting studies.

NSIGHT consortium grantees published a special supplement in *Pediatrics* that addressed the technological and ethical challenges that come with genomic testing in pediatric populations. This work informs pilot studies investigating the use of genomic information for newborn screening purposes, helping parents decide the type of genomic information they want to receive about their children (Lantos, 2016).

Recently, the four sites published a marker paper describing the consortium in *Pediatrics*. "Newborn Sequencing in Genomic Medicine and Public Health" examined some of the challenges of newborn sequencing in three distinct clinical settings (diagnostic, preventive, and predictive), described the four projects, and put the NSIGHT consortium's research in the context of current and future strategies for newborn screening and sequencing of newborns in the clinic (Berg et al., 2017).

Trans-NIH Initiatives

Because of the foundational and cross-cutting nature of genomics, NHGRI also is involved in several trans-NIH initiatives that have implications for women's health.

The Cancer Genome Atlas (TCGA)

The TCGA was initiated in 2006 as a collaborative program directed and funded jointly by NCI and NHGRI. TCGA investigators are generating the atlas of genomic and molecular changes present in the genomes of numerous cancers, including reproductive cancers, breast ductal and lobular carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma, endometrial carcinoma, and uterine carcinoma. TCGA data are made rapidly and publicly accessible to enable researchers anywhere in the world to make important discoveries (www.cancergenome.nih.gov).

Findings from TCGA have been important in understanding and treating female reproductive cancers. For example, a comprehensive genomic analysis of nearly 400 endometrial tumors suggests that certain molecular characteristics—such as the frequency of specific mutations—could complement current pathology methods and help distinguish between principal types of endometrial tumors, as well as provide novel insights into treatment strategies. In addition, the study revealed four novel tumor subtypes while also identifying genomic similarities between endometrial and other cancer types, including breast, ovarian, and colorectal cancers. Similar recent publications characterizing cervical and invasive lobular breast cancers provide important insights into their biology and potential treatments.

Insight into the Genetic Profile of Cervical Cancers

Recent work demonstrated striking APOBEC mutagenesis patterns and identified *SHKBP1*, *ERBB3*, *CASP8*, *HLA-A*, and *TGFBR2* as novel significantly mutated genes in cervical cancer. Novel

amplifications in immune targets and a lncRNA that has been associated with response to lapatinib also were observed. Human papilloma virus (HPV) integration was seen in all HPV18-related cases and in 76 percent of HPV16-related cases, and it was associated with structural aberrations and increased target gene expression. Researchers also identified a unique set of endometrial-like cervical cancers, comprised predominantly of HPV-negative tumors with high frequencies of *KRAS*, *ARID1A*, and *PTEN* mutations. Integrative clustering of 178 samples identified keratin-low squamous, keratin-high squamous, and adenocarcinoma-rich subgroups. These molecular analyses have revealed new potential therapeutic targets for cervical cancers.

Molecular Characterization of Lobular Breast Cancer

Invasive lobular carcinoma (ILC) is the second most prevalent histologic subtype of invasive breast cancer. Recent work identified mutations targeting *PTEN*, *TBX3*, and *FOXA1* as ILC-enriched features. *PTEN* loss was highest in ILC among all breast cancer subtypes. Spatially clustered *FOXA1* mutations correlated with increased *FOXA1* expression and activity. Proliferation and immune-related signatures determined three ILC transcriptional subtypes associated with survival differences. Mixed invasive ductal carcinoma (IDC)/ILC cases were molecularly classified as ILC-like and IDC-like, revealing no true hybrid features. This multidimensional molecular atlas sheds new light on the genetic bases of ILC and provides potential clinical options.

Knockout Mouse Phenotyping Program (KOMP2)

The Common Fund's KOMP2 provides broad, standardized phenotyping of a genome-wide collection of mouse knockouts. KOMP2 has led the way in ensuring reproducibility and ensuring transparency, as well as in considering sex as a biological variable in research. Each knockout is assessed for phenotype in both male and female cohorts of mice and all data are analyzed and

reported by sex. The researchers have found that 10 to 15 percent of phenotypes demonstrate sex differences, and a manuscript describing these sexual dimorphisms is in press at Nature Communications. As with other projects supported by NHGRI, KOMP2 provides a foundational resource that will provide important data for a vast array of projects concerning women's health.

Genomics Research in Africa: Human Heredity and Health in Africa (H3Africa)

As part of the Common Fund Global Health Initiative, in partnership with the Wellcome Trust, Human Heredity and Health in Africa (H3Africa) aims to facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases with the goal of improving the health of African populations. To accomplish this, the H3Africa Initiative is contributing to the development of the necessary expertise among African scientists and establishing networks of African investigators. Integrating research and training, the program funds several large research collaborations and smaller research projects investigating the genomic and environmental contributors to both communicable and noncommunicable diseases in Africa. NIH-funded projects cover a large range of diseases, including kidney disease, cervical cancer, tuberculosis, stroke, cardiometabolic diseases (CMDs), neurological disorders, respiratory diseases, fevers of unknown origin, trypanosomiasis, and schizophrenia. In addition, several projects look at the ELSI of genomics research in Africa, including cultural concepts and understanding, ethics of biobanking, public health interventions, and stigma. Finally, H3Africa encompasses the infrastructure necessary for genomics research, including biorepositories to enable future use of samples and a pan-African

informatics network to enable analysis of genomic-scale data. Several projects within H3Africa are focused on women's health issues and are discussed below.

The Role of the Microbiome in Cervical Cancer in Nigeria: The African Collaborative Center for Microbiome and Genomics Research

As part of H3Africa, NHGRI supports the African Collaborative Center for Microbiome and Genomics Research (ACCME) (*U54 HG006947*). ACCME was established to study the associations between the vaginal microenvironment, HPV genomics, and germline and somatic mutations in cervical cancer. The group has investigated the challenges and potential strategies to reduce cancer caused by co-infection of HPV in women who are HIV positive (Adebamowo, et al., 2014). Cervical cancer caused by HPV is a major contributor to women's preventable morbidity and mortality in Africa. In addition to contributing to knowledge about the complex vaginal microbiome, HPV persistence, and cervical carcinogenesis, ACCME also develops capacity by training postdoctoral students to become the new generation of African scientific leaders, while also empowering hundreds of African scientists to conduct research in microbiome and genomics.

Exploring Sex Differences in Genomic and Environmental Risk Factors for Cardiometabolic Disease in Africans

This Wits-INDEPTH (University of the Witwatersrand–International Network for the Demographic Evaluation of Populations and Their Health in Low- and Middle-Income Countries)

H3Africa Collaborative Centre (CC) (U54 HG006938) conducts projects that aim to study the genetic and environmental risk factors for obesity and related CMDs across four African countries—Ghana, Burkina Faso, Kenya, and South Africa—as well as an urban study site in Soweto (Johannesburg), South Africa. The study has examined the genetic architecture of these African populations and is investigating genomic contributions to body fat distribution, considering the relevant environmental and social contexts, to contribute to an understanding of CMD susceptibility. This project received supplemental funding to increase the power to examine sex as a biological variable in their cohort, given the clear sexual dimorphisms in several phenotypic variables, including age of onset.

Elucidating the Differential Gender Impact of Hereditary Neurological Disorders in the Malian Population

Hereditary neurological disorders are very disabling diseases that are understudied in Africa. This project (U01 HG007044) aims to clinically characterize these disorders in the Malian population, identify gene mutations related to neurological diseases, and explore their effects in cell culture models to further our understanding of their function and interactions and our knowledge of common disease mechanisms. Supplemental funding was provided to explore sex differences in these important and debilitating disorders.

Stigma in African Genomics Research

Another way that women are disproportionately impacted by hereditary disorders and genomic studies in many African populations, including the study in Mali, is that mothers often are held responsible for hereditary diseases of their children. In a cultural environment where women are often valued for their ability to produce healthy offspring, stigma associated with genetic disorders

often can result in severe societal and economic consequences for a woman who may or may not actually be a carrier, as well as for her family.

The H3Africa Ethics and Regulatory Working Group, the H3Africa Community Engagement Working Group, and a funded research project studying the Stigma in African Genomics Research on Schizophrenia and Rheumatic Heart Disease (U01 HG008226) are working on aspects of this issue to provide support to women, families, and communities to understand and manage hereditary risk factors and disorders in a way that reduces the burden of blame and stigma that often falls disproportionately to women.

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National Library of Medicine (NLM)

Executive Summary

The mission of the National Library of Medicine (NLM) is to acquire, organize, disseminate, and preserve the biomedical knowledge of the world for the benefit of the public health. Through advanced information systems, a cutting-edge informatics research portfolio, and extensive information dissemination partnerships, NLM plays a pivotal role in enabling biomedical research, supporting health care and public health, and promoting healthy behavior. Its National Center for Biotechnology Information (NCBI) serves as a national resource for molecular biology information, developing new information technologies to aid in the understanding of fundamental molecular and genetic processes that control health and disease. As the largest biomedical library in the world, NLM provides access to online information services that are used by millions of scientists, health professionals, and the public billions of times each year.

NLM research programs related to women's health and sex differences include medical informatics and bioinformatics approaches to diagnosis, treatment, prediction, and prevention of women's health conditions. Its information resource programs focus on enhancing access to and use of online health information systems that offer authoritative information related to women's health.

In Fiscal Year (FY) 15–16, NLM supported informatics and molecular biology research projects addressing Goal 2 of the Office of Research on Women's Health (ORWH) Strategic Plan, related to design and application of new technologies. Informatics research projects employed machine learning, clinical decision support, data mining, and advanced imaging tools to address diagnostic issues in breast and cervical cancer. For example, the goal of one extramural project was to develop a computational framework to identify biomarkers in triple-negative breast cancer (TNBC) from next-

generation sequencing data, which ultimately would allow clinicians to develop personalized treatment plans for women with this type of disease. In another project, intramural researchers developed advanced imaging tools for cervical cancer research that allow experts to mark boundaries on digitized images.

Molecular biology research projects addressed gene regulation, causal pathway analysis, and genome-wide associations (GWAS). For example, one extramural project sought new causal pathway discovery methods to improve understanding of molecular mechanisms that cause and control the development and progression of breast cancer. Another conducted GWAS studies on breast and lung cancer to gain new knowledge about their genetic basis. A third project developed data mining methods for analyzing molecular biomarker profile data, generating new experimental data for early detection of breast cancer.

Information resource projects address Objective 5 of the ORWH Strategic Plan related to communication and social networking technologies. Information portals that contain information directly related to women's health issues include: AIDSinfo and AIDSsource, HealthReach, the Health Services Research Information Center portal, and the HSRProj database for health services research projects in progress but not yet published. In addition, the LactMed® database, one of a suite of NLM resources related to chemicals and human impact of toxic chemicals, contains information on drugs and other chemicals to which breastfeeding mothers may be exposed.

Accomplishments and Activities

Highlighted on the next page are significant NLM research accomplishments related to women's health.

Breast Cancer

Computational Personalized Medicine Approach to Detect Biomarkers of Breast Cancer

Resistance (Goal 2, Objectives 2.5 and 2.7)

The objective of this study, titled “Novel integrative method to detect biomarkers of breast cancer resistance,” is to develop a computational framework, based on signal processing and machine learning techniques, to more accurately and efficiently identify novel cisplatin response candidate biomarkers in TNBC from next-generation sequencing data. Successful completion of this project will result in two important public health impacts: (1) candidate “response” biomarkers of cisplatin chemotherapy-responsive TNBCs, and (2) a computational approach supporting personalized medicine for TNBC. Furthermore, once established, this framework can be extended to the detection of biomarkers in other tumor types, and can contribute to improving the drug development process and the effectiveness of cancer care (Nabavi, 2016; Nabavi et al., 2016).

A Clinical Decision Support System for Making Personalized Assessments and Recommendations Concerning Breast Cancer Patients (Goal 2, Objectives 2.3 and 2.7)

Even a modest improvement in the efficacy of clinical decisionmaking has the potential to significantly improve patient outcomes and reduce health care costs. This project aims to develop a novel decision support system that utilizes both the clinical features and the genomic profile of a breast cancer patient to assist the physician in integrating information about a specific patient (e.g., diagnostic subtype, tumor stage and grade, age, comorbidities) to make therapeutic plans for the patient (Cai et al., 2016; Jiang et al., 2015a; Jiang et al., 2015b).

Detecting Genome-Wide Epistasis with Efficient Bayesian Network Learning (Goal 2, Objective 2.4)

Learning gene-gene interactions from GWAS data is an important and challenging task in genetic epidemiology. This project aims to develop and evaluate a pilot GWAS system for performing this task. Advances obtained in analyzing GWAS data sets could enable us to learn the genetic

basis of many diseases and thereby substantially improve the quality of personalized patient care. Specifically, the principal investigator proposes to conduct GWAS studies on breast cancer and lung cancer, with potential for providing important new knowledge about the genetic basis of these diseases of high relevance to women’s health (Jiang, 2016; Neapolitan et al., 2015).

Weighted Sampling Software Improves Mutual Exclusivity Analysis (Goal 2, Objectives 2.1 and 2.4)

Mutual exclusivity is a widely recognized property of many cancer drivers, including in breast cancer. Knowledge about these relationships can provide important insights into cancer drivers, cancer-driving pathways, and cancer subtypes. It also can be used to predict new functional interactions between cancer-driving genes and uncover novel cancer drivers. Most mutual exclusivity analyses are performed with a limited set of genes, in part due to the high computational requirements. To reduce the computing cost and perform less restricted mutual exclusivity analysis, the WeSME software uses a weighted sampling method to estimate p-values while controlling the mutation rates of individual patients and genes, similar to the permutation test. This type of comprehensive mutual exclusivity analysis allows uncovering many mutually exclusive pairs with relatively low mutation rates, which often have been missed in previous analyses. This method has been successful in providing support for the hypothesis that APOBEC activity is the underlying process that causes *TP53* mutations in a subset of breast cancer cases, as well as for identifying a set of related driver genes that are highly predictive of patient survival (Kim et al., 2016).

Integrating Machine Learning and Physician Expertise for Breast Cancer Diagnosis (Goal 2, Objective 2.5)

This project aims to develop clinical decision support tools that will integrate computerized data analysis techniques with physician expertise, resulting in a system that will estimate breast cancer risk from breast biopsy results more accurately than either the physician or the computer

alone. The researchers are testing a completely new methodology called Advice-Based-Learning, which establishes an innovative, collaborative cycle between computer learning and physician expertise. This cycle is expected to increase accuracy beyond what either the computer or human can accomplish alone. The project will result in a computerized decision tool that will estimate the probability of malignancy after breast biopsy more accurately than can current clinical practice. This will help address the challenges of delays in diagnosis and reduce unnecessary surgeries, and improve overall care for thousands of women with breast cancer and at risk for breast cancer (Benndorf et al., 2015; Ferreira et al., 2015).

Bayesian Rule Learning Methods for Disease Prediction and Biomarker Discovery (Goal 2, Objective 2.5)

This project is designed to develop highly needed data mining methods for analyzing the large number of data sets arising from high-throughput technologies for molecular biomarker profiling. It is generating new experimental data for early detection of breast cancer, and has the potential to help create new diagnostic screening tools for two of the most common cancers in the world—lung and breast cancers—and amyotrophic lateral sclerosis, a rare neurodegenerative disease (Gopalakrishnan et al., 2015; Pineda et al., 2015).

Gene Regulation in Metastasis and New Methods to Analyze its Microarray Profiles (Goal 2, Objective 2.4)

The goal of this project is to carry out an integrative study of tumor metastasis progression by analysis of gene expression, transcription regulation, and DNA copy number variation. Chromatin immunoprecipitation experiments with antibodies for key regulators of the epithelial-mesenchymal transition (EMT) are being performed to identify their target genes during tumor metastasis. New algorithms are being developed for analyzing perturbed gene expression profiles to build a regulatory subnetwork specific to the EMT process and identify other EMT regulators for further *ChIP*-chip experiments. The project is designed to

identify the DNA-binding sites of two key regulators of tumor metastasis (*Twist* and *Snail*), develop new algorithms to analyze perturbed expression profiles for reverse-engineering the regulatory subnetworks involving metastasis-related genes, and develop new algorithms to analyze array-based comparative genomic hybridization data for discovering DNA duplication and deletion events during tumor metastasis progression. This research has the potential of shedding new light on the process by which cancer cells spread throughout the body, and may contribute to development of new cancer therapies (Nogales-Cadenas et al., 2016).

Reproductive and Child Health

Elucidating the Role of the Genetic and Environmental Determinants of Preterm Birth Using Integrative Computational Approaches (Goal 2, Objectives 2.3, 2.4, and 2.7)

Given the wealth and availability of genomic and environmental exposure data, computational methods provide a powerful opportunity to identify population-specific determinants of disease. The goal of this proposal is to develop computational approaches to integrate diverse genetic and environmental exposure data sets to elucidate factors that affect disease in diverse populations and apply them to the study of preterm birth. The methodology developed as part of this project can be extended and applied to other phenotypes of interest and inform precise population-specific diagnostic and therapeutic strategies. This award was made in FY 16. (Grant Number: 1K01LM012381-01; University of California, San Francisco).

Women's Health—Advanced Medical Imaging Tools: Cervical Cancer Imaging Tools (Goal 2, Objective 2.5)

NLM intramural scientists are conducting several research and development activities that support women's health. One is to develop advanced imaging tools for cervical cancer research, including the Boundary Marking Tool (BMT), Virtual Microscope (VM), and the Teaching Tool (TT). The BMT is a system that allows experts to

mark boundaries on digitized images and record diagnostic or interpretive data that apply to these individual boundaries, or to the image as a whole. It has been used in multiple studies by the National Cancer Institute on the correlation between visual observations of the cervix and biopsy-based diagnoses. The VM provides Web access to digitized histology images for expert review and evaluation. Since these images tend to be very large, the VM incorporates technology to access and display only the part of the image that corresponds to the user's current pan and zoom level. The VM is used in studies of histology images of the uterine cervix. The TT is designed for teaching and training physicians in colposcopy—diagnosing cervical cancer from uterine cervix images. It allows the display of images alongside text that prompts the user for input related to the images. The typical use for the TT is to administer an exam or for self-training in this image-based medical discipline. The TT is used by the American Society for Colposcopy and Cervical Pathology at more than 100 institutions nationwide (e.g., Mayo Clinic) for administering their professional exams (Xu et al., 2017; Xu et al., 2015).

Standardization of Newborn Screening (Goal 2, Objective 2.3)

Of relevance to the health of women and families is newborn screening (NBS)—a complex public health program working to identify seemingly healthy infants who have serious conditions, begin treatment before they suffer significant disability or death, and in doing so, decrease the burden of disease on society. Until recently, most U.S. NBS programs and laboratories were not using coding standards or electronic methods to report NBS results to hospitals or other providers, and there was a gap in some coding standards when it came to NBS terms. NLM is working with multiple agencies to create new codes for NBS, as well as national guidance for standardization and electronic reporting of newborn screening results using HL7 messages that contain a prescribed set of Logical Observations Identifiers, Names, Codes (LOINC) and SNOMED CT codes, report quantitative test results, and use standardized units of measure. The standard terms and codes would allow NBS

programs to efficiently collect interoperable long-term follow-up data, and regional and national registries to improve screening and treatment protocols, all with the ultimate goal of improving patient outcomes (Abhyankar et al., 2015, PMID:PMC4433800).

NLM Highlights of Scientific and Related Organizational Activities

Discoveries from Clinical Data

Informatics Research for Women's Health (Goal 2, Objective 2.3)

Large database collections of clinical data—from longitudinal research projects, electronic health records (EHRs), and health information exchanges—provide opportunities to examine controversial findings from smaller scale clinical studies and to conduct retrospective epidemiological studies in areas that lack clinical trials. Given the importance of such databases to future research strategies, NLM has obtained access to and continues to gain research experience with MIMIC II and MIMIC III (deidentified longitudinal intensive care databases developed by the Massachusetts Institute of Technology) and the Centers for Medicare & Medicaid Services' Data Enclave. Study topics have included developing a method for extracting key maternal data from neonatal clinical notes, as well as treatment protocols for heart disease, dialysis, and liver function. This research aligns closely with the National Institutes of Health's (NIH) Big Data to Knowledge initiative and the data science efforts of the NIH and NLM (Rodriguez et al., 2016).

Responsive Additions to Health Data Standard Vocabularies for Women's Health Topics (Goal 2, Objective 2.3)

Electronic data capture using EHRs for clinical research, as well as clinical care and administrative purposes, requires clear vocabulary and definitions. NLM is the U.S. Department of Health and Human Services (HHS) coordinating body for clinical terminology standards, responsible for collaborating or working directly with clinical

terminology standards organizations for conditions (SNOMED CT) and laboratory tests and assessments (LOINC), as well as medications (RxNorm).

In FY 15 and 16, NLM and its partner standard development organizations assessed and, where needed, added or refined terms and codes to support more accurate data capture for a number of topics related to women's health, including pregnant women and newborns. These included new or revised clinical terminology to address the diagnosis, detection, and management of the Zika and Ebola viruses; clarification of concepts representing sex, gender, and identity; and terminology to support the routine clinical reporting by EHRs of key social and behavioral health indicators.

Women's Health Information Resources

AIDSinfo and AIDSsource Feature Women's Health Topics (Goal 5, Objective 5.1)

AIDSinfo (www.aidsinfo.nih.gov) is the HHS resource providing information on HIV/AIDS clinical trials and federally approved HIV treatment and prevention guidelines, information on HIV/AIDS treatment, clinical trials, and other HIV/AIDS-related research information for health care providers, researchers, people affected by HIV/AIDS, and the general public. AIDSinfo provides federally approved HIV/AIDS medical practice guidelines that include the use of antiretroviral agents in HIV-1-infected adults and adolescents, including information for HIV-infected women. AIDSinfo also provides guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents and a health topic on women that includes treatment resources, related conditions, prevention, clinical research, and more. (www.aidsinfo.nih.gov/hiv-aids-health-topics/357/women)

AIDSsource is a portal that provides current content that addresses the specific needs of women related to prevention, treatment, and living with HIV/AIDS, regardless of age. (www.aids.nlm.nih.gov/topic/1203/specific-populations/1228/women)

HealthReach: Multilingual Women's Health Resources (Goal 5, Objective 5.1)

HealthReach (www.healthreach.nlm.nih.gov) is a resource of multilingual and multicultural health information for those working with or providing care to women with limited English proficiency. HealthReach has materials in more than 40 languages and in multiple formats, including audio, video, and print. At the request of a partner, the Association of Health Refugee Coordinators, NLM funded the translation of the following women's health documents in print and audio formats:

- A Healthy Pregnancy www.healthreach.nlm.nih.gov/document/91/A-Healthy-Pregnancy
- Birth Control Methods www.healthreach.nlm.nih.gov/document/94/Birth-Control-Methods
- Having a Pelvic Exam and Pap Test www.healthreach.nlm.nih.gov/document/101/Having-a-Pelvic-Exam-and-Pap-Test
- Healthy Living Toolkit: Violence In the Home www.healthreach.nlm.nih.gov/document/122/Healthy-Living-Toolkit-Violence-In-the-Home
- How to Prepare for a Mammogram and Pap Test www.healthreach.nlm.nih.gov/document/118/How-to-Prepare-for-a-Mammogram-and-Pap-Test
- No One Has the Right to Hurt You, Even Someone You Love www.healthreach.nlm.nih.gov/document/120/No-One-Has-the-Right-to-Hurt-You-Even-Someone-You-Love

LactMed® for Breastfeeding Women (Goal 5, Objective 5.1)

The LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to ensure scientific validity and accuracy. LactMed® also is available as an app.

Developmental and Reproductive Toxicology Database (DART) (Goal 5, Objectives 5.1, 5.2, and 5.6)

DART provides more than 370,000 journal references covering teratology and other aspects of developmental and reproductive toxicology. DART is funded by the U.S. Environmental Protection Agency, the National Institute of Environmental Health Sciences, the National Center for Toxicological Research of the U.S. Food and Drug Administration, and NLM.

Dietary Supplement Label Database (DSLDD) (Goal 5, Objective 5.1)

DSLDD is a joint project of the NIH Office of Dietary Supplements and NLM and contains the full label contents from a sample of dietary supplement products marketed in the United States. The database contains more than 600 products for women and 39 dietary ingredient names for women.

Disaster Health Information Highlights Women's Health (Goal 5, Objective 5.1)

The Disaster Health Information program collects information on reproductive health and gender equality and violence against women in disasters and public health emergencies. For example, the Disaster Lit database (www.disasterlit.nlm.nih.gov/) lists more than 100 resources on women and Zika virus infection and more than 125 resources on gender issues. NLM also provides a Web page on "Health Resources: Pregnant Women in Disasters and Emergencies." (www.sis.nlm.nih.gov/dimrc/pregnantwomen.html)

Chemical Hazards Emergency Medical Management (CHEMM) and Radiation Emergency Medical Management (REMM) (Goal 5, Objective 5.1)

NLM's CHEMM and REMM tools provide information on "specific populations" that may have unique responses and/or needs compared to other populations during a chemical or radiation exposure event. This includes medical management information for pregnant women and their fetuses, infants, and children; seniors; populations with pre-existing disease(s) or conditions, such as being

immune-suppressed; and persons with a disability. (www.chemm.nlm.nih.gov/specialpops.htm and www.remm.nlm.nih.gov/specialpops.htm)

HSRProj Database: Captures Ongoing Health Research on Women and Families (Goal 5, Objective 5.1)

The HSRProj database (www.wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm) contains detailed information on health services research (HSR) projects in progress but not yet published; the database can be searched by researcher, funder, and topic and contains more than 32,000 project descriptions from the mid-1990s to the present, representing more than 350 funders of HSR. Health disparities and women's issues figure frequently in these research projects. Examples of such studies included in the database in 2015 and 2016 included—

- [Adverse childhood experiences in the parent generation: impact on family engagement and program efficacy of Maternal Infant Early Childhood Home Visiting \(MIECHV\)](#) (Record #HSRP20162029)
- [Reproductive health disparities and sexual orientation in girls and women](#) (Record #HSRP20154019)

HSRInformation Central (HSRIC) Added Domains Critical to Women's Health (Goal 5, Objective 5.1)

The HSRIIC database (www.nlm.nih.gov/hsrinfo/domestic_violence.html) is a Web portal for the health services research community. This resource contains topic pages that allow focused tracking and identification of high-quality grey literature, data sets, tools, and other resources in a particular domain, plus structured search strategies for PubMed and other resources. NLM recently added two new pages on critical domains related to women's health. In addition to the FY 15, development and launch of the Domestic Violence topic page, NLM similarly launched a Behavioral and Mental Health topic page (www.nlm.nih.gov/hsrinfo/behavioral_mental_health.html) in FY 16.

Outreach Projects Addressing Women's Health

United and Southern Eastern Tribes Partnership to Support Maternal and Family Health (Goal 5, Objectives 5.1 and 5.3)

NLM continued its partnership with the Tribal Epidemiology Center, United and Southern Eastern Tribes, Inc. (USET). USET is a strategic partner with NLM in increasing the awareness and utilization of NLM and NIH health resources and meeting NLM's long-range goals of improving health literacy, informing the American public, and reducing health disparities among vulnerable populations. In FY 16, NLM funded an information dissemination and health literacy outreach project focusing on women as the main information gatherer and health decision influencer in the family. The "Indian Peer-to-Peer Family Curriculum" project incorporates traditional parenting methods to improve pre- and postnatal care and strengthen the maternal role in the tribal community. The Florida State University Home Visiting Curriculum, a nationally recognized, research-based, practice-informed curriculum, was adapted to support traditional American Indian/Alaska Native parenting styles. USET worked with NLM to develop training materials, search strategies, and demonstrations for NLM and NIH online resources. There is growing evidence that nutrition, education, and fetal growth during pregnancy and early life can impact chronic disease and mental health in adulthood. The program is a step towards long-term impacts in Indian Country. The support groups will incorporate the use of NIH online materials to teach mothers and other family members how to access such important information as drug interactions, medication side effects, and various drug categories to ensure safe medication use while pregnant, nursing, and/or lactating. The project is ongoing.

AIDS Information and Outreach Projects for Women's Health (Goal 5, Objectives 5.1 and 5.3)

NLM continued funding for AIDS Community Information Outreach Projects in FY 15 and FY 16. This program provides support to community-based organizations, patient advocacy groups, faith-based organizations, departments of health, and libraries

for HIV/AIDS-related outreach efforts to design local programs that improve information access for HIV/AIDS patients and the affected community, as well as their caregivers. Several projects focused on women during this reporting period.

ACIOP FY 15 Black Girl Health: "HIV News Access"

Black Girl Health used social media to reach young, minority women by launching "HIV News Access," a mobile-friendly initiative on Facebook to increase the use of NLM HIV/AIDS prevention and treatment resources by the intended audience. Black Girl Health partnered with a regional health clinic that serves at-risk populations by providing substance abuse treatment and recovery services, as well as HIV prevention and treatment services. Black Girl Health developed an HIV/AIDS tutorial that was shared with social media users and utilized in a classroom setting.

ACIOP FY 16 Black Girl Health: "Pop the Question"

"Pop the Question" is an outreach project designed to increase the knowledge of HIV/AIDS by using social media to connect black and Hispanic women to NLM online resources and testing services offered by a local health clinic. To accomplish this goal, Black Girl Health plans to develop and launch a social media video campaign through a short-form video sharing service. The video will communicate NLM HIV/AIDS resources and promote HIV testing. Black Girl Health will evaluate the impact of the video campaign by partnering with a health clinic located in Harrisburg, Pennsylvania, to measure the increase in HIV testing in the focus demographic. The project builds on a prior successful NLM project and an existing relationship with the clinic. The clinic established a popular Facebook page to disseminate NLM articles and build HIV/AIDS awareness among minority women. They also developed a tutorial to be used in a classroom setting.

Youth Technology Health (YTH): "TRANSCONNECT"

TRANSCONNECT is a user-centered, design-based mobile application to reduce health disparities faced

by transgender youth (TGY) and young adults, ages 16–28 years. The application will increase availability, access, and utilization of critical HIV prevention information and resources from NLM for TGY and TGY-serving providers. TRANSCONNECT builds upon YTH's 16 years of successful HIV/AIDS education and outreach to minority youth and their providers through the design and implementation of a unique trauma-informed mobile app that addressed the HIV prevention needs of TGY while addressing the additional sexual, mental health, and social needs (e.g., housing, employment, transportation) that TGY face in their everyday lives. The app will offer a providers' module that supports service providers who engage with TGY. It will allow providers to take a comprehensive sexual and social history, access resources/guidelines, and provide services and referrals in a TGY-competent manner. All TRANSCONNECT elements will drive traffic to NLM's HIV/AIDS information resources.

Exhibitions on Women's Health Topics (Goal 5, Objective 5.1)

In FY 15, NLM opened [Confronting Violence: Improving Women's Lives](#), an exhibit examining the origins of activism by nurses and others in the United States to assist abused women and address the health impacts of abuse. In FY 16 another exhibit, [Fire and Freedom: Food and Enslavement in Early America](#), opened. This exhibit addresses how power is exchanged between and among different peoples, races, genders, and classes. NLM's many and diverse traveling exhibits extend the reach and impact of its [historical collections and resources](#) throughout the United States.

Inclusion

Enabling Discovery from Clinical Data for Research and Practice: Common Data Elements Related to Sex and Gender (Goal 2, Objective 2.3)

NLM chairs the trans-NIH Clinical Common Data Elements Task Force of the NIH Scientific Data Council, which encourages the development and use of well-specified human and machine-readable definitions of variables to be collected and analyzed for clinical care, research, patient registries, and surveillance studies. In FY 15–16, variables related

to sex and gender were a continuing priority, as were specific tests and assessments relevant to women's health issues.

ClinicalTrials.gov Enhances Capabilities Related to Women's Health Data (Goal 2, Objective 2.3)

NIH issued a Final Rule on Clinical Trials Registration and Results Information Submission on September 16, 2016 (42 CFR Part 11). The Final Rule details the requirements for submitting registration and summary results information for specific clinical trials of drug and device products to ClinicalTrials.gov, the clinical trial registry and results data bank operated by NLM. The rule expands the submission requirements specified in Title VIII of the FDAAA and requires a breakout of participants by sex for all applicable clinical trials. An associated NIH policy requires breakout data by sex for all NIH-funded clinical trials. ClinicalTrials.gov is designed to enable the reporting of clinical trial results by sex, in compliance with FDAAA and NIH policies.

NLM STEM Efforts (Goal 6, Objective 6.1)

NLM's NCBI worked with the Society for Canadian Women in Science and Technology to help them set up their first "hackathon," which was scheduled for October 2016 at the annual meeting of the American Society of Human Genetics.

An NLM intramural scientist participated in a Women in Government meeting consisting of a select group of Federal agency personnel, including Megan Smith, the U.S. Chief Technology Officer in the Office of Science and Technology Policy. The session involved seeking ways to encourage women to enter Government positions in science and technology. Examples of specific suggestions presented include partnering with the Anita Borg Institute and key governmental organizations to effectively highlight Federal research programs at major conferences and fairs, with the aim of attracting women with science and technology backgrounds into the Federal service.

NLM scientists actively participated in the Grace Hopper Celebration of Women in Computing event in Houston, Texas. In addition to such notable speakers as Ginny Rometty, President and CEO of IBM, the breakout sessions included career panels

and workshops organized to inspire, inform, and encourage women to pursue careers in computing, science, and technology. This provided CBB staff the opportunity to meet with undergraduate and graduate students in computer science (some from the nearby Universities of Maryland and Delaware) and encourage the students to consider the programs of NCBI and NLM in their future careers.

NLM scientists have specifically looked to mentor female students. For example, in summer 2015, one group mentored a female student in computational biology. The student was recognized as an Intel Science Talent Search semifinalist for research done in the group.

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Office of Behavioral and Social Sciences Research (OBSSR)

Executive Summary

Situated within the Office of the Director's Division of Program Coordination, Planning, and Strategic Initiatives, the National Institutes of Health (NIH) Office of Behavioral and Social Sciences Research (OBSSR) furthers the mission of the NIH by emphasizing the critical role that behavioral and social factors play in health, health care, and well-being. As a coordinating office, OBSSR serves as the focal point for the coordination and development of policies, goals, and objectives in the behavioral and social sciences at the NIH, but does not hold or administer any grant awards, only co-funding to the 27 NIH Institutes and Centers. In Fiscal Years (FY) 15 and 16, OBSSR co-funded many grants and initiatives with a women's health focus, particularly the behavioral and social sciences aspect of gender and health, health disparities, inclusion of women in clinical research, women in biomedical science careers, trauma, and sex and gender influences in health and disease.

Communications and Education Initiatives

In FY 15–16, OBSSR promoted women's health research, research results, and training initiatives through our communication channels, such as blog posts, social media, and newsletters:

- Hosting several blog posts on research developments regarding behavioral and social health and the role gender and sex as a biological variable plays in research and health outcomes.
- Advertising events and workshops concerning women's health and behavioral and social sciences.

- Linking to our sister office, the Office of Research on Women's Health (ORWH) for relevant events and research results.

Funding

Behavioral and social sciences research

OBSSR supported and continues to support research in women's health in the area of behavioral and social science. Examples include research on mindfulness and its relationship with age-related cognitive decline (R01AG049369) and research on the basic biobehavioral mechanisms on personality and health in midlife (R01AG056043). Additionally, OBSSR helped support research on prenatal and postpregnancy influences, particularly social interactions and behaviors concerning weight gain and smoking (R21HD087734, R01HD073237, R01HL119245, and R21CA198036).

Health disparities

Knowledge of demographic differences among women helps to better understand sociological and biological factors of health. OBSSR has supported research regarding health disparities in fertility (R01HD075560), breast cancer among different populations (R03CA193078, R03TW009406, R03CA178763), and alcohol use (R01AA024127).

Inclusion of women in clinical research

A key to effective, robust, and useful research is to ensure women of all ages are included in clinical trials. OBSSR supports several initiatives that aim to include women in clinical trials. OBSSR participated in the planning of the clinical trial, PregSource, hosted at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. PregSource will both provide and gather data for currently pregnant women to better understand their experiences of pregnancy. Additionally, OBSSR supported several grants on

women in clinical trials, including MsFLASH, a clinical trial on menopause (R01AG048209). OBSSR continues to support trainings and workshops on methods and measurement infrastructure, with the goals of developing novel and reproducible clinical trials and sampling of research participants. New approaches improve inclusion of women across the lifespan into clinical research.

Women in biomedical science careers

During FY 15–16, OBSSR developed a new Strategic Plan for 2017–2021, which identified training the next generation of behavioral and social scientists, both internal and external to the NIH, as a foundational process to which OBSSR contributes. OBSSR actively supported research detailing the behavioral and social science workforce, including gender differences in the workforce (U01GM094141). OBSSR also supported training awards for community-based participatory research for breast cancer through a program called *Quick Start* (R25CA188482). Additionally, OBSSR and its staff have been involved in mentoring and communications efforts for women in biomedical science careers. In June 2016, OBSSR staff served as roundtable mentors for ORWH's Building Interdisciplinary Research Careers in Women's

Health Program Meeting, and hosted a panel titled “Women in Science: Tales and Trajectories” at Real Life, Labs, Research: Matilda White Riley Day, where four women with distinguished careers in health research presented on their career achievements and offered advice for women researchers in the audience.

Trauma

During FY 15–16, OBSSR continued to support awards regarding understanding trauma manifestation and treatment among women, particularly regarding posttraumatic stress disorder and sexual assault (R01AR064700).

Sex and gender influences in health and disease

Many health and disease issues affect the sexes differently, and recently, OBSSR has been contributing to awards in understanding prevention and treatment of these diseases. One disease that affects women more often than men is urinary tract infections; OBSSR co-funded this effort through the Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Scientific and Data Coordinating Center (U01DK106786).

Office of Disease Prevention—Office of Dietary Supplements (ODP-ODS)

Executive Summary

The Office of Dietary Supplements (ODS) was created in 1995 in the Office of Disease Prevention, Office of the Director, National Institutes of Health (NIH), to meet the requirements of the Dietary Supplement Health and Education Act (DSHEA) of 1994. DSHEA defined the purposes and responsibilities of ODS as follows:

Purposes

- To explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care.
- To promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions.

Responsibilities

- To conduct and coordinate scientific research within the NIH related to dietary supplements and the extent to which the use of dietary supplements can limit or reduce the risk of diseases.
- To collect and compile the results of scientific research related to dietary supplements, including scientific data from foreign sources.
- To serve as the principal advisor to the Secretary and to the Assistant Secretary for Health and provide advice to the Director of the NIH, the Director of the Centers for Disease Control and Prevention (CDC), and the Commissioner of the Food and Drug Administration (FDA) on issues related to dietary supplements. These issues include dietary intake regulations, the safety of dietary supplements, the claims characterizing

the relationship between the use of dietary supplements and the prevention of disease or other health conditions and the maintenance of health, and scientific issues arising in connection with the labeling and composition of dietary supplements.

- To compile a database of scientific research on dietary supplements and individual nutrients.
- To coordinate funding relating to dietary supplements for NIH.

Subsequent congressional mandates directed ODS to develop a botanical research center initiative (1999), conduct evidence-based reviews of the efficacy and safety of dietary supplements (2001), accelerate the validation of analytic methods and reference materials for dietary supplements (2001), and support the development of a dietary supplement label database (2004).

ODS developed its mission statement as part of its first strategic planning process in 1998. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

Initiatives

ODS Extramural Investments

ODS' guidelines and criteria for initiating, expanding, or otherwise modifying its extramural investments have reflected DSHEA and Congressional mandates. These guidelines are a response to gaps in scientific knowledge, opportunities for research relevant to dietary supplements, requests for research support from investigators, requests for information, and available resources. ODS extramural investments

are categorized into four broad areas: (1) research support, (2) research tools, (3) communications, and (4) science-policy interactions.

The Office's key activities are grouped into 15 programs under these four areas (see below); these 15 programs capture most of ODS' activities. In Fiscal Year (FY) 16, the ODS budget was \$25.3 million, with \$21.3 million of that amount awarded to research projects, including grants, contracts, and interagency agreements.

Communication and science policy efforts rely heavily on investments of ODS staff time and expertise rather than direct funding. An ODS staff member is responsible for overseeing each of the 15 ODS programs that supports extramural research, and most ODS staff members are active in more than one program. Each program interacts with one or more stakeholder community, including researchers; educators and teachers; health practitioners; research and educational institutions; agencies of the Federal Government; dietary supplement, food, and related industries; media; consumer, and public interest groups; and members of the public. The four areas and 15 programs are described briefly below.

Area 1: Research Support

Research Grant Portfolio. This portfolio consists of grants administered by NIH Institutes and Centers that receive funding from ODS for research components related to dietary supplements. This investment supports the development of new knowledge on the health effects of dietary supplements.

Botanical Dietary Supplement Research Centers (BDSRCs). ODS currently supports three BDSRCs and two Centers for Advancing Natural Products Innovation and Technology (CANPIT) in response to a Congressional mandate. The Office administers these Centers (which together comprise the NIH Centers for Advancing Research on Botanicals and Other Natural Products, or CARBON Program) in partnership with the National

Center for Complementary and Integrative Health (formerly the National Center for Complementary and Alternative Medicine). These Centers expand the scientific base for botanical dietary supplements with a strong focus on those used by postmenopausal women, and have participated in the ODS Analytical Methods and Research Materials Program. These Centers also train new transdisciplinary dietary supplement researchers and the BDSRC support pilot project programs to foster innovation in botanical dietary supplement research. The CANPITs are mandated to actively work to disseminate both the innovative methods they are charged with developing and discipline-specific “good practices” critical to research reproducibility.

Training and Career Development. These extramural investments consist primarily of co-funding for selected NIH research training and career grants. These grants enable junior scientists to develop research programs related to dietary supplements. In addition, ODS each year organizes the Mary Frances Picciano Dietary Supplements Research Practicum. The Practicum offers a multiday opportunity for faculty, students, and practitioners to acquire a broad, fundamental understanding of dietary supplements. The 2017 Practicum will be filmed and broadly made available.

Conferences and Workshops. ODS funds research conferences and workshops, primarily through NIH grant mechanisms, although it also supports conferences and workshops initiated by the NIH. These conferences and workshops bring together key scientists to discuss and define the research needs for various dietary supplements. In 2015, ODS supported a workshop titled “[Options for Consideration of Chronic Disease Endpoints for Dietary Reference Intakes \(DRIs\)](#),” to gather expert input on research needed to support the use of chronic disease endpoints, related, for example, to metabolic syndrome or osteoporosis, in developing DRIs. In 2016, ODS contributed to a workshop titled “[Addressing Challenges in Assessing Botanical Dietary Supplement Safety](#).” Dietary supplement

use is most prevalent among women in the United States, and in 2016, ODS also supported a conference on “Iron Screening and Supplementation of Iron-Replete Pregnant Women and Young Children.”

Area 2: Research Tools

Analytical Methods and Reference Materials.

ODS established this program in response to a Congressional mandate and administers it primarily through contracts originated by ODS. Supporting the development of analytic methods and reference materials for dietary supplements has been key to making informative studies of dietary supplements possible.

Surveys of Dietary Supplement Use. ODS provides intellectual and financial support to Federal agencies conducting national nutritional surveys that include use of dietary supplements. As part of this effort, the Population Studies Program focuses on the evaluation of dietary supplement use, including the assessment of biological measures of supplement exposure and associated health effects in nationally representative populations, to evaluate nutrients of concern for inadequacy or excess. In collaboration with other Government agencies and academia, the efforts of this program are building our capacity to analyze population data (including economic cost), such as those from the National Health and Nutrition Examination Survey, and will serve as a training environment for postdoctoral fellows.

Dietary Supplement Databases. ODS provides intellectual and financial support and leadership to Federal agencies that are establishing databases to enable the interpretation of survey data on public nutrition habits and use of dietary supplements. ODS and its Federal partners at the U.S. Department of Agriculture, CDC, the National Library of Medicine (NLM), and FDA have created a data set of dietary supplement ingredients (the Dietary Supplement Ingredient Database) and

a comprehensive database of information on supplement labels (the Dietary Supplement Label Database).

Evidence-Based Reviews. In response to encouragement from Congress, ODS provides intellectual and financial support, primarily to the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, to conduct reviews that are critical to determining the research needs for selected dietary supplements. These reviews are published on the AHRQ website and in peer-reviewed journals. Evidence-based reviews are key to identifying the status of scientifically validated knowledge about dietary supplements and the important gaps in research. ODS recently sponsored evidence based-reviews with relevance to women’s health through the AHRQ Evidence-Based Practice Center Program:

1. The Effects of Omega-3 Fatty Acids on Health Outcomes in Children
2. An update of the 2009 evidence report, “Vitamin D and Calcium: Systematic Review of Health Outcomes.”

Area 3: Communications

Communications. ODS’ communication activities include a broad spectrum of outreach activities, such as the ODS website, Twitter feed, and public information pieces in three versions—one for health care professionals and two for consumers, one in English and one in Spanish—related to dietary supplements.

Computer Access to Research on Dietary Supplements (CARDS). ODS developed this consumer-friendly, Internet-based database in response to the DSHEA mandate to compile a database of scientific research on dietary supplements. CARDS contains information on federally funded research projects pertaining to dietary supplements.

PubMed Dietary Supplement Subset. ODS and NLM partnered to create this Dietary Supplement Subset of PubMed. The subset is designed to limit search results to citations from a broad spectrum of dietary supplement literature, including vitamin, mineral, phytochemical, ergogenic, botanical, and herbal supplements in human nutrition and animal models.

Federal Dietary Supplement Working Group. ODS established the Federal Dietary Supplement Working Group in 2005 to share information and discuss issues related to dietary supplements among Federal agencies.

Area 4: Science-Policy Interactions

These programs reflect the philosophy that good policy is founded on good science. ODS furnishes expertise in nutritional sciences to address public health issues related to dietary supplements.

Nutrient Initiatives. ODS leads and sponsors several efforts to advance scientific understanding of the importance of vitamin D to health. These efforts have included: (1) measurement of vitamin D levels in foods, (2) assessment of vitamin D status of the U.S. population, (3) development of a reference measurement procedure and standard reference materials to precisely measure this nutrient, (4) systematic review of scientific literature used in updating the vitamin D recommended dietary allowances and safe levels of intake, and (5) an international effort to standardize measurement of serum vitamin D levels in populations around the world (Vitamin D Standardization Program). Through initiatives on folate and iodine, ODS and other Federal partners are examining the efficacy and safety of the relevant fortification programs in the United States.

Dietary Supplement Use in the Military. This partnership with the U.S. Department of Defense is evaluating the impact of dietary supplement use by military personnel.

Dietary Reference Intakes. ODS supports Federal programs to evaluate the reference standards for intakes of nutrients, including vitamins and minerals.

ODS Strategic Plan

Goal 1: Expand the scientific knowledge base on dietary supplements by stimulating and supporting a full range of biomedical research and by developing and contributing to collaborative initiatives, workshops, meetings, and conferences.

Goal 2: Enhance the dietary supplement research workforce through training and career development.

Goal 3: Foster development and dissemination of research resources and tools to enhance the quality of dietary supplement research.

Goal 4: Translate dietary supplement research findings into useful information for consumers, health professionals, researchers, and policymakers.

Grant Funding—Research on Women’s Health

FY 15: \$2,127,458

- Botanical Dietary Supplements for Women’s Health
- Botanical Estrogens: Mechanisms, Dose, and Target Tissues
- Cardiovascular Protection by Phytosterols in Dyslipidemic Mothers and Progeny
- Mechanistic Basis of Probiotic Prevention of Osteoporosis
- The Global Network and Preconception Maternal Nutrition
- Prevention of Estrogen-Mediated Mammary Carcinogenesis by Mixtures of Tocopherols
- Trial of Vitamin D Supplementation and Neuromuscular Function in Older Adults

- Determinants and Consequences of Low Vitamin D in Populations of African Descent
- Established Investigator Award Anti-Inflammatory Exposures in Cancer Prevention

FY 16: \$2,144,746

- Botanical Chemicals and Ovotoxicity
- Botanical Dietary Supplements for Women's Health
- Cardiovascular Protection by Phytosterols in Dyslipidemic Mothers and Progeny
- Docosahexaenoic Acid Supplementation in Pregnancy to Reduce Early Preterm Birth
- Prevention of Estrogen-Mediated Mammary Carcinogenesis by Mixtures of Tocopherols
- The Global Network and Preconception Maternal Nutrition
- Obesity, Body Fat Distribution, and Cancer Risk in the Multiethnic Cohort
- Trial of Vitamin D Supplementation and Neuromuscular Function in Older Adults
- Mechanistic Basis of Probiotic Prevention of Osteoporosis
- Exploring the Fuel-Mediated Programming of Neonatal Growth

ORWH Strategic Plan Goals and Objectives

Many of the awards co-funded by the ODS in FY 15 and FY 16 further ORWH's Goal 2, in particular, objectives 2.1, 2.2, 2.3, 2.5, and 2.7.

- 2.1. Encourage the development of technologies that will address sex-based differences at all scales of detail, from the nanometer to the whole person.
- 2.2. Develop novel animal, *in vitro*, and computational (virtual) models to study sex differences in diseases and conditions.
- 2.3. Develop the information systems needed for collecting, sharing, and comparing clinical data for diseases and conditions of women and girls.
- 2.4. Develop computational models that will utilize multiple levels of analyses to address both qualitative and quantitative outcomes of clinical research related to women.
- 2.5. Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.
- 2.7. Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

Office of Research Infrastructure Programs (ORIP)

Division of Program Coordination, Planning, and Strategic Initiatives

Executive Summary

Established in December 2011, the Office of Research Infrastructure Programs (ORIP) is located within the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), NIH Office of the Director (OD). ORIP brings together research activities managed by the Division of Comparative Medicine (DCM), the Division of Construction and Instruments, and the Office of Science Education, which is home to the Science Education Partnership Awards (SEPA) Program. ORIP's overall mission is to provide research infrastructure, research-related resource programs, and coordination of NIH's science education efforts. ORIP's infrastructure programs are trans-NIH in nature and align with DPCPSI's mission to ensure that NIH effectively and efficiently addresses and coordinates important areas of emerging scientific opportunities to improve human health.

ORIP stimulates innovation and leverages shared resources to—

- Develop and provide access to critical animal models, including those relevant to women's health.
- Provide access to state-of-the-art technologies and instruments that enable biomedical research and clinical investigations of a multitude of health issues, including those of consequence to women and girls.
- Explore strategies for consideration of sex differences in animals and cell lines used in NIH-funded studies as a means of enhancing the experimental design and increasing reproducibility in preclinical research in women's health and other research disciplines.
- Train veterinarian-scientists to become valuable partners in an integrated, multidisciplinary approach to biomedical/translational research.

- Provide funding to upgrade existing animal research facilities to conduct studies critical to human health.
- Improve public understanding of medical research and provide adults and children with information about healthy living and science career opportunities, including issues of importance to women and girls.
- Plan, develop, and coordinate comprehensive science education programs across the NIH to strengthen and enhance NIH's efforts to attract young people, especially girls and underrepresented minorities, to biomedical and behavioral science careers and to improve science literacy in adults and children.

Research on women's health utilizes many of the animal models supported by ORIP, from invertebrates, such as worms and fruit flies, to vertebrates, such as fish and mammals, including rodents, swine, and nonhuman primates (NHPs). This report highlights one featured program from ORIP, the National Primate Research Centers (NPRCs), which supports the implementation of the first three goals of the NIH Strategic Plan for Women's Health Research. This report also provides an overview of ORIP's accomplishments and activities within its broad-based research portfolio on women's health, including research on the impact of such diseases as HIV/AIDS and cardiovascular disease on women's health, the neurosciences, sex differences, the microbiome, reproductive health, puberty, and behavior.

Included within this report are highlights of ORIP's initiatives to enhance education and diversity of the future biomedical workforce through training and mentoring programs that focus on veterinary students and veterinarians and precollege science, technology, engineering, and mathematics (STEM) educational programs focusing on girls, underrepresented minorities,

and underserved communities. In addition, this report describes several ORIP-sponsored initiatives, including program announcements, conferences, and workshops with a focus on women's health and related trans-NIH research and training programs.

NIH Strategic Plan for Women's Health Research

This section highlights NPRCs, one featured ORIP program that supports the implementation of the NIH Strategic Plan for Women's Health Research.

NPRCs

Monkeys provide critical models for understanding many issues related to the health of all humans, including areas specific to women and girls and areas where it is important to study the difference between males and females. Of all widely available animal models, monkeys are closest to humans in physiology, behavior, and genetic relatedness. Furthermore, the environment and diet of monkeys can be controlled rigorously, thus eliminating variables that often confound preclinical research in humans.

NIH awarded support more than 55 years ago for the NPRCs to facilitate the use of NHPs for basic and translational research related to human health. The NPRCs were established as it is neither cost-effective nor feasible to duplicate these specialized facilities at every institution. Collectively, the seven NPRCs facilitate more than 1,000 individual projects involving more than 1,400 researchers per year. Each NPRC is a national resource and can accommodate the needs of a researcher located anywhere in the United States. The NPRCs support research projects funded by all NIH Institutes and Centers, as well as scientific foundations and other research entities. The NPRC Research and Capabilities website (www.nprcresearch.org/primate) provides comprehensive information for researchers and the public regarding the range of available NPRC programs, resources, and achievements.

ORIP's Division of Comparative Medicine manages NPRC activities aligned with three of the ORWH/NIH Strategic Plan Goals and Objectives described below.

Goal 1: Increase sex differences research in basic sciences studies. Studies using systems biology-based approaches, such as DNA and RNA sequencing and proteomic analysis, are performed at the NPRCs to enable a better understanding of sex differences at the genetic and molecular levels (Objectives 1.1, 1.3, and 1.8). For example, monkeys exhibit many of the same behaviors as humans, including those related specifically to the well-being of women and girls. Female monkeys living in large groups experience varying levels of social stress, depending on the dominance status of the particular female. The effects of stress on female physiology and gene expression are studied at the NPRCs, as is the impact of controlled diet and caloric intake. This permits analysis of the differential effects of maternal nutrition on female versus male fetuses, which also can lead to differences in newborn and neonatal health. The sophisticated molecular analysis is being used to understand the genes and physiological processes in the fetus and placenta that are affected by maternal nutrition.

Goal 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs. Female monkeys can serve as an animal model of many diseases and conditions that women experience, including diabetes, endometriosis, polycystic ovary syndrome (PCOS), HIV/AIDS, and Zika virus (ZIKV) infection. For example, a major priority in HIV/AIDS prevention is the development of new devices or therapies that give women personal control (Objective 2.7). The NPRCs have pioneered many studies using a monkey model of human AIDS, which involves analysis of animals infected with simian immunodeficiency virus (SIV), the monkey analog of HIV. In addition to testing strategies for AIDS vaccines, the NPRCs have supported the development and testing of potential microbicides, compounds that women can use as

a vaginal preparation to decrease acquisition of HIV. Other research avenues include prevention of maternal transmission of AIDS to infants and examination of the pathobiology of ZIKV infection on the developing fetus.

Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women. The NPRCs conduct studies on all aspects of the female reproductive cycle, as most aspects of the female reproductive life cycle are the same in monkeys and humans, including fertility, conception, pregnancy, and menopause. NPRC investigators are developing novel nonsurgical contraceptives, exploring epigenetic control of puberty, and studying the effects of various hormones on menopausal transition, with the aim of describing and ultimately finding new treatments for weight gain, loss of libido, metabolic syndrome, and cardiovascular disease that some women experience as a result of menopause (Objective 3.1). Studies in pregnant monkeys evaluate disease impact on the developing fetus and provide the groundwork for developing safe and effective interventions in pregnant women (Objective 3.3).

The projects described above are just a few examples of the many studies related to women's health that are performed at the NPRCs.

Accomplishments and Activities

This section provides an overview of ORIP's accomplishments and activities within its broad-based research portfolio on women's health research.

Disease

HIV/AIDS: Treatment of HIV-exposed newborns with antibodies to clear the infection.

In the developing world, HIV infection in newborns and children is almost exclusively due to mother-to-child transmission (MTCT) from HIV-infected mothers. Although screening of pregnant mothers and access to antiretroviral drugs has reduced

MTCT in the United States to less than 1 percent, babies continue to be infected by HIV in resource-poor areas (Hessell et al., 2016). Researchers at the Oregon NPRC have been studying the potential of treating exposed newborns with potent human neutralizing antibodies (Hessell et al., 2016; Pegu et al., 2017). These researchers have used a rhesus monkey model of oral infection of newborns with simian HIV (SHIV) to model MTCT. In this model, SHIV infection can be detected in lymph tissue as early as 1 day after oral exposure, with the virus spreading rapidly to nearly all tissues. Scientists tested a cocktail of purified human monoclonal antibodies given after SHIV exposure and observed that treated animals cleared the infection even after the treatment antibodies were no longer detected. These data have exciting implications as a potential cure for HIV infection in babies born to infected mothers. (Funded by OD/ORIP, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NICHD], and the National Institute of Allergy and Infectious Diseases [NIAID].)

HIV/AIDS: Mechanisms of vaginal HIV transmission and effects of hormones.

More than half of HIV-infected patients are women, and vaginal HIV transmission accounts for more than 70 percent of all new infections worldwide. In collaboration with bioengineers at Northwestern University, the Tulane NPRC is using HIV viruses labeled with multiple fluorochromes to detect and tract vaginal infection. Results show that HIV enters the vaginal mucosa at weak points in the epithelial barrier. The presence of semen does not appear to influence vaginal infection rates or penetration of HIV into vaginal tissue (Allen et al., 2015). Specific immune cells, CD4+ CCR6+ T cells, are the first cells infected (Stieh et al., 2016), and the virus rapidly flows through the entire female reproductive tract. Infected cells are found in the ovaries and draining lymph nodes as early as 2 days after vaginal viral exposure (Stieh et al., 2014). Tulane NPRC researchers also were the first to reveal that progesterone reduces the vaginal epithelial thickness, resulting in increased vaginal SIV/HIV transmission rates.

These findings recently were confirmed in multiple human trials, which demonstrated a markedly increased HIV infection rate in women taking long-acting progestin-based contraceptives. Recent NHP studies confirm that Depo-Provera, a long-acting progestin-based contraceptive, results in the breakdown of intercellular and tight junctions in vaginal epithelium, which permits increased antigen entry resulting in recruitment of activated CD4+ T cells that serve as targets for HIV infection (Carias et al., 2016). Researchers propose that women are more susceptible to HIV transmission during times of progesterone dominance, such as menses, pregnancy, or menopause. Collectively, these studies suggest prevention methods must act quickly to prevent systemic infection after vaginal exposure and the way women are counseled may need to be modified. (Funded by OD/ORIP and NIAID.)

HIV/AIDS: Prevention of vaginal HIV transmission through microbicides.

Defining the molecular mechanisms by which HIV attaches and enters vaginal tissues is important for designing effective prevention strategies. The Tulane NPRC has shown that several agents, including those that prevent CD4 or CCR5 binding in mucosal surfaces, can prevent vaginal transmission of HIV (Malcolm et al., 2014). Additional pharmacokinetic studies to characterize microbicides after vaginal, rectal, and systemic administration (Andrews et al., 2015) indicate the timing of protective drug levels in plasma and vaginal fluids. A small protein originally derived from hepatitis virus (C5a peptide) also has been shown to prevent vaginal HIV transmission in monkey models (Veazey et al., 2015a). Tulane NPRC researchers, in collaboration with investigators at Case Western Reserve University, have shown that a vaginal type 2 interferon treatment can successfully protect monkeys against a pathogenic vaginal virus challenge (Veazey et al., 2016), suggesting that vaccines or immunomodulators that induce the proper immune response may be able to prevent vaginal transmission. (Funded by OD/ORIP and NIAID.)

HIV/AIDS: Prevention of vaginal HIV transmission through vaccines.

Developing vaginal vaccines is an attractive method to induce protection from vaginal transmission of HIV. To date, mucosal immunization has had limited success. One approach to improving immunogenicity is to develop adjuvants that are effective and safe at mucosal surfaces. Tulane NPRC researchers immunized rhesus monkeys using an experimental design that maximized the number of adjuvants screened while reducing animal usage. Monkeys were immunized by intranasal, sublingual, and intrarectal routes with three model protein antigens: keyhole limpet haemocyanin (KLH), beta-galactosidase, and ovalbumin, in combination with six different experimental adjuvants. Of the routes used, only intranasal immunization with KLH and adjuvant Resiquimod (R848) induced a detectable IgG and IgA antibody response in vaginal secretions. When compared to intramuscular immunization, the intranasal administration gave slightly lower levels of antigen-specific antibody in the plasma but enhanced vaginal responses. These studies suggest that nasal or intramuscular antigen administration, particularly with an R848 adjuvant, can induce high antibody levels in vaginal secretions (Veazey et al., 2015b). Yerkes NPRC investigators also showed that adjuvants, such as R848 and 3M052, delivered in nanoparticles with protein-based HIV vaccines, induce robust and long-lived antibody responses in serum and mucosa (Kilgore et al., 2015). These antibodies provide significant protection against vaginal SIV infection in rhesus monkeys. The protective effects of the antibody response were negated when the vaccine induced a strong SIV-specific CD4 T cell response in mucosal tissue (Burton et al., 2015). These results demonstrate the need for the development of HIV vaccines that induce a potent antibody response but a limited tissue resident CD4 T cell response. Collectively, these studies have important implications for the development of effective HIV vaccines. (Funded by OD/ORIP and NIAID.)

Cardiovascular Disease: Poor nutrition during pregnancy can cause early aging of baby's heart.

Restricted dietary intake during pregnancy can cause problems for the fetus, resulting in abnormal structure and function of developing organs, such as the heart. Data suggest that these offspring will suffer chronic illnesses later in life. Researchers working in collaboration with the Southwest NPRC chose to study the baboon heart because this model closely mimics human development and aging (Kuo et al., 2016). Using magnetic resonance imaging (MRI) scanning to study the hearts of male and female baboons whose mothers ate 30 percent less than the normally fed baboons, researchers found that the offspring of diet-restricted mothers showed signs of reduced heart function that is normally associated with aging. By 5 years of life, equivalent to 20 human years, the structure and function of the heart already was impaired. (Funded by OD/ORIP and NICHD.)

Neurosciences

Estrogen and the Aging Brain: Estradiol (E2) promotes synaptic health and cognitive performance.

E2 has been shown to promote synaptic events thought to underlie memory and learning in multiple animal models and some clinical studies. However, clinical results have been inconsistent, generating controversy regarding women's cognitive health. Researchers from the Icahn School of Medicine at Mount Sinai and the California NPRC have been studying relationships between synaptic health, cognitive performance, and aging; they have focused on the prefrontal cortex (PFC) of the rhesus monkey brain, an area particularly well-developed in primates and linked to cognitive function vulnerable to aging. An important class of synapses in the PFC were protected by E2 treatment in ovariectomized, aged monkeys (Hara et al., 2016). The frequency of these synapses correlated with healthy mitochondria, required for optimal synaptic function and cognitive performance. In a related study, it was shown that a key estrogen receptor, G protein-coupled estrogen receptor 1, is present in synapses within PFC and positioned to

support key functions related to synaptic health and plasticity (Crimins et al., 2016). Both studies add new structural and molecular targets for developing therapeutic approaches aimed at maintaining synaptic health, which also may help prevent Alzheimer's disease. (Funded by OD/ORIP and the National Institute on Aging [NIA].)

Neurodevelopment: Stress and obesity synergize to impair neurobehavioral development in females.

Using a rhesus monkey model of social subordination stress, Yerkes NPRC investigators are examining whether prenatal stress experienced by the mother synergizes with postnatal social stress to alter neurobehavioral development from infancy through puberty and if these adverse consequences are exacerbated by obesity. Female rhesus monkeys are maintained from birth in either a dietary condition where only a low caloric diet (LCD) is available or where they have a choice between an LCD and a calorically dense diet (CDD). Outcomes to be obtained during development from 2 weeks of age to young adulthood include social and emotional behavior, brain structural and functional connectivity using neuroimaging, and stress hormone and proinflammatory signaling. Preliminary analysis of scans obtained at 6 months of age suggests that orbitofrontal cortex connectivity with the amygdala and nucleus accumbens is stronger in subordinate versus dominant infants and that these differences are associated with increased infant behavioral reactivity (e.g., tantrums, screams) and daily caloric consumption. In contrast, medial prefrontal cortex connectivity with the nucleus accumbens was affected by both dietary condition and the mother's rank. The data suggest that even during infancy, the effects of social subordination and a CDD already are detectable in specific neurocircuits involved in the control of emotional reactivity, impulsivity, and reward (Drury et al., 2016; Sanchez et al., 2015). This research will provide crucial information to help shape clinical interventions and social policy to optimize neurodevelopment in girls. (Funded by OD/ORIP and NICHD.)

Sex Differences

Sex differences in the social brain.

Social interactions are governed by dominance relationships in most mammalian species. These hierarchical relationships are established and maintained by agonistic behaviors, including aggression. Data indicate that mechanisms in the brain underlying aggression and dominance also make individuals resilient to social stress, while mechanisms underlying subordinate status increase susceptibility to social stress. Despite the relationship between social status and stress, mechanisms that underlie dominance have received limited attention in males and almost no attention in females. Current research at the Yerkes NPRC addresses this knowledge gap by studying whether agonistic behaviors responsible for formation and maintenance of dominance relationships are regulated differently in each sex. Researchers propose that serotonin inhibition promotes the dominant status and stress-resistant phenotype in males, whereas serotonin activation promotes dominance and stress resistance in females. These results expand knowledge of sex differences in brain chemistry that define social phenotypes and provide sex-specific strategies for promoting resistance to social stress. (Funded by OD/ORIP and the National Institute of Mental Health [NIMH].)

Sex differences of poor nutrition during pregnancy on kidney function in offspring.

Early life malnutrition results in structural alterations in the kidney, predisposing offspring to later life renal dysfunction. A study at the Southwest NPRC examined whether these dysfunctions were tied to alterations in mitochondrial function (Pereira et al., 2015). Female baboons were fed the normal chow diet or 70 percent of control diet. These studies found that transcripts encoding fetal renal mitochondrial energy metabolism proteins were nutrition-sensitive in a sex-dependent manner. Researchers speculated that these differences led to reduced mitochondrial fitness, contributing to renal dysfunction later in life. (Funded by OD/ORIP and NICHD.)

Microbiome

Vaginal and Gastrointestinal (GI) Microbiome: Effect of menstrual cycle and antibiotics.

A challenge in developing interventions to prevent sexually transmitted infections (STIs) is a poor understanding of how bacterial species may influence inflammation and infection. Widely used antibiotics also disrupt the composition of the GI and vaginal microbiome, which may impact host immunity. Investigators at the Washington NPRC are analyzing samples from these regions in rhesus and pigtail monkeys under different conditions to provide the framework for future investigations on the role of the microbiome in infection and immunity. To date, the data indicate the monkey vaginal microbiota is diverse, dynamic, and resembles human vaginal microbiota. Antibiotics reversibly disrupt the composition of the microbiota at each site evaluated, which altered the community of immune cells, as well as energy sources available. (Funded by OD/ORIP.)

Reproductive Health

PCOS: NHP model.

PCOS emerges in adolescence and is characterized by excess androgen production, infertility, and the presence of a polycystic ovary. The causes are likely multifactorial, involving genetic and environmental factors, with therapy being palliative, not curative. Oregon NPRC researchers designed an NHP model to assess whether chronic exposure to androgen (testosterone) beginning at menarche/puberty causes many of the features of PCOS, and whether a high-fat western-style diet (WSD) would exacerbate PCOS features. Three projects are evaluating metabolic and neuroendocrine data, adipose/fat deposit, and ovary and reproductive tract function. The data suggest that chronic androgen exposure after puberty, especially when combined with a high-fat diet, can lead to many features of PCOS (Bishop et al., 2016; Rodrigues et al., 2015; Xu et al., 2015; Varlamov, 2016). Thus, reduction or antagonism of excess androgen, combined with diet/lifestyle changes, may prevent or cure PCOS in adolescents or young women.

Additional studies are planned to examine these treatment effects on female fertility and maternal-fetal-placenta function. At the Wisconsin NPRC, evidence suggests that genetic defects leading to ovarian and adrenal hyperandrogenism contribute to PCOS (Abbott et al., 2016). The absence of naturally occurring PCOS in animal models has been an impediment to genetic studies. Recently, researchers have identified a subset of rhesus monkeys that exhibit core PCOS traits (Abbott et al., 2017). Genetic analyses of these animals to identify gene variants associated with PCOS-like traits and evaluation of the pathogenesis as it naturally develops may provide new avenues for identifying girls at risk for developing PCOS and testing of new therapeutic approaches. (Funded by OD/ORIP, OD/ORWH, and NICHD.)

STIs: Models and prevention by topical microbicides.

Although infections with *Chlamydia trachomatis* can be eliminated with antibiotics, treatment does not reverse detrimental outcomes resulting from genital tract infection. These consequences often are not readily apparent because most infected women are asymptomatic. The potential for plasmid-deficient *Chlamydia trachomatis* to serve as a live attenuated vaccine to prevent genital tract infection and disease was studied in rhesus monkeys at the California NPRC (Qu et al., 2015). Early *Chlamydia*-specific T cell responses were associated with infection control. Protected animals also shared common major histocompatibility complex alleles, suggesting that genetic differences may play a role in determining infection outcome. At the Washington NPRC, the pigtail monkey model is used to develop new therapies to prevent STIs. Evaluations include excipient characteristics, the pharmacokinetics of active pharmaceutical agents, drug delivery efficiency, product effects to sites of administration with intended use regimen, and efficacy in preventing infection or disease. Preventive methodologies for *C. trachomatis* and *Trichomonas vaginalis* were evaluated for efficacy (Fernandez-Romero et al., 2015). Development of a monkey model of *Mycoplasma genitalium* infection will allow the study of this recently identified

human reproductive tract disease (Wood et al., 2016). (Funded by OD/ORIP, NIAID, and The Hartwell Foundation.)

Fertility and Contraception: Preserving fertility for female cancer survivors.

Side effects of chemo- or radiotherapies leave cancer survivors facing infertility due to ovarian failure and adverse health effects associated with premature menopause. Clinics worldwide are cryopreserving ovarian tissue with the hope that the individual's ovarian tissue may be used in the future, but techniques to restore ovarian function and fertility are still experimental. Recent advances in cryobiology, transplantation, and ovarian tissue culture are emerging from preclinical research in rhesus monkeys that allow systematic studies to improve and inform clinical practice for preserving fertility. At the Oregon NPRC, a method known as vitrification was successfully used for freezing rhesus monkey ovarian tissue in a closed system; post-thaw survival of the tissue has been demonstrated *in vivo* and *in vitro* (Duncan et al., 2016; Merz et al., 2015; Rodrigues et al., 2015; Laronda et al., 2016). Combining expertise in state-of-the-art cryobiology, clinical ovarian transplantation, and *in vitro* follicle culture is necessary to advance current technology for more rapid translation to clinical practice. Oncofertility issues also have provided a platform for the development of a science outreach curriculum for high school teachers and students (Castle et al., 2016). (Funded by OD/ORIP and NICHD.)

Fertility and Contraception: Permanent nonsurgical contraception for women.

There is a significant, worldwide need for readily available, nonsurgical contraception for women, and the baboon is an ideal translational model for testing potential contraceptives. Administration of a single dose of a polidocanol foam through the baboon's cervix occluded the fallopian tubes and prevented pregnancy (Jensen et al., 2016). The results of this preliminary Southwest NPRC study will support further preclinical contraceptive studies. (Funded by OD/ORIP and the Gates Foundation.)

Pregnancy: ZIKV pathogenesis and fetal risk in pregnancy.

The emergence of ZIKV in the Americas coincided with the recognition of congenital Zika syndrome, a collection of birth defects associated with *in utero* ZIKV infection. The pathogenesis of ZIKV in pregnancy is poorly understood. Investigators at the Wisconsin NPRC showed that experimental infection of pregnant monkeys is possible, infection during pregnancy results in prolonged detection of circulating virus relative to nonpregnant monkeys, and fetuses of infected mothers consistently have detectable ZIKV nucleic acids in their tissues at birth (Buechler et al., 2016; Dudley et al., 2016; O'Connor et al., 2016; Pardee et al., 2016). The risk of complications associated with babies infected with ZIKV *in utero* may be higher than currently understood. Additional results suggest that women who are infected during childhood will likely be resistant to complications of ZIKV during pregnancy (Aliota et al., 2016). A unique component of these studies was the availability of data in real time through a website portal (Kallas and O'Connor, 2016). Initial findings from the Oregon NPRC demonstrate that ZIKV infection during the second trimester results in persistent maternal viremia, placental viral transfer, and infection of multiple fetal tissues in NHPs. Despite the seemingly normal fetal growth, evidence of placental vascular compromise and altered fetal brain development was detected by novel advanced noninvasive *in vivo* imaging. The data suggest that ZIKV infection during pregnancy results in a spectrum of placental and neonatal outcomes that may present with varying degrees of adverse developmental consequences. At the Washington NPRC, investigators followed brain lesions in the fetus of a Cambodian strain Zika-infected pregnant pigtail monkey using MRI with neuropathology of the brain tissue assessed at necropsy (Waldorf et al., 2016). Arrested fetal brain development in the ZIKV-infected fetus was similar to that observed in humans. Additional studies are focusing on sex differences in ZIKV infection and sexual transmission of ZIKV. The project includes assessments of gene expression profiles, innate

and adaptive immune responses, viral loads, and the microbiome. (Funded by OD/ORIP, NIAID, and NICHD.)

Pregnancy: MTCT of cytomegalovirus (CMV) infection.

Congenital CMV infection is the leading cause of infectious disease resulting in severe neurological birth defects in newborns. Researchers at the Tulane NPRC and Duke University are characterizing a rhesus monkey model of placental CMV transmission for studying pathogenesis and developing a maternal CMV vaccine. Using monkeys bred to be free of CMV and all herpes viruses, researchers discovered that in the absence of the CD4+ helper T cells, pregnant monkeys infected with CMV mounted a delayed antibody and cytotoxic T cell immune response against CMV, resulting in viral transmission across the placenta, fetal infection, and miscarriage (Bialas et al., 2015). A high prevalence of CMV replication and virus shedding also was observed in infant and juvenile monkeys infected postnatally; this was associated with functional defects in CD4+ T cell immunity (Antoine et al., 2014). (Funded by OD/ORIP, NIAID, NICHD, and the National Cancer Institute [NCI].)

Pregnancy: Bacterial infectious disease during pregnancy.

Premature infants are at higher risk for brain injury from hypoxia-ischemia or intrauterine infection and often show continued developmental consequences. There currently is no effective prenatal therapy for preventing adverse neurologic outcomes in prematurely born infants, particularly those exposed to bacterial infection *in utero*. The Oregon NPRC supports research on the most common *in utero* bacterial infection, *Ureaplasma parvum*, which results in preterm birth and adverse neurological outcomes (Grigsby, 2016). Adverse neonatal outcomes in rhesus monkeys infected with *U. parvum* can be prevented with prenatal antibiotic therapy (Kelleher et al., 2017). Maternal azithromycin (AZI) treatment delays preterm birth, reduces the severity of fetal lung injury, and provides protection of neuronal tissue. Neonatal behavioral and cognitive development also is

improved in those infants born to mothers who received antibiotic treatment. (Funded by OD/ORIP and NICHD.)

Pregnancy: The *in utero* measurement of placental blood flow by MRI.

Abnormalities in placental function contribute to pregnancy complications, including preterm labor, preeclampsia, fetal growth restriction, and stillbirth. Children of pregnancies with placental dysfunction also have a higher risk of long-term disease. Researchers at the Oregon NPRC have developed placenta-specific MRI protocols to measure maternal blood flow to the placenta (Frias et al., 2015; Schabel et al., 2016). Using a contrast agent to aid visualization of blood flow as the standard, this project studies pregnant rhesus monkeys to validate a newly developed MRI method that avoids the need for a contrast agent. The study allows for blood flow measurement under normal conditions and temporary disruption of flow while in the MRI scanner. Once validated, the noncontrast MRI method could safely be used in pregnant women to potentially detect pregnancies at risk for placental insufficiency and may facilitate the development of interventional strategies. (Funded by OD/ORIP and NICHD.)

Pregnancy: Noninvasive MRI methodology for assessing fetal brain sensitivity to ethanol exposure.

Alcohol consumption prior to pregnancy awareness contributes to fetal alcohol spectrum disorder in the United States. Methods for early detection of adverse effects of alcohol exposure on brain development would facilitate new therapeutic intervention strategies. Research at the Oregon NPRC is under way to characterize fetal brain development throughout pregnancy with recently developed *in utero* noninvasive MRI methods (Frias et al., 2015; Khan et al., 2015; Wang et al., 2015). The trajectory of development in normal and ethanol-exposure fetuses throughout the first trimester are being quantified to determine anatomical abnormalities associated with fetal ethanol exposure. (Funded by OD/ORIP, NICHD, the National Institute of Biomedical Imaging and Bioengineering, the National Institute of Neurological Disorders and Stroke, the National

Institute on Alcohol Abuse and Alcoholism, and the National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK].)

Menopause: Effects of hormone therapy and diet on postmenopausal females.

With extended human lifespans, menopause has become a significant risk factor for depression, anxiety, loss of cognitive functions, weight gain, metabolic disease, osteoporosis, cardiovascular disease, neurodegenerative diseases, and other conditions. Initiation of estrogen replacement therapy (ERT) with or without progesterone during the perimenopausal period has been shown to be beneficial on the above systems in some studies, but not others. Researchers at the Oregon NPRC developed a postmenopausal rhesus monkey resource with aged ovario-hysterectomized animals on a high-fat WSD. ERT administered immediately after the initiation of menopause prevented deleterious effects of WSD on metabolism for only 6 months, after which WSD overcame ERT's protective effects and metabolic endpoints deteriorated. However, WSD-fed monkeys treated with ERT were more active and showed better acquisition of a hippocampus-dependent spatial maze task than placebo-treated animals. In contrast, WSD for 6 months blocked the beneficial effect of immediate ERT on gene expression related to serotonin neural function (Bethea et al., 2015; Bethea and Reddy, 2015). Thus, depending on the endpoint studied, WSD can block ERT's beneficial effects over time. This research addresses key questions related to formulation and timing of ERT. (Funded by OD/ORIP.)

Puberty

Epigenetic regulation of female puberty.

The initiation of puberty appears to require coordinated activity of gene networks controlling the balance of excitatory and inhibitory inputs involved in pubertal activation of gonadotropin-releasing hormone (GnRH) release. Research from the Oregon NPRC suggests a dual mechanism of epigenetic regulation affecting neuronal transcriptional activity involved in stimulating

GnRH release plays a fundamental role in the timing of puberty (Lomniczi et al., 2015a). Transcriptional silencers in the polycomb group (PcG) and two members of the zinc finger proteins (Lomniczi et al., 2015b) may be major components of the repressive arm of this mechanism, preventing the premature initiation of female puberty by silencing the *Kiss1* gene in hypothalamic neurons. In contrast, the trithorax group of transcriptional activators accumulate at the controlling regions of genes involved in the stimulatory control of puberty when PcG control subsides (Lomniczi and Ojeda, 2016). These advances provide novel insights into the pathways engaged by the environment to affect neuroendocrine reproductive development. (Funded by OD/ORIP, NICHD, and NIDDK.)

Behavior

Stress and the genome: testing the impact of social effects on immune gene regulation.

How chronic social stress causally affects immune gene regulation and infection risk is under study at the Yerkes NPRC. Established female social groups were rearranged midway through the study to impose new social ranks. Blood samples were collected throughout the study to determine gene expression patterns and for testing of pathogens. Behavioral data and physiological phenotypes were determined. Dominance rank has strong effects on social relationships in the absence of kin, suggesting that social status and social connectedness be considered when investigating health and fitness consequences. Low rank also was shown to induce a socially isolated, passive behavioral phenotype and was associated with altered stress hormone regulation, decreased immune cell sensitivity to glucocorticoids, and down-regulation of genes involved in immune cell adhesion (Kohn et al., 2016; Snyder-Mackler et al., 2016a,b). These studies demonstrate causal but reversible social status effects on immune cell proportions, cell type-specific gene expression levels, and the gene expression response to infection. These findings provide insight into the direct biological effects of social inequality on immune function in females. (Funded by OD/ORIP and the National Institute of General Medical Sciences.)

Neuroadaptations that sustain emotional feeding in females.

Overconsumption of CDDs are thought to be a primary cause of the obesity epidemic in the United States. Emotional feeding resulting from chronic exposure to psychosocial stressors likely is a key factor. Researchers at the Yerkes NPRC are studying how chronic exposure to social stressors interact with the dietary environment to initiate and sustain excessive food consumption (Ulrich-Lai et al., 2015). Social subordination in adult female rhesus monkeys produces stress-related characteristics similar to those observed in women, including a compromised dopamine reward circuitry. The data suggest that excessive consumption of high-fat, high-sugar diets is a form of self-medication in the face of unrelenting stressors of being subordinate (Michopoulos et al., 2016). Studies show that stress hormone signals are important in maintaining the excessive consumption of these diets, as short-term administration of a stress hormone antagonist attenuates emotional feeding in subordinate female rhesus monkeys (Moore et al., 2015). This research also is investigating whether a behavioral intervention to alleviate chronic stress improves dopamine function and diminishes emotional feeding. These studies increase our understanding of factors that sustain emotional feeding despite a healthy dietary environment. (Funded by OD/ORIP and NIDDK.)

Career Development Activities and Programs Advancing Women in Biomedical Science Careers

Development Awards (Parent K01) assist graduate veterinarians to become independent investigators in research related to comparative medicine. The T32 and T35 Training Grants offer opportunities for career development, providing long- and short-term support for training highly qualified veterinarians and veterinary students for research careers in biomedical areas related to comparative medicine, comparative pathology, or other disciplines to improve and extend healthy lives and prevent illness. The Research Education Grant (R25) program provides research education for veterinarians interested in pursuing a career

in laboratory animal medicine focusing on biomedical investigations, with an emphasis on performing collaborative research, development, and maintenance of animal models for translational research activities, and professional direction for animal resource/research programs. Women are well represented as mentors, trainees, and participants in each of these programs. Women represent slightly more than 70 percent of K01 grantees and 75 percent of trainees in the T32 and T35 mentoring/training program, and approximately 75 percent of the participants within the R25 research education program. DCM also supports research supplements to promote diversity in health-related research (PA-16-288). Underrepresented minority (Hispanic origin and African-American) women represent all trainees supported by DCM through this research supplement program.

STEM Efforts

The SEPA Program

The SEPA program, established in 1991, supports workforce diversity by providing opportunities for students from underrepresented minorities and underserved communities—including Indians/Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders, low-income populations, and rural populations—to consider careers in basic or clinical research. SEPA encourages partnerships with NIH's institutional development awards, research centers in minority institutions, and clinical and translational science award programs, as well as with other Federal agencies. Examples of SEPA-funded projects include SEPA Community-Based Participatory Research projects on disease prevention, including obesity, diabetes, and cardiovascular disease. SEPA-funded Informal Science Education projects include science center and traveling health exhibits, public service announcements on radio and television, documentaries, and films. Outreach activities, such as Science Cafes and Community Health Fairs, educate students, teachers, and the community on the correlation between lifestyle and health,

including issues of importance to women and girls. More than 60 percent of SPEA project principal investigators are women.

Hispanic Role Models in Health Care Careers.

The National Association of Hispanic Nurses (NAHN), in association with the Hispanic Communications Network (HCN), proposes to address the shortage of bilingual professionals in all health fields by recruiting and interviewing bilingual role models and arranging to broadcast those interviews nationwide. Leveraging HCN's nationally broadcast health education radio shows, this project has the potential to reach one out of every three U.S. Hispanics. This media campaign is intended to inspire Hispanic parents to encourage their children to study science and aspire to careers in the biomedical professions. It is intended to inspire and empower Spanish-speaking adults to consider careers in the health professions. All broadcasts will tie to NAHN's interactive website, so students and adults interested in changing careers can find mentors and educational resources. NAHN also will use YouTube, Facebook, mobile phone applications, and other new and popular social media technologies to reach a broad cross-section of English-speaking youth and young adults.

PIPES: Possibilities in Postsecondary Education and Science Among Rural Appalachian Youth.

The goal in this SEPA project is to develop effective and rigorously evaluated interventions that both reduce contextual barriers (via mentoring and support) and increase interest in (via direct exposure to research and career options) pipeline science, technology, engineering, mathematics, and medical science (STEMM) majors among Appalachian youth. The research objective is to quantify the extent to which such a multifaceted intervention strategy leads to increased intentions to pursue an undergraduate STEMM degree. The project's specific aims are to (1) understand the role of barriers to and support for higher education in Appalachian high school students' interest in pursuing STEMM-related undergraduate degrees, and (2) develop sustainable interventions that decrease barriers to and increase support for higher education and that increase STEMM-related self-efficacy and interest.

Achieving these aims will provide concrete tools for schools across rural Appalachia to use to increase the number of students equipped with the skill sets required to join the high-growth biomedical and clinical research industry workforce.

FUNDING INITIATIVES, WORKSHOPS, AND CONFERENCES

Program Announcements

ORIP led several funding opportunities in FY 15 and FY 16. Those that included a focus on women and related trans-NIH topics are listed below.

PAR: HIV/AIDS Vaccine Scholars Program (K01) (PAR-16-028)

As part of a joint initiative between ORIP and the Office of AIDS Research (OAR), these K01 grants explore new HIV vaccine approaches and develop opportunities for new investigators in the HIV vaccine field, enabling them to translate promising preclinical vaccine studies in male and female NHPs to clinical trials in humans of both sexes.

PAR: Conference for Early Stage HIV/AIDS Vaccine Researchers (R13) (PAR-16-351)

As part of a joint initiative between ORIP and OAR, these R13 grants support intensive conferences to address the needs of early-stage HIV/AIDS vaccine researchers. Conference topics include, but are not limited to, critical aspects of human vaccine development, including statistical considerations and host genetics; methods to translate NHP challenge results to human clinical trials in both sexes; and methods to develop milestone-driven projects.

PA: Development of Novel and Emerging Technologies to Support Zebrafish Models for Biomedical Research (R43/R44 – PA-15-086) (R41/R42 – PA-15-087)

These technology transfer and innovation research project applications from small business concerns propose innovative research and development of technology, including reagents and high-throughput equipment, to support different aspects

of the creation, detection, identification, sex determination, and characterization of zebrafish models of human disease and preservation of genetic stocks.

Conferences and Workshops (in chronological order)

One Health: Integrating the Veterinarian Scientist into the Biomedical Research Enterprise, April 7–8, 2015

One Health is defined as the integrative effort of multiple disciplines working together to attain optimal health for people, animals, and the environment. The purpose of the workshop was to identify how the concept of One Health can advance NIH's mission relative to basic and applied research, including training of the biomedical workforce, concentrating on veterinarian scientists of both sexes.

NIH SciED Conference, May 20–23, 2015; May 9–12, 2016

The goal of the annual NIH Science Education Partnership Award SciEd Conference is to establish collaborations, identify best practices for each type of project, and document rigorous and appropriate evaluation tools. The 2015 and 2016 conferences continued to expand information exchange between NIH-funded projects and the lead Federal agencies engaged in STEM education, namely the U.S. Department of Energy, the National Aeronautics and Space Administration, the National Oceanographic and Atmospheric Administration, and the National Science Foundation.

Linking Disease Model Phenotypes to Human Conditions Symposium, September 10–11, 2015

The purpose of this symposium was to discuss the status of phenomics and its role in closing the gap that exists between biomedical research and clinical medical practice involving animal models and human patients of both sexes. The symposium highlighted how the integration of this data with detailed disease descriptions, phenotype information from appropriate animal models, and identification of environmental conditions can provide better candidates for disease gene

effectors to use in precision medicine targeting heterogeneous human patients of both sexes.

Cryopreservation of *Drosophila* Strains, July 13, 2016

Although *Drosophila melanogaster* is widely used in the biomedical research community to study development, model human diseases in both sexes, and undertake high-throughput drug discovery, reliable and cost-effective approaches for long-term preservation of *Drosophila* stocks are lacking. The objective of this workshop was to evaluate the potential and practicality of developing efficient preservation methods of germplasm from both sexes for long-term storage of *Drosophila* stocks.

Mobil Laboratory Coalition (MLC) Conference, July 13–15, 2016

The MLC Conference is specifically for STEM educators, professionals, and other partners from around the world. Targeted at both new and established informal science education programs, this conference allows attendees to learn about advances in informal science education, share ideas, and collaborate with industry leaders.

Enabling Biomedical Research—From Fundamental Science to Precision Medicine: Eleventh Comparative Medicine Resource Directors Meeting, August 9–10, 2016

The goals of this biennial meeting were to provide a forum for exchange of new information, advances and ideas; facilitate development and continuation of synergistic working groups, interactions, and collaborations among resources and between resources and the various NIH Institutes, Centers, and Offices; and offer opportunities for sharing experiences, strategies, and best practices for optimizing access, use, and administration of valuable resources. Reproducibility and studying both sexes in animal disease models were some of the topics discussed during a session reviewing new NIH policies on rigor and transparency and sex as a biological variable.

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Appendix B. ORWH-Co-funded Research Summaries

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2015	Comprehensive Alcohol Research Centers (P60)	Etiology and Treatment of Alcohol Dependence	Hesselbrock, Victor M	University of Connecticut Sch of Med/Dnt	3 P60 AA003510-38S1	RePORTER Proj Info
2016	Comprehensive Alcohol Research Centers (P60)	Environmental Approaches to Prevention	Gruenewald, Paul J	Pacific Institute for Res and Evaluation	3 P60 AA006282-34S1	RePORTER Proj Info
2016	Specialized Alcohol Research Centers (P50)	Alcohol Research Center - Treatment and Implications	Becker, Howard C	Medical University of South Carolina	3 P50 AA010761-21S1	RePORTER Proj Info
2016	Nathan Shock Centers of Excellence in Basic Biology of Aging (P30)	Comparative Energetics and Aging	Austad, Steven N	University of Alabama at Birmingham	3 P30 AG050886-02S1	RePORTER Proj Info
2015	Asthma and Allergic Diseases Cooperative Research Centers (U19)	Host and Viral Determinants of Infant and Childhood Allergy and Asthma	Peebles, Ray Stokes	Vanderbilt University Medical Center	6 U19 AI095227-06	RePORTER Proj Info
2015	Asthma and Allergic Diseases Cooperative Research Centers (U19)	Airway Inflammation and Airway Remodeling	Broide, David H	University of California San Diego	5 U19 Ai070535-10	RePORTER Proj Info
2015	Asthma and Allergic Diseases Cooperative Research Centers (U19)	Role Of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin I	Baseman, Joel Barry	University of Texas Health Science Center	5 U19 AI070412-10	RePORTER Proj Info
2015	Asthma and Allergic Diseases Cooperative Research Centers (U19)	Epithelial Genes in Allergic Inflammation	Khurana Hershey, Gurjit K	Cincinnati Childrens Hosp Med Ctr	5 U19 AI070235-10	RePORTER Proj Info
2015	Asthma and Allergic Diseases Cooperative Research Centers (U19)	T Cell Effector and Regulatory Mechanisms in Asthma and Food Allergy	Luster, Andrew D	Massachusetts General Hospital	5 U19 Ai095261-05	RePORTER Proj Info
2015	Asthma And Allergic Diseases Cooperative Research Centers (U19)	Epithelial Barrier Programs in Asthma and Allergic Disease	Holtzman, Michael J	Washington University	5 U19 AI070489-10	RePORTER Proj Info
2015	Asthma and Allergic Diseases Cooperative Research Centers (U19)	Airway Inflammation and HLA-G in Asthma	White, Steven R; Ober, Carole	University of Chicago	5 U19 Ai095230-05	RePORTER Proj Info
2015	Asthma and Allergic Diseases Cooperative Research Centers (U19)	Pathophysiologic and Therapeutic Mechanisms of Aspirin Exacerbated Respiratory Disease	Boyce, Joshua A	Brigham and Women's Hospital	5 U19 AI095219-05	RePORTER Proj Info
2016	Genomics of Transplantation Cooperative Research Program (U01, U19)	Genomics of Kidney Transplantation Admin	Matas, Arthur J	University of Minnesota	3 U19 AI070119-10S1	RePORTER Proj Info
2015	Centers of Excellence For Translational Research (CETR) (U19)	Center for Research in Diagnostics and Discovery	Lipkin, W Ian	Columbia University Health Sciences	5 U19 AI109761-02	RePORTER Proj Info

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2016	Limited Competition - Multicenter AIDS Cohort Study: Center for the Coordination, Analysis, and Management of the MACS (CAMACS) (UM1)	Center/Coordination, Analysis and Management/MACS	D'souza, Gypsyamber; Jacobson, Lisa P	Johns Hopkins University	5 UM1 AI035043-24	RePORTER Proj Info
2015	NIAMS Clinical Trial Outcome Instrument Development Grant Program (U01)	Developing an Alopecia Areata Disease Activity Index (ALADIN)	Christiano, Angela M	Columbia University Health Sciences	3 U01 AR067173-01S1	RePORTER Proj Info
2015	Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium (U19)	AAD-PEPE: Asthma and Atopic Dermatitis Validation of PROMIS Pediatric Instruments	Gershon, Richard; Paller, Amy S	Northwestern University at Chicago	1 U19 AR069526-01	RePORTER Proj Info
2015	Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium (U19)	The Child-Centered Outcomes in Practice and Research (COPR) Center of Excellence: Strengthening the Clinical Validity Evidence Base for PROMIS Measures in Chronically Ill Children	Forrest, Christopher B	Children's Hosp of Philadelphia	1 U19 Ar069525-01	RePORTER Proj Info
2015	Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium (U19)	Enhancing Clinical Meaningfulness and Usefulness of PROMIS Pediatric Measures Via Validation in Children and Adolescents with Rheumatic Disease, Cancer, or Inflammatory Bowel Disease	Reeve, Bryce B; Schanberg, Laura E	Univ of North Carolina Chapel Hill	1 U19 AR069522-01	RePORTER Proj Info
2015	Validation of Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium (U19)	The Midwest Child Patient Reported Outcomes (M-cPROS) Consortium	Panepinto, Julie A	Medical College of Wisconsin	1 U19 AR069519-01	RePORTER Proj Info
2016	Mechanistic Research on CAM Natural Products (R01)	Mechanisms and Active Compounds in the Cognitive Effects of Centella Asiatica	Soumyanath, Amala	Oregon Health & Science University	3 R01 AT008099-03S1	RePORTER Proj Info
2015	Person-Centered Outcomes Research Resource (U2C)	The National Person-Centered Assessment Resource (PCAR)	Cella, David	Northwestern University at Chicago	5 U2C CA186878-02	RePORTER Proj Info
2016	Person-Centered Outcomes Research Resource (U2C)	The National Person-Centered Assessment Resource (PCAR)	Cella, David	Northwestern University at Chicago	5 U2C CA186878-03	RePORTER Proj Info
2016	NIH Blueprint for Neuroscience Research Grand Challenge on the Transition From Acute to Chronic Neuropathic Pain (R01)	Proteolysis of Myelin as a Source of Neuropathic Pain	Strongin, Alex Y; Yaksh, Tony L; Shubayev, Veronica	University of California San Diego	3 R01 DE022757-05S1	RePORTER Proj Info
2015	Limited Competition of The MAPP Research Network(U01)	University of Michigan MAPP Research Network Discovery Site	Clauw, Daniel J; Clemens, J Quentin	University of Michigan	5 U01 DK082345-07	RePORTER Proj Info
2015	Limited Competition of the MAPP Research Network (U01)	MAPP Research Network Second Phase	Mayer, Emeran A; Rodriguez, Larissa	University of California Los Angeles	5 U01 DK082370-07	RePORTER Proj Info
2016	Limited Competition of The MAPP Research Network (U01)	University of Michigan MAPP Research Network Discovery Site	Clauw, Daniel J; Clemens, J Quentin	University of Michigan	3 U01 DK082345-08S1	RePORTER Proj Info

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2016	Limited Competition Of The MAPP Research Network (U01)	University Of Michigan MAPP Research Network Discovery Site	Clauw, Daniel J; Clemens, J Quentin	University of Michigan	5 U01 DK082345-08	RePORTER Proj Info
2016	Limited Competition Of The MAPP Research Network (U01)	MAPP Research Network Second Phase	Mayer, Emeran A; Rodriguez, Larissa	University of California Los Angeles	5 U01 DK082370-08	RePORTER Proj Info
2015	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Clinical Centers (Plus-CCs) (U01)	University of Pennsylvania+ Plus Clinical Center (Penn+Plus CC)	Newman, Diane K; Arya, Lily A	University of Pennsylvania	1 U01 DK106892-01	RePORTER Proj Info
2015	Prevention of Lower Urinary Tract Symptoms In Women: Bladder Health Clinical Centers (Plus-CCs) (U01)	LUTS Prevention In Adolescent Girls and Women Across the Lifespan	Sutcliffe, Siobhan; Colditz, Graham A	Washington University	1 U01 DK106853-01	RePORTER Proj Info
2016	Prevention of Lower Urinary Tract Symptoms In Women: Bladder Health Clinical Centers (Plus-Ccs) (U01)	University of Pennsylvania+ Plus Clinical Center (Penn+Plus CC)	Newman, Diane K; Arya, Lily A	University of Pennsylvania	5 U01 DK106892-02	RePORTER Proj Info
2016	Prevention of Lower Urinary Tract Symptoms In Women: Bladder Health Clinical Centers (Plus-CCs) (U01)	LUTS Prevention In Adolescent Girls and Women Across the Lifespan	Sutcliffe, Siobhan; Colditz, Graham A	Washington University	5 U01 DK106853-02	RePORTER Proj Info
2015	Limited Competition for the Continuation of the Diabetes Prevention Program Outcomes Study (DPPOS) (U01)	Diabetes Prevention Program Outcomes Study Follow-Up	Temprosa, Marinella; Larsen, Michael Dean	George Washington University	2 U01 DK048489-22	RePORTER Proj Info
2016	Limited Competition for the Continuation of The Diabetes Prevention Program Outcomes Study (DPPOS) Biostatistics Research Center (Collaborative U01)	22/22 Diabetes Prevention Program Outcomes Study (DPPOS) Phase 3 - Biostatistics Center	Temprosa, Marinella; Larsen, Michael Dean	George Washington University	2 U01 DK048489-23	RePORTER Proj Info
2016	Brain Initiative: Theories, Models And Methods for Analysis of Complex Data From the Brain (R01).	Novel Bayesian Linear Dynamical Systems-Based Methods for Discovering Human Brain Circuit Dynamics in Health And Disease	Menon, Vinod	Stanford University	1 R01 EB022907-01	RePORTER Proj Info
2016	Children's Environmental Health and Disease Prevention Centers (P01)	Neurodevelopment and Improving Children's Health Following ETS Exposure (Niches)	Murphy, Susan Kay	Duke University	3 P01 ES022831-04S1	RePORTER Proj Info
2016	Outstanding New Environmental Scientist (ONES) Award (R01)	Functional Interaction Between the Gut Microbiome and Arsenic Exposure	Lu, Kun	University of Georgia	3 R01 ES024950-02S1	RePORTER Proj Info
2015	Pelvic Floor Disorders Network Clinical Sites (U10)	Pelvic Floor Disorders Network Clinical Sites (U10)	Arya, Lily A	University of Pennsylvania	5 U10 HD069010-05	RePORTER Proj Info
2015	Pelvic Floor Disorders Network Clinical Sites (U10)	Pittsburgh Pelvic Floor Research Program	Zyczynski, Halina M	Magee-Women's Res Inst and Foundation	5 U10 HD069006-05	RePORTER Proj Info

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2015	Pelvic Floor Disorders Network Clinical Sites (U10)	Cleveland Clinic Clinical Site	Barber, Matthew	Cleveland Clinic Lerner Com-CWRU	5 U10 HD054215-10	RePORTER Proj Info
2015	Pelvic Floor Disorders Network Clinical Sites (U10)	Pelvic Floor Disorders Network - Duke University Clinical Site	Visco, Anthony G	Duke University	5 U10 HD041267-16	RePORTER Proj Info
2015	Pelvic Floor Disorders Network Clinical Sites (U10)	Perioperative Pelvic Floor Rehab: A Randomized Trial	Richter, Holly E	University Of Alabama At Birmingham	5 U10 HD041261-15	RePORTER Proj Info
2015	Pelvic Floor Disorders Network Clinical Sites (U10)	RCT Of Hypnotherapy vs Tpolterodine for OAB: Voiding and Brain Activation Changes	Rogers, Rebecca Glenn	University Of New Mexico Health Scis Ctr	5 U10 HD069025-05	RePORTER Proj Info
2015	Pelvic Floor Disorders Network Clinical Sites (U10)	Brown/WIH Pelvic Floor Disorders Network Site	Sung, Vivian W	Women and Infants Hospital-Rhode Island	5 U10 HD069013-05	RePORTER Proj Info
2015	Pelvic Floor Disorders Network Clinical Sites (U10)	Pelvic Floor Disorders Network	Lukacz, Emily S	University of California San Diego	5 U10 HD054214-10	RePORTER Proj Info
2015	Prevention of HIV Transmission/ Acquisition Through a Better Understanding of Reproductive Health (R01)	Modulation Of Innate Immunity, Microbiome and HIV Transmission by Depo-Provera	Chang, Theresa L; Yang, Liying	RBHS-New Jersey Medical School	5 R01 AI110372-03	RePORTER Proj Info
2015	Women's Reproductive Health Research (WRHR) Career Development Program (K12)	OHSU Womens Reproductive Health Research K12 Program	Caughey, Aaron B	Oregon Health & Science University	1 K12 HD085809-01	RePORTER Proj Info
2016	Women's Reproductive Health Research (WRHR) Career Development Program (K12)	OHSU Womens Reproductive Health Research K12 Program	Caughey, Aaron B	Oregon Health & Science University	5 K12 HD085809-02	RePORTER Proj Info
2015	BRAIN Initiative: Planning for Next Generation Human Brain Imaging (R24)	Imaging the Brain in Motion: The Ambulatory Micro-Dose, Wearable PET Brain Imager	Brefczynski-Lewis, Julie Ann	West Virginia University	3 R24 MH106057-02S1	RePORTER Proj Info
2015	Leveraging a Recovery Act Resource to Accelerate Research on Neurodevelopment (R01)	Neurodevelopmental Features of Sexual Dimorphism in Pediatric Psychopathology	Singh, Manpreet K	Stanford University	1 R56 MH107243-01	RePORTER Proj Info
2015	BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01)	Mechanisms of Neural Circuit Dynamics in Working Memory	Brody, Carlos D; Witten, Ilana; Tank, David W; Wang, Samuel Sheng-Hung; Bialek, William; Seung, Hyunjune Sebastian	Princeton University	5 U01 NS090541-02	RePORTER Proj Info
2015	BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01)	Crowd Coding in The Brain:3D Imaging and Control of Collective Neuronal Dynamics	Kanold, Patrick O; Plenz, Dietmar; Losert, Wolfgang	Univ of Maryland, College Park	5 U01 NS090569-02	RePORTER Proj Info
2015	BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01)	Integrative Functional Mapping of Sensory-Motor Pathways	Dickinson, Michael H; Holmes, Philip J; Mann, Richard S; Wilson, Rachel	California Institute of Technology	5 U01 NS090514-02	RePORTER Proj Info

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2015	BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01)	The Role of Patterned Activity in Neuronal Codes for Behavior	Maunsell, John HR; Histed, Mark H; Fellin, Tommaso	University of Chicago	5 U01 NS090576-02	RePORTER Proj Info
2016	BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01)	Mechanisms of Neural Circuit Dynamics in Working Memory	Brody, Carlos D; Witten, Ilana; Tank, David W; Wang, Samuel Sheng-Hung; Bialek, William; Seung, Hyunjune Sebastian	Princeton University	5 U01 NS090541-03	RePORTER Proj Info
2016	BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01)	Crowd Coding in The Brain:3D Imaging and Control of Collective Neuronal Dynamics	Kanold, Patrick O; Plenz, Dietmar; Losert, Wolfgang	Univ of Maryland, College Park	5 U01 NS090569-03	RePORTER Proj Info
2016	BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01)	Integrative Functional Mapping of Sensory-Motor Pathways	Dickinson, Michael H; Holmes, Philip J; Mann, Richard S; Wilson, Rachel	California Institute of Technology	5 U01 NS090514-03	RePORTER Proj Info
2016	BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01)	The Role of Patterned Activity in Neuronal Codes for Behavior	Maunsell, John HR; Histed, Mark H; Fellin, Tommaso	University of Chicago	5 U01 NS090576-03	RePORTER Proj Info
2016	BRAIN Initiative: Research Opportunities Using Invasive Neural Recording and Stimulating Technologies in the Human Brain (U01)	Understanding the Neural Basis of Volitional State Through Continuous Recordings in Humans	Cash, Sydney S	Massachusetts General Hospital	1 U01 NS098968-01	RePORTER Proj Info
2015	Dietary Supplement Research Centers: Botanicals (P50)	Botanical Estrogens: Mechanisms, Dose and Target Tissues	Helferich, William G	University of Illinois at Urbana-Champaign	3 P50 AT006268-05S1	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Careers in Women's Health	Hartmann, Katherine E	Vanderbilt University Medical Center	5 K12 HD043483-16	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Maryland's Organized Research Effort in Womens Health	Tracy, J Kathleen	University of Maryland Baltimore	4 K12 HD043489-15	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	UIC Program for Interdisciplinary Careers in Women's Health Research	Geller, Stacie E	University of Illinois at Chicago	4 K12 HD055892-10	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	University of Minnesota Building Interdisciplinary Research Careers In Women's He	Vinogradov, Sophia	University of Minnesota	4 K12 HD055887-10	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Career Development Program In Women's Health Research At Penn State	Weisman, Carol S	Pennsylvania State Univ Hershey Med Ctr	4 K12 Hd055882-10	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers In Women's Health	Building Interdisciplinary Research Careers in Women's Health in Pittsburgh	Sadovsky, Yoel; Roberts, James M	Magee-Women's Res Inst and Foundation	4 K12 HD043441-15	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Careers in Women's Health	Andrews, Nancy Catherine	Duke University	4 K12 HD043446-15	RePORTER Proj Info

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2016	Building Interdisciplinary Research Careers in Women's Health	Tulane Building Interdisciplinary Research Careers in Women's Health (BIRCWH)	Krousel-Wood, Marie A	Tulane University of Louisiana	4 K12 HD043451-15	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Women's Health at MUSC	Brady, Kathleen T	Medical University of South Carolina	4 K12 HD055885-10	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Career Development in Womens Health (CDWH)	Dunaif, Andrea	Northwestern University at Chicago	4 K12 HD055884-10	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	The Colorado Building Interdisciplinary Research Careers in Women's Health Program	Regensteiner, Judith G; Santoro, Nanette F	University of Colorado Denver	4 K12 HD057022-10	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Career in Women's Health (BIRCWH) Scholars	Burnside, Elizabeth S	University of Wisconsin-Madison	4 K12 HD055894-10	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Oregon BIRCWH: Scholars in Women's Health Research Across the Lifespan	Guise, Jeanne-Marie; Dorsa, Daniel Michael	Oregon Health & Science University	4 K12 HD043488-15	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Kentucky BIRCWH Program: Training the Next Generation Of Women's Health Scholars	Curry, Thomas E	University of Kentucky	4 K12 DA035150-05	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Careers in Women's Health	Hartmann, Katherine E	Vanderbilt University Medical Center	6 K12 HD043483-15	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Careers in Women's Health	Hartmann, Katherine E	Vanderbilt University	5 K12 HD043483-14	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Maryland's Organized Research Effort In Womens Health	Tracy, J Kathleen	University Of Maryland Baltimore	5 K12 Hd043489-14	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers In Women's Health	UIC Program for Interdisciplinary Careers in Womens Health Research	Geller, Stacie E	University of Illinois at Chicago	5 K12 HD055892-09	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Career Development Program in Womens Health Research at Penn State	Weisman, Carol S	Pennsylvania State Univ Hershey Med Ctr	5 K12 HD055882-09	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Careers in Women's Health In Pittsburgh	Sadovsky, Yoel; Roberts, James M	Magee-Women's Res Inst and Foundation	5 K12 HD043441-14	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Careers in Womens Health	Andrews, Nancy Catherine	Duke University	5 K12 Hd043446-14	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Tulane Building Interdisciplinary Research Careers in Women's Health (BIRCWH)	Krousel-Wood, Marie A	Tulane University of Louisiana	5 K12 HD043451-14	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	University Of Minnesota Building Interdisciplinary Research Careers in Women's He	Raymond, Nancy Cox	University of Minnesota	5 K12 HD055887-09	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Career in Women's Health (BIRCWH) Scholars	Burnside, Elizabeth S	University of Wisconsin-Madison	5 K12 HD055894-09	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Womens Health at MUSC	Brady, Kathleen T	Medical University of South Carolina	5 K12 HD055885-09	RePORTER Proj Info

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2015	Building Interdisciplinary Research Careers in Women's Health	Career Development in Women's Health (CWDH)	Dunaif, Andrea	Northwestern University at Chicago	5 K12 HD055884-09	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Oregon BIRCWH: Scholars in Women's Health Research Across the Lifespan	Guise, Jeanne-Marie; Dorsa, Daniel Michael	Oregon Health & Science University	5 K12 HD043488-14	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	The Colorado Building Interdisciplinary Research Careers in Women's Health Program	Regensteiner, Judith G; Santoro, Nanette F	University of Colorado Denver	5 K12 HD057022-09	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Kentucky BIRCWH Program: Training The Next Generation of Womens Health Scholars	Curry, Thomas E	University of Kentucky	5 K12 DA035150-04	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Center for Neurovisceral Sciences & Women's Health	Mayer, Emeran A	University of California Los Angeles	3 P50 DKK064539-14S1	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Molecular and Epidemiologic Basis of UTI in Women	Hultgren, Scott J	Washington University	3 P50 DK064540-14S1	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Sex Differences and Progesterone Effects on Impulsivity, Smoking & Cocaine Abuse	Carroll, Marilyn E	University of Minnesota	5 P50 DA033942-04	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function	Kohrt, Wendy M	University of Colorado Denver	5 P50 HD073063-04	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Birth, Muscle Injury and Pelvic Floor Dysfunction	Delancey, John O L	University of Michigan	5 P50 HD044406-14	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Sex-Specific Risk for Vascular Dysfunction and Cognitive Decline	Miller, Virginia M	Mayo Clinic Rochester	5 P50 AG044170-04	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Center for Neurovisceral Sciences & Women's Health	Mayer, Emeran A	University of California Los Angeles	5 P50 DK064539-14	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Sex Differences in Musculoskeletal Conditions Across the Lifespan	Lane, Nancy E	University of California at Davis	5 P50 AR063043-04	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Genes, Androgens and Intrauterine Environment In PCOS	Dunaif, Andrea	Northwestern University at Chicago	5 P50 HD044405-14	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Molecular and Epidemiologic Basis of UTI in Women	Hultgren, Scott J	Washington University	5 P50 DK064540-14	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	ORWH: SCOR on Sex and Gender Factors Affecting Womens Health	Brady, Kathleen T	Medical University of South Carolina	5 P50 DA016511-14	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Yale SCOR on Gender-Sensitive Treatment for Tobacco Dependence	McKee, Sherry Ann	Yale University	5 P50 DA033945-04	RePORTER Proj Info
2015	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Prepubertal Stress, Windows of Risk & Sex Bias for Affective Disturbance	Epperson, C Neill Neill	University of Pennsylvania	5 P50 MH099910-04	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Center for Neurovisceral Sciences & Women's Health	Mayer, Emeran A	University of California Los Angeles	4 P50 DK064539-15	RePORTER Proj Info

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2016	Specialized Centers of Research on Sex Differences	Molecular and Epidemiologic Basis of UTI in Women	Hultgren, Scott J	Washington University	4 P50 DK064540-15	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Prepubertal Stress, Windows of Risk & Sex Bias for Affective Disturbance	Epperson, C Neill Neill	University of Pennsylvania	4 P50 MH099910-05	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Sex-Specific Risk for Vascular Dysfunction and Cognitive Decline	Miller, Virginia M	Mayo Clinic Rochester	4 P50 AG044170-05	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Sex Differences in Musculoskeletal Conditions Across the Lifespan	Lane, Nancy E	University of California at Davis	4 P50 AR063043-05	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Sex Differences and Progesterone Effects on Impulsivity, Smoking & Cocaine Abuse	Carroll, Marilyn E	University of Minnesota	4 P50 DA033942-05	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	ORWH: SCOR on Sex and Gender Factors Affecting Women's Health	Brady, Kathleen T	Medical University of South Carolina	4 P50 DA016511-15	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Yale SCOR on Gender-Sensitive Treatment for Tobacco Dependence	McKee, Sherry Ann	Yale University	4 P50 DA033945-05	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function	Kohrt, Wendy M	University of Colorado Denver	4 P50 HD073063-05	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Birth, Muscle Injury and Pelvic Floor Dysfunction	Delancey, John OL	University of Michigan	4 P50 HD044406-15	RePORTER Proj Info
2016	Specialized Centers of Research on Sex Differences	Genes, Androgens and Intrauterine Environment in PCOS	Dunaif, Andrea	Northwestern University at Chicago	4 P50 HD044405-15	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	UTMB Women's Health Research Scholars Program	Berenson, Abbey B	University of Texas Medical Br Galveston	5 K12 HD052023-12	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Mayo Clinic Building Interdisciplinary Research Careers in Women's Health	Miller, Virginia M	Mayo Clinic Rochester	5 K12 HD065987-07	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Hormones and Genes in Women's Health: Bench to Bedside	Goldstein, Jill M	Brigham and Women's Hospital	5 K12 HD051959-12	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Training in Sex and Gender Differences Research To Improve Women's Health	Epperson, C Neill Neill	University of Pennsylvania	5 K12 HD085848-02	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	UNC BIRCWH	Boggess, Kim A	Univ of North Carolina Chapel Hill	5 K12 HD001441-17	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Emory University BIRCWH Program	Sterk, Claire E	Emory University	5 K12 HD085850-02	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Careers in Women's Health at UC Davis	Gold, Ellen B	University of California at Davis	5 K12 HD051958-12	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	UCSF-Kaiser Building Interdisciplinary Research Careers in Women's Health Program	Brindis, Claire D; Adler, Nancy E	University of California, San Francisco	5 K12 HD052163-17	RePORTER Proj Info
2016	Building Interdisciplinary Research Careers in Women's Health	Utah Building Interdisciplinary Research Careers in Women's Health Career Development Program	Varnier, Michael W	University of Utah	5 K12 HD085852-02	RePORTER Proj Info

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2016	Building Interdisciplinary Research Careers in Women's Health	The Johns Hopkins Clinical Research Scholars in Women's Health (BIRCWH)	Ford, Daniel Ernest	Johns Hopkins University	5 K12 HD085845-02	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	UTMB Women's Health Research Scholars Program	Berenson, Abbey B	University of Texas Medical Br Galveston	2 K12 HD052023-11	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Mayo Clinic Building Interdisciplinary Research Careers in Womens Health	Miller, Virginia M	Mayo Clinic Rochester	2 K12 HD065987-06	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Training in Sex And Gender Differences Research to Improve Womens Health	Epperson, C Neill Neill	University of Pennsylvania	1 K12 HD085848-01	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Emory University BIRCWH Program	Sterk, Claire E	Emory University	1 K12 HD085850-01	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Building Interdisciplinary Research Careers in Women's Health at UC Davis	Gold, Ellen B	University of California at Davis	2 K12 HD051958-11	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	UCSF-Kaiser Building Interdisciplinary Research Careers in Women's Health Program	Brindis, Claire D; Adler, Nancy E	University of California, San Francisco	2 K12 HD052163-16	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Utah Building Interdisciplinary Research Careers in Women's Health Career Development Program	Varnier, Michael W	University of Utah	1 K12 HD085852-01	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	The Johns Hopkins Clinical Research Scholars in Womens Health (BIRCWH)	Ford, Daniel Ernest	Johns Hopkins University	1 K12 HD085845-01	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	Hormones and Genes in Womens Health: Bench to Bedside	Goldstein, Jill M	Brigham and Women's Hospital	2 K12 HD051959-11	RePORTER Proj Info
2015	Building Interdisciplinary Research Careers in Women's Health	UNC BIRCWH	Boggess, Kim A	Univ of North Carolina Chapel Hill	2 K12 HD001441-16	RePORTER Proj Info
2016	Mechanisms, Measurement, and Management of Pain in Aging: From Molecular to Clinical (R01)	Brain Mechanisms for Clinical Placebo in Chronic Pain	Apkarian, Apkar Vania	Northwestern University at Chicago	3 R01 AT007987-04s1	RePORTER Proj Info
2015	Mechanisms, Models, Measurement, and Management in Pain Research (R01)	Central Mechanisms Involved in the Interactions Between Muscle Pain and Exercise	Sluka, Kathleen A	University of Iowa	3 R01 AR061371-04s1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Genetic Epidemiology of Rare and Regulatory Variants for Metabolic Traits	Mohlke, Karen L	Univ of North Carolina Chapel Hill	3 R01 DK093757-05s1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Cellular Protein Involved in Trafficking Of HIV-1	Carter, Carol A	State University New York Stony Brook	5 R01 GM111028-08	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Determination of the Mechanisms by Which Igfbp-2 Stimulates Bone Remodeling	Rosen, Clifford James; Clemmons, David Robert	Maine Medical Center	3 R01 AR061164-05S1	RePORTER Proj Info
2015	NIH Support for Conferences and Scientific Meetings (Parent R13/U13)	Society for Prevention Research Annual Meetings, 2012-2016	Gorman-Smith, Deborah	Society for Prevention Research, Inc.	5 R13 DA033149-04	RePORTER Proj Info

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2016	NIH Support for Conferences and Scientific Meetings (Parent R13/U13)	Society for Prevention Research Annual Meetings, 2012-2016	Gorman-Smith, Deborah	Society for Prevention Research, Inc.	4 R13 DA033149-05	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Pediatric CFS in a Community-Based Sample	Jason, Leonard A	De Paul University	5 R01 HD072208-03	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Pediatric CFS in a Community-Based Sample	Jason, Leonard A	De Paul University	4 R01 HD072208-04	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Application of Two Animal Models in Pursuit of Myopia Control	Wildsoet, Christine Frances	University of California Berkeley	3 R01 EY012392-14S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Regeneration of the Lower Urinary Tract in Nonhuman Primates	Williams, James Koudy	Wake Forest University Health Sciences	3 R01 DK083688-07S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Mapping Hypothalamic Neurocircuits Controlling Physical Activity	Ingraham, Holly A	University of California, San Francisco	3 R01 DK099722-02S1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Modulation of Colonic Response to Stress by Peripheral Crf2 Receptors	Mulugeta, Million	University of California Los Angeles	3 R01 DK078676-08S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Face Processing Systems in Schizophrenia Spectrum Disorders	Chen, Yue	McLean Hospital	3 R01 MH096793-04S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Specificity and Validity of Oxidative Stress Model of Chronic Fatigue Syndrome	Shungu, Dikoma C	Weill Medical Coll of Cornell Univ	5 R01 MH100005-03	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Specificity and Validity of Oxidative Stress Model of Chronic Fatigue Syndrome	Shungu, Dikoma C	Weill Medical Coll of Cornell Univ	4 R01 MH100005-04	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Brain Injury Due to Soccer Heading and Opportunities for its Mitigation	Lipton, Michael Lawrence	Albert Einstein College of Medicine	3 R01 NS082432-03S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Brain Endothelial Cell Function Under Adenosine Receptor Signaling Directive	Bynoe, Margaret S	Cornell University	3 R01 NS078018-04S1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Consequences of Prolonged Febrile Seizures in Childhood	Shinnar, Shlomo	Albert Einstein College of Medicine, Inc	3 R37 NS043209-15S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Mechanisms Underlying Persistent Lentivirus Replication in Follicular T Cells	Connick, Elizabeth; Skinner, Pamela J	University of Colorado Denver	5 R01 AI096966-03	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	The Interaction of Varenicline, Ethanol, and CNS Development	Dubois, Dustin W	Texas A&M University Health Science Ctr	1 R56 AA021844-01A1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Role of Notch Signaling in Osteocytes	Canalis, Ernesto	University of Connecticut Sch of Med/Dnt	3 R01 AR063049-04S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Sclerostin Antibody Therapy for Treatment of Osteogenesis Imperfecta	Kozloff, Kenneth M	University of Michigan	3 R01 AR062522-04S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Influence of PTSD Symptoms on Chronic Pain Development After Sexual Assault	McLean, Samuel A	Univ of North Carolina Chapel Hill	5 R01 AR064700-02	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Translational Studies Of GAA Deficiency In Bioengineered Human Muscle	Bursac, Nenad; Koeberl, Dwight D	Duke University	3 R01 AR065873-02S1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	HSV-2 Immune Evasion as a Virulence Factor	Friedman, Harvey Michael	University of Pennsylvania	5 R01 AI104854-03	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Influence of PTSD Symptoms on Chronic Pain Development After Sexual Assault	McLean, Samuel A	Univ of North Carolina Chapel Hill	5 R01 AR064700-03	RePORTER Proj Info

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2016	Research on The Health of LGBTI Populations [R01]	Identity Stress and Health in Three Cohorts of LGB Individuals	Meyer, Ilan H	University of California Los Angeles	5 R01 HD078526-03	RePORTER Proj Info
2016	Research on the Health of LGBTI Populations [R01]	Impact of Supportive Policies on Minority Stress, Drinking and Health Among Women	Hughes, Tonda L	University of Illinois at Chicago	2 R56 AA013328-10	RePORTER Proj Info
2015	NIH Support for Conferences and Scientific Meetings (Parent R13/U13)	Organization for the Study of Sex Differences Annual Meeting	Meisel, Robert L	University of Minnesota	5 R13 HD080243-02	RePORTER Proj Info
2016	NIH Support for Conferences and Scientific Meetings (Parent R13/U13)	Organization for the Study of Sex Differences Annual Meeting	Meisel, Robert L	University of Minnesota	5 R13 HD080243-03	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Adrenomedullin Signaling at the Maternal-Fetal Interface	Caron, Kathleen M	Univ of North Carolina Chapel Hill	2 R01 HD060860-06A1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Sensorimotor Learning in Children with Cerebral Palsy	Kurz, Max	University of Nebraska Medical Center	3 R01 HD086245-02S1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	FSH And IGF1R Signaling Crosstalk in Ovarian GCS	Stocco, Carlos Oscar	University of Illinois at Chicago	1 R56 HD086054-01A1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Ovarian-Specific Transcription Networks Regulated by the TFIID Subunit TAF4B	Freiman, Richard Neil	Brown University	2 R56 HD065445-06A1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Altering The Physical Microenvironment and Enhancing Lipid Availability for In Vitro Follicle and Oocyte Development	Songsasen, Nucharin	Smithsonian Institution	1 R56 OD018304-01A1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Improving Heart Transplant Allocation to Reduce High Waitlist Mortality in Women	Hsich, Eileen Michelle	Cleveland Clinic Lerner Com-CWRU	1 R56 HL125420-01A1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Impact of Prenatal Hypoxia on Mitochondrial Function of Offspring Hearts	Thompson, Loren P	University of Maryland Baltimore	5 R56 HL126859-01	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Immune Modulation of Hypertension	Sandberg, Kathryn L	Georgetown University	1 R01 HL119380-01A1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Mechanisms Governing the Estrogenic Modulation of Sleep	Mong, Jessica Aurora	University of Maryland Baltimore	3 R01 HL129138-02S1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Sex Differences in Angiotensin-Induced Vascular Diseases	Cassis, Lisa A	University of Kentucky	2 R01 HL107326-05	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Pain Management for Older Adults Living in Nursing Homes	Lapane, Kate L	Univ of Massachusetts Med Sch Worcester	1 R56 NR015498-01A1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Innate Immunity and Autoantibodies in the Pathogenesis of Sjögren's Syndrome	Deshmukh, Umesh S	Oklahoma Medical Research Foundation	3 R01 DE025030-01A1S1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	The Mechanistic Control of Bone Extracellular Matrix Material Properties by TGFB	Alliston, Tamara N	University of California, San Francisco	3 R01 DE019284-08S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Expression and Iron-Independent Functions of Siderophores in Urinary Tract Infect	Henderson, Jeffrey P	Washington University	3 R01 DK099534-02S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Mitochondrial Function and Insulin Sensitivity in African American Women	Delany, James	University of Pittsburgh at Pittsburgh	2 R56 DK091462-04A1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	The Female Urinary Microbiome and Urinary Incontinence	Brubaker, Linda; Wolfe, Alan J	Loyola University Chicago	1 R56 DK104718-01	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Role of SerpinB1 in Beta Cell Growth	Kulkarni, Rohit N	Joslin Diabetes Center	3 R01 DK103215-03S1	RePORTER Proj Info

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2016	Research Project Grant (Parent R01)	BPA And Phthalates: Effects on Inflammatory Markers in the Breast and Breast Density in Young Women	Sturgeon, Susan R; Arcaro, Kathleen Frances	University of Massachusetts Amherst	1 R56 ES026177-01A1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Phthalates and Ovarian Toxicity	Flaws, Jodi A	University of Illinois at Urbana-Champaign	1 R56 ES025147-01A1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Adolescent Maturation of the Prefrontal Cortex: Modulation by Cannabinoids	Tseng, Kuei-Yuan	Rosalind Franklin Univ of Medicine & Sci	3 R01 MH105488-02S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Estradiol and Hippocampal Development	McCarthy, Margaret M	University of Maryland Baltimore	2 R56 NS050525-10	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Role of Neuropeptides in Stress-Induced Escalation of Alcohol Drinking	Gilpin, Nicholas W	LSU Health Sciences Center	3 R01 AA023305-02S1	RePORTER Proj Info
2015	Research Project Grant (Parent R01)	Bone Robustness as a Biomarker of Skeletal Aging and Fragility	Jepsen, Karl J	University of Michigan	3 R01 AR065424-02S1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Impact of Pregnancy on Tuberculosis	Ellner, Jerrold J	Boston Medical Center	5 R01 AI124217-02	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Psychological Effects of Helping Behavior in Older Adults	Brown, Stephanie L	State University New York Stony Brook	1 R56 AG049795-01A1	RePORTER Proj Info
2016	Research Project Grant (Parent R01)	Regulation of Craving Under Stress: Novel Model And Neural Mechanisms	Kober, Hedy	Yale University	1 R56 DA040699-01A1	RePORTER Proj Info
2016	Academic Research Enhancement Award (Parent R15)	Alcohol Use, Relationship Factors, Minority Stress, and Psychological Well-Being: A Daily Process Examination Among Young Adult Females	Lewis, Robin J	Old Dominion University	2 R15 AA020424-02	RePORTER Proj Info
2015	NIH Support for Conferences and Scientific Meetings (Parent R13/U13)	Oncofertility Consortium Annual Conference	Woodruff, Teresa K	Northwestern University at Chicago	2 R13 HD063248-05A1	RePORTER Proj Info
2015	NIH Support for Conferences and Scientific Meetings (Parent R13/U13)	SAR 2015: Reaching Across Disciplines to Broaden the Acupuncture Research Network	Napadow, Vitaly; Harris, Richard E	Society For Acupuncture Research, Inc.	1 R13 AT008760-01	RePORTER Proj Info
2016	NIH Support for Conferences and Scientific Meetings (Parent R13/U13)	How Can Precision Medicine Be Applied to Temporomandibular Disorders and Its Comorbidities?	Cowley, Allen W	TMJ Association	1 R13 DE026363-01	RePORTER Proj Info
2015	Administrative Supplement Program	Identity Stress and Health in Three Cohorts Of LGB Individuals	Meyer, Ilan H	University of California Los Angeles	3 R01 HD078526-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	The RAP80-BRCC36 Deubiquitinating Complex In DNA Repair	Greenberg, Roger A	University of Pennsylvania	3 R01 CA138835-06A1S1	RePORTER Proj Info
2015	Administrative Supplement Program	Pregnancy as a Window to Future Cardiovascular Health: Adverse Pregnancy Outcomes Supplement Request	Parker, Corette Breeden	Research Triangle Institute	3 U10 HL119991-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	Imaging Brain Function in Real World Environments & Populations With Portable MRI	Garwood, Michael G; Vaughan, John T	University of Minnesota	3 R24 MH105998-02S1	RePORTER Proj Info
2016	Administrative Supplement Program	Impact of Exercise on Body Composition in Premature Infants: New Approaches	Cooper, Dan M	University of California-Irvine	3 R01 HL110163-05S1	RePORTER Proj Info
2015	Research on Chronic Overlapping Pain Conditions (R01)	Circulating MicroRNAs and TLR8 Activation in Chronic Pain	Khan, Asma	Univ of North Carolina Chapel Hill	1 R56 DE025399-01	RePORTER Proj Info

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2016	Research On Chronic Overlapping Pain Conditions (R01)	Proteins, MicroRNAs and Genes Associated With TMD and Overlapping Pain Conditions	Nackley Neely, Andrea G; Slade, Gary Douglas	Duke University	1 R56 DE025298-01A1	RePORTER Proj Info
2015	Administrative Supplement Program	Effects of Fetal Sex on the First Trimester Transcriptome	Pisarska, Margareta	Cedars-Sinai Medical Center	3 R01 HD074368-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	Impact of Sex of Embryo on Morphogenesis and Therapy in Diabetic Pregnancy	Zhao, Zhiyong	University of Maryland Baltimore	3 R01 HD076245-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	The Role Of CHD5 in Chromatin-Mediated Regulation of Neural Stem Cells and Glioma	Mills, Alea A	Cold Spring Harbor Laboratory	3 R01 CA190997-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	(PQB-4) Single Cell Analysis Strategy for Monitoring Drug Responses of Tumors	Tian, Qiang	Institute For Systems Biology	3 R01 CA190122-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	(PDQ6) Hypothalamic Inflammation in the Initiation of Cachexia	Marks, Daniel L	Oregon Health & Science University	3 R01 CA184324-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Smooth Muscle Mineralocorticoid Receptors in Vascular Aging and Hypertension	Jaffe, Iris Z	Tufts Medical Center	3 R01 HL119290-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Mitochondrial Quality in Cardioprotection: Overcoming Co-Morbidities	Gottlieb, Roberta A	Cedars-Sinai Medical Center	3 P01 HL112730-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	Disruption of The Clock O-GlcNAc Axis in Diabetic Cardiomyopathy	Chatham, John C; Young, Martin Elliot	University of Alabama at Birmingham	3 R01 HL122975-01A1S1	RePORTER Proj Info
2015	Administrative Supplement Program	Regulations of Myoendothelial Function by Signaling Microdomains in Hypertension	Nelson, Mark T	University Of Vermont & St Agric College	3 R01 HL121706-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Directed Culturing of Pneumocystis Using Metatranscriptomics	Cushion, Melanie T; Porollo, Alexey	University of Cincinnati	3 R01 HL119190-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	Development of Prognostic Platelet RNA Biomarkers to Tailor Antiplatelet Therapy	Voora, Deepak	Duke University	3 R01 HL118049-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	Functional Hierarchy of Remnant Lipoprotein Receptors	Fazio, Sergio	Oregon Health & Science University	3 R01 HL057986-18S1	RePORTER Proj Info
2015	Administrative Supplement Program	Mass Spectrometry Tools in Pursuit of Salivary Biomarkers of Sjögren's Syndrome	Hall, Steven C	University of California, San Francisco	3 R01 DE022031-04S1	RePORTER Proj Info
2015	Administrative Supplement Program	Gender Differences in Stress-Induced Pain Transition After Surgery	Tao, Feng	Texas A&M University Health Science Ctr	3 R01 DE022880-05S1	RePORTER Proj Info
2015	Administrative Supplement Program	Role of ACSL5 in Intestinal and Liver Triacylglycerol Metabolism	Greenberg, Andrew S	Tufts University Boston	3 R01 DK098606-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Accounting for Effect Size Differences Between Sexes in Genome-Wide Association Studies Using Mixed Models and Meta-Analysis	Eskin, Eleazar	University of California Los Angeles	3 R01 ES022282-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	Nitrite Dependent Protection Against Cl2 Gas Toxicity Role Of Chlorinated Lipids	Patel, Rakesh Pravinchandra	University of Alabama at Birmingham	3 U01 ES023759-03S1	RePORTER Proj Info

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2015	Administrative Supplement Program	Admin Suppl to Study Sex/Gender Differences and HIV-1 Viral Particle Transmission Capability	Carter, Carol A	State University New York Stony Brook	3 R01 GM111028-07S3	RePORTER Proj Info
2015	Administrative Supplement Program	Form And Function Function of Our Janus Faced Genome	Ambati, Jayakrishna	University of Kentucky	3 Dp1 GM114862-01S1	RePORTER Proj Info
2015	Administrative Supplement Program	The Role of Sex in the Evolution and Spread of Virulent Infectious Disease	Potts, Wayne K; Adler, Frederick R	University of Utah	3 R01 GM109500-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	REM Sleep and Memory	Poe, Gina R	University of Michigan	3 R01 MH060670-14S1	RePORTER Proj Info
2015	Administrative Supplement Program	Stressor Controllability: The Role of the MPFC in Producing Resiliency	Maier, Steven F	University of Colorado	3 R01 MH050479-23S1	RePORTER Proj Info
2015	Administrative Supplement Program	Neurophysiological Markers of Hand and The Impact of Aging: Evidence From Meg	Wilson, Tony W	University of Nebraska Medical Center	3 R01 MH103220-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Epigenome Interactions in Complex Neurogenetic Disorders	Ross, Margaret Elizabeth; Mason, Christopher Edward	Weill Medical Coll of Cornell Univ	3 R01 NS076465-05S1	RePORTER Proj Info
2015	Administrative Supplement Program	Basal Ganglia and Sleep Related Motor Disorders	Lai, Yuan-Yang	Sepulveda Research Corporation	3 R01 NS082242-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Neuroprotection in the Aging Female Brain	Sohrabji, Farida	Texas A&M University Health Science Ctr	3 R01 NS074895-06S1	RePORTER Proj Info
2015	Administrative Supplement Program	Regulatory Control of Glutamate - Induced Superoxide Production [Admin Supplement]	Swanson, Raymond A	Northern California Institute/Res/Edu	3 R01 NS081149-04S1	RePORTER Proj Info
2015	Administrative Supplement Program	The Role of ASICs In Migraine Pathophysiology	Dussor, Gregory O	University of Texas Dallas	3 R01 NS072204-04S1	RePORTER Proj Info
2015	Administrative Supplement Program	Beta Endorphin Neurons and the Control of Homeostasis	Kelly, Martin Jeffrey	Oregon Health & Science University	3 R01 NS038809-15S1	RePORTER Proj Info
2015	Administrative Supplement Program	Nociceptor Mechanisms in the Transition From Acute to Chronic Pain	Levine, Jon David	University of California, San Francisco	3 R01 NS084545-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Role of Lipid Droplets in Neurovascular Inflammation	Rutledge, John Calvert; Villablanca, Amparo C	University of California at Davis	3 R01 AG045541-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Modeling The Influence of Sex on Natural Killer Cell Networks	Blish, Catherine A	Stanford University	3 Dp2 AI112193-01S1	RePORTER Proj Info
2015	Administrative Supplement Program	Frailty and Risk Prediction in Older Adults Considering Kidney Transplantation	Segev, Dorry L	Johns Hopkins University	3 R01 AG042504-03S2	RePORTER Proj Info
2015	Administrative Supplement Program	Tailored Inhibitory Control Training to Reverse EA-Linked Deficits in Mid-Life	Berkman, Elliot Todd	University of Oregon	3 R01 AG048840-02S1	RePORTER Proj Info
2015	Administrative Supplement Program	Cell Autonomous and Non-Autonomous Mechanisms of Aging	Robbins, Paul D	Scripps Florida	3 P01 AG043376-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	Quantifying Changes in Neural Stem Cell Lineages in the Aging Niche	Temple, Sally; Cohen, Andrew Robert	Regenerative Research Foundation	3 R01 AG041861-04S1	RePORTER Proj Info
2015	Administrative Supplement Program	The Impact Of HPA Axis Dysregulation on the Interceptive Effects of Alcohol - Admin Supplement	Besheer, Joyce	Univ of North Carolina Chapel Hill	3 R01 AA019682-05S1	RePORTER Proj Info
2015	Administrative Supplement Program	Sex Differences in the Cannabinoid Regulation of Energy Homeostasis	Wagner, Edward J	Western University of Health Sciences	3 R15 DA024314-02A1S1	RePORTER Proj Info

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2015	Administrative Supplement Program	Modulation of Norepinephrine by Cannabinoids	Van Bockstaele, Elisabeth J; Valentino, Rita	Drexel University	3 R01 DA020129-08S1	RePORTER Proj Info
2015	Administrative Supplement Program	Sex Differences in Adolescent Exposure to Morphine on Reward-Related Behaviors in Subsequent Offspring	Byrnes, Elizabeth M	Tufts University Boston	3 R01 DA025674-06S1	RePORTER Proj Info
2015	Administrative Supplement Program	Behavioral and Epigenetic Mechanisms in Extinction of Cocaine-Induced Memories	Lattal, K Matthew; Wood, Marcelo Andres	Oregon Health & Science University	3 R01 DA025922-07S2	RePORTER Proj Info
2015	Administrative Supplement Program	Utilizing Interaction to Identify Novel Genetic Factors for Nicotine Dependence	Hancock, Dana B	Research Triangle Institute	3 R01 DA035825-03S1	RePORTER Proj Info
2015	Administrative Supplement Program	Synaptic Actin Dynamics and The Selective Vulnerability of Drug-Associated Memory	Miller, Courtney A	Scripps Florida	3 R01 DA034116-03S1	RePORTER Proj Info
2016	Drug Abuse Prevention Intervention Research (R01)	Comparing Novel Strategies for Reducing Drug Abuse in Male and Female Rhesus Monkeys	Carroll, Marilyn E	University of Minnesota	1 R56 DA042618-01	RePORTER Proj Info
2016	Administrative Supplement Program	Pluripotent Stem Cells: Modeling Syncytiotrophoblast Development and Pathogenesis	Ezashi, Toshihiko; Schust, Danny J	University of Missouri-Columbia	3 R01 HD077108-04S1	RePORTER Proj Info
2016	Administrative Supplement Program	Molecular Basis for the Impact of Sex Brain Tumorigenesis	Rubin, Joshua B	Washington University	3 R01 CA174737-03S1	RePORTER Proj Info
2016	Administrative Supplement Program	The Relief Study: Neuromuscular Mechanisms Underlying Spinal Manipulation Treatments	Thomas, James S; Clark, Brian C	Ohio University Athens	3 R01 AT006978-05S1	RePORTER Proj Info
2016	Administrative Supplement Program	Preclinical Investigation of a Bioengineered Vascular Graft	Ameer, Guillermo Antonio; Kibbe, Melina Rae	Northwestern University	3 R01 EB017129-04S1	RePORTER Proj Info
2016	Administrative Supplement Program	Estrogen Receptor Signaling in Airway Inflammation	Venkatachalem, Sathish	Mayo Clinic Rochester	3 R01 HL123494-02S1	RePORTER Proj Info
2016	Administrative Supplement Program	Genetics of Gene Expression in Human Left Ventricular Myocardium	Muehlschlegel, Jochen Daniel	Brigham and Women's Hospital	3 R01 HL118266-04S1	RePORTER Proj Info
2016	Administrative Supplement Program	Cardiovascular Cell Therapy Research Network	Willerson, James T; Perin, Emerson Carvalho	Texas Heart Institute	3 UM1 HL087365-10S1	RePORTER Proj Info
2016	Administrative Supplement Program	Modeling Susceptibility to Chemotherapy-Induced Cardiotoxicity Using Human iPSCs	Wu, Joseph C	Stanford University	3 R01 HL123968-03S1	RePORTER Proj Info
2016	Administrative Supplement Program	Obesity-Induced Sympathoexcitation: Role of Brain Insulin	Brooks, Virginia L	Oregon Health & Science University	3 R01 HL128181-01A1S1	RePORTER Proj Info
2016	Administrative Supplement Program	Predicting the Causative SNPs In LD Blocks by Allele-Specific Structural Analysis	Laederach, Alain T; Weeks, Kevin M	Univ of North Carolina Chapel Hill	3 R01 HG008133-02S2	RePORTER Proj Info
2016	Administrative Supplement Program	Microbiome and Pain Supplement	Heitkemper, Margaret Mclean; Shulman, Robert	University of Washington	3 R01 NR014479-03S2	RePORTER Proj Info
2016	Administrative Supplement Program	Video Information Provider For HIV-Associated Non-AIDS (VIP-HANA) Symptoms	Schnall, Rebecca	Columbia University Health Sciences	3 R01 NR015737-02S1	RePORTER Proj Info
2016	Administrative Supplement Program	The Role of Hepatic Insulin Resistance On SR-BI Dependent HDL Cholesterol Uptake	Graf, Gregory A; Van Der Westhuyzen, Deneys Rem	University of Kentucky	3 R01 DK100892-04S1	RePORTER Proj Info

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2016	Administrative Supplement Program	Signaling Of The Pregnane X Receptor	Yan, Bingfang	University of Rhode Island	3 R01 GM061988-11S1	RePORTER Proj Info
2016	Administrative Supplement Program	Integrative Informatics Approach to Develop Safe Glucocorticoid Therapies	Budunova, Irina; Dudley, Joel Thomas	Northwestern University at Chicago	3 R01 GM112945-02S1	RePORTER Proj Info
2016	Administrative Supplement Program	The Central Amygdala Circuits in Fear Learning and Fear Expression	Li, Bo	Cold Spring Harbor Laboratory	3 R01 MH101214-03S1	RePORTER Proj Info
2016	Administrative Supplement Program	Novel Mechanisms for Distal Transport in Developing and Mature Neurons	Weimer, Jill M	Sanford Research/ USD	3 R01 NS082283-03S1	RePORTER Proj Info
2016	Administrative Supplement Program	Circadian Dysfunction And GSK3 In Neurodegenerative Disease	Gamble, Karen L	University of Alabama at Birmingham	3 R01 NS082413-04S1	RePORTER Proj Info
2016	Administrative Supplement Program	Neutralizing Epigenomes in Neurodevelopment Disorders	Iwase, Shigeki	University of Michigan	3 R01 NS089896-02S1	RePORTER Proj Info
2016	Administrative Supplement Program	Functional Genetics of the Neuronal Sodium Channel Gene SCN8A	Meisler, Miriam H	University of Michigan	3 R01 NS034509-20S1	RePORTER Proj Info
2016	Administrative Supplement Program	Ischemic Preconditioning: Mechanisms of Neuroprotection	Perez-Pinzon, Miguel A	University of Miami School of Medicine	3 R01 NS034773-16S1	RePORTER Proj Info
2016	Administrative Supplement Program	Ionic Currents and Spiking in Cerebellar Nuclear Neurons	Raman, Indira M	Northwestern University	3 R37 NS039395-16S1	RePORTER Proj Info
2016	Administrative Supplement Program	A Megakaryocyte/PGE2/ Osteoblast Triad In The Normal and Aged Niche	Pelus, Louis M; Kacena, Melissa A	Indiana Univ-Purdue Univ at Indianapolis	3 R01 AG046246-04S1	RePORTER Proj Info
2016	Administrative Supplement Program	Wisconsin Registry for Alzheimer's Prevention: Sex Differences in DNA Methylation	Johnson, Sterling C	University of Wisconsin-Madison	3 R01 AG027161-09S1	RePORTER Proj Info
2016	Administrative Supplement Program	Administrative Supplement: Cortical Biobehavioral Disruption After Thiamine Deficiency and Chronic Alcohol	Savage, Lisa M	State University Of NY, Binghamton	3 R01 AA021775-03S1	RePORTER Proj Info
2016	Administrative Supplement Program	Runx1 Control of Bone Resorption During Fracture Repair Supplement	Drissi, Hicham M; Lorenzo, Joseph A	University of Connecticut Sch of Med/Dnt	3 R01 AR063661-04S1	RePORTER Proj Info
2016	Administrative Supplement Program	The Role of Tweak and FN14 In the Pathogenesis and Treatment of Neuropsychiatric	Putterman, Chaim	Albert Einstein College Of Medicine, Inc	3 R01 AR065594-03S1	RePORTER Proj Info
2016	Administrative Supplement Program	Sex Differences in Tendon Growth And Remodeling	Mendias, Christopher L	University of Michigan	3 R01 AR063649-04S1	RePORTER Proj Info
2016	Administrative Supplement Program	Elucidating the Mechanisms of Arthritic Flare and Developing Treatments	Schwarz, Edward M	University of Rochester	3 R01 AR056702-07S1	RePORTER Proj Info
2016	Administrative Supplement Program	Suppression of Bone Mechanotransduction by the Beta 2 Adrenergic Receptor	Gardiner, Edith M	University of Washington	3 R01 AR066710-02S1	RePORTER Proj Info
2016	Administrative Supplement Program	Macrophage and Fibroblast Modulation Toward Chronic Vocal Fold Scar Restoration	Thibeault, Susan; Hahn, Mariah S	University of Wisconsin-Madison	3 R01 DC013508-03S1	RePORTER Proj Info
2016	Administrative Supplement Program	Acute Hepatitis C Infection in Young Injectors	Page, Kimberly	University of New Mexico Health Sci Ctr	3 R01 DA016017-14S1	RePORTER Proj Info
2016	Administrative Supplement Program	Cognitive Control in Children of SUD Parents: A Longitudinal Multimodal MRI Study	Hoven, Christina W	New York State Psychiatric Institute	3 R01 DA038154-02WS1	RePORTER Proj Info

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2016	Administrative Supplement Program	Vulnerability to Drug Use & HIV: Advancing Prevention for Rural African Americans	Brody, Gene H	University of Georgia	3 P30 DA027827-08S2	RePORTER Proj Info
2016	Administrative Supplement Program	Combining Varenicline and Naltrexone for Smoking Cessation in Heavy Drinkers	Ray, Lara A	University of California Los Angeles	3 R01 DA041226-02S1	RePORTER Proj Info
2016	Administrative Supplement Program	Homeostatic Plasticity in the Control of Neuropathic Pain	Jin, Xiaoming	Indiana Univ-Purdue Univ at Indianapolis	3 R01 DA039530-03S1	RePORTER Proj Info
2016	Administrative Supplement Program	Involvement of Hypocretin-Orexin in the Regulation of Dopamine Signaling and Reinforcement Processes in Females	Espana, Rodrigo Amilcar	Drexel University	3 R01 DA031900-04S1	RePORTER Proj Info
2016	Administrative Supplement Program	Single Cell Mapping of Developmental Trajectories Underlying Health and Disease	Pe'er, Dana	Sloan-Kettering Inst Can Research	7 DP1 HD084071-04	RePORTER Proj Info
2016	Administrative Supplement Program	PTPN22 and Autoimmunity	Bottini, Nunzio	University of California San Diego	7 R01 AI070544-08	RePORTER Proj Info
2015	Methodology and Measurement in the Behavioral and Social Sciences (R01)	Computational Characterization of Language Use in Autism Spectrum Disorder	Van Santen, Jan P	Oregon Health & Science University	3 R01 DC012033-04S1	RePORTER Proj Info
2015	NICHD Program Project Grant (P01)	Spinal Circuits and the Musculoskeletal System	English, Arthur W	Emory University	3 P01 HD032571-19S1	RePORTER Proj Info
2016	NICHD Program Project Grant (P01)	Importance of Endothelial Cell-Cell Communication at the Maternal Fetal Interface	Bird, Ian M	University of Wisconsin-Madison	3 P01 HD038843-14S1	RePORTER Proj Info
2015	Resource Related Research Projects for Development of Animal Models and Related Materials (R24)	Postmenopausal Monkey Resource	Bethea, Cynthia Louise	Oregon Health & Science University	3 R24 OD011895-04S1	RePORTER Proj Info
2015	Silvio O. Conte Centers for Basic and Translational Mental Health Research (P50)	Kynurenic Acid and Cognitive Abnormalities in Schizophrenia	Schwarcz, Robert	University of Maryland Baltimore	3 P50 MH103222-02S1	RePORTER Proj Info
2015	Predictive Multiscale Models for Biomedical, Biological, Behavioral, Environmental and Clinical Research (Interagency U01)	A Multi-Scale Modeling Construct of Knee Mechanics Following ACL Reconstruction	Dhafer, Yasin Yousef; Thelen, Darryl G	Rehabilitation Institute of Chicago	3 U01 EB015410-03S1	RePORTER Proj Info
2015	Social Neuroscience and Neuroeconomics of Aging (R01)	Stress and Decision-Making in Older Persons: Toward a Neurobehavioral Phenotype	Denburg, Natalie L	University of Iowa	1 R56 AG046539-01A1	RePORTER Proj Info
2015	Biodemography of Aging (R01)	Biodemography of Aging in Wild Chimpanzees	Thompson, Melissa Emery; Wrangham, Richard W; Rosati, Alexandra G; Mitani, John Cary	University of New Mexico	1 R01 AG049395-01	RePORTER Proj Info
2016	Biodemography of Aging (R01)	Biodemography of Aging in Wild Chimpanzees	Thompson, Melissa Emery; Wrangham, Richard W; Rosati, Alexandra G; Mitani, John Cary	University of New Mexico	5 R01 AG049395-02	RePORTER Proj Info
2016	Administrative Supplement Program	Urinary Knowledge Study (U-Know)	Kramer, Holly Joy	Loyola University Chicago	1 R01 DK104842-01A1	RePORTER Proj Info

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2016	Accelerating the Pace of Drug Abuse Research Using Existing Data (R01)	Understanding the Beliefs, Concerns, and Needs of Pregnant Patients Who Use Marijuana and of the Obstetrics Providers Caring for Them	Chang, Judy C	Magee-Women's Res Inst and Foundation	1 R56 DA040617-01	RePORTER Proj Info
2015	NIH/NSF Ecology of Infectious Diseases Program: Joint Program for Multidisciplinary Research	The Evolution and Spread of Virulent Infectious Disease	Potts, Wayne K; Adler, Frederick R	University of Utah	5 R01 GM109500-03	RePORTER Proj Info
2016	Innovative Research In Cancer Nanotechnology (IRCN) (U01)	Tunable Polymer-Graphene Oxide Composite for Single Cell Analysis of Breast Cancer CTCs & CSCs	Nagrath, Sunitha; Kim, Jinsang; Wicha, Max S	University of Michigan	1 R56 CA203290-01	RePORTER Proj Info
2016	Molecular and Cellular Substrates of Complex Brain Disorders (R01)	Interactions of 17beta Estradiol and Ketamine on Depression-Like Behavior, Hippocampal Synaptic Function, and Cognition in Ovariectomized Rats	McMahon, Lori Lynn	University of Alabama at Birmingham	1 R56 MH107190-01A1	RePORTER Proj Info
2016	Emerging Global Leader Award (K43)	Gestational Diabetes Mellitus, Gestational Hypertension and Risk of Metabolic Syndrome	Osofi, Alfred Onyango	University of Nairobi	1 K43 TW010363-01	RePORTER Proj Info
2015	2011 NIH Directors Pioneer Award Program (DP1)	Broad Spectrum Molecular Therapy for Blinding Retina Disorders	Bennett, Jean	University Of Pennsylvania	5 DP1 EY023177-05	RePORTER Proj Info
2015	Human Heredity and Health in Africa (H3Africa): Collaborative Centers (U54)	African Collaborative Center for Microbiome and Genomics Research (ACCME)	Adebamowo, Clement Adebayo	Institute Of Human Virology	5 U54 HG006947-03	RePORTER Proj Info
2015	Evaluation of Multi-Omic Data in Understanding the Human Microbiomes Role in Health and Disease (U54)	A Multi-Omic Analysis of the Vaginal Microbiome During Pregnancy	Buck, Gregory Allen; Jefferson, Kimberly Kay; Strauss, Jerome F	Virginia Commonwealth University	3 U54 HD080784-03S1	RePORTER Proj Info
2015	2014 NIH Pioneer Award Program (DP1)	Single Cell Mapping of Developmental Trajectories Underlying Health and Disease	Pe'er, Dana	Columbia Univ New York Morningside	5 DP1 HD084071-02	RePORTER Proj Info
2015	2014 NIH Pioneer Award Program (DP1)	Form and Function of our Janus Faced Genome	Ambati, Jayakrishna	University of Kentucky	5 DP1 GM114862-02	RePORTER Proj Info
2016	Library of Integrated Network-Based Cellular Signatures (LINCS): Perturbation-Induced Data and Signature Generation Centers (U54)	Drug Combination Signatures for Prediction and Mitigation of Toxicity	Iyengar, Srinivas Ravi V; Sobie, Eric A; Birtwistle, Marc R	Icahn School of Medicine at Mount Sinai	3 U54 HG008098-03S1	RePORTER Proj Info
2015	Computational Analyses Exploiting Reference Epigenomic Maps (R01)	Building the Foundation of Epigenomics Roadmaps	Li, Zhaoyu; Asmann, Yan W	Mayo Clinic Jacksonville	3 R01 ES024871-02S1	RePORTER Proj Info
2016	Limited Competition: Knockout Mouse Production and Phenotyping Project (UM1)	Consortium for Large-Scale Production and Phenotyping of Knockout Mice (UM1)	Beaudet, Arthur L; Dickinson, Mary E	Baylor College of Medicine	2 UM1 HG006348-06	RePORTER Proj Info
2015	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	Global Health Fellows and Scholars Research Training	Riley, Lee W; Ko, Albert Icksang; Madhivanan, Purnima; Barry, Michele	University of California Berkeley	5 R25 TW009338-04	RePORTER Proj Info

						RePORTER Project Info.
2015	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	Fogarty Global Health Fellows Coordinating Center	Chi, Benjamin H	Univ of North Carolina Chapel Hill	5 R25 TW009340-04	RePORTER Proj Info
2015	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	University of California Global Health Institute Program for Fellows and Scholars	Cohen, Craig R; Strathdee, Steffanie A	University of California, San Francisco	5 R25 TW009343-04	RePORTER Proj Info
2015	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	Northern/Pacific Universities Global Health Research Training Consortium	Zunt, Joseph Raymond; Nerurkar, Vivek Ramchandra; Kolars, Joseph C; Olson, Debra K	University of Washington	5 R25 TW009345-04	RePORTER Proj Info
2015	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	Vanderbilt-Emory-Cornell-Duke Consortium for Global Health Fellows (VECDOR)	Vermund, Sten H; Heimbürger, Douglas Corbett	Vanderbilt University	5 R25 TW009337-04	RePORTER Proj Info
2016	Limited Competition: Global Health Program For Fellows And Scholars (Global Health Fellows) (R25)	Vanderbilt-Emory-Cornell-Duke Consortium for Global Health Fellows (VECDOR)	Heimbürger, Douglas Corbett	Vanderbilt University Medical Center	5 R25 TW009337-06	RePORTER Proj Info
2016	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	Global Health Fellows and Scholars Research Training	Riley, Lee W; Ko, Albert Icksang; Madhivanan, Purnima; Barry, Michele	University of California Berkeley	4 R25 TW009338-05	RePORTER Proj Info
2016	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	Fogarty Global Health Fellows Coordinating Center	Chi, Benjamin H	Univ of North Carolina Chapel Hill	4 R25 TW009340-05	RePORTER Proj Info
2016	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	University of California Global Health Institute Program for Fellows and Scholars	Cohen, Craig R; Strathdee, Steffanie A	University of California, San Francisco	4 R25 TW009343-05	RePORTER Proj Info
2016	Limited Competition: Global Health Program for Fellows and Scholars (Global Health Fellows) (R25)	Northern/Pacific Universities Global Health Research Training Consortium	Zunt, Joseph Raymond; Nerurkar, Vivek Ramchandra; Kolars, Joseph C; Prasad, Shailendra	University of Washington	4 R25 TW009345-05	RePORTER Proj Info
2015	International Tobacco and Health Research and Capacity Building Program (R01)	Tobacco Control Network Among Women In Parana, Brazil - II	Scarinci, Isabel C	University of Alabama At Birmingham	5 R01 TW009272-04	RePORTER Proj Info
2016	International Tobacco and Health Research and Capacity Building Program (R01)	Tobacco Control Network Among Women in Parana, Brazil - II	Scarinci, Isabel C	University of Alabama at Birmingham	4 R01 TW009272-05	RePORTER Proj Info
2015	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	UZCHS-Promote Excellence In Research and Faculty Enhanced Career Training (Perfect Program)	Hakim, James Gita	College Of Health Scis Univ Of Zimbabwe	1 D43 TW010137-01	RePORTER Proj Info

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2015	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Strengthening of Research Capacity for Junior Faculty in Tanzania	Mteta, Alfred Kien	Kilimanjaro Christian Medical College	1 D43 TW010138-01	RePORTER Proj Info
2015	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Building Research And Innovation In Nigeria's Science - (BRAINS)	Ogunsola, Folasade Tolulope	University of Lagos-College of Medicine	1 D43 TW010134-01	RePORTER Proj Info
2015	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Partnership For Health Research Training In Kenya (P-HERT)	Wamalwa, Dalton Chekoko	University of Nairobi	1 D43 TW010141-01	RePORTER Proj Info
2015	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Nurture: Research Training and Mentoring Program for Career Development of Faculty at Makerere University College of Health Sciences	Sewankambo, Nelson K	Makerere University	1 D43 TW010132-01	RePORTER Proj Info
2016	Limited Competition: Research Training For Career Development Of Junior Faculty In Medical Education Partnership Initiative (MEPI) Institutions (D43)	UZCHS-Promote Excellence in Research and Faculty Enhanced Career Training (Perfect Program)	Hakim, James Gita	College of Health Scis Univ of Zimbabwe	5 D43 TW010137-02	RePORTER Proj Info
2016	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Strengthening of Research Capacity for Junior Faculty in Tanzania	Mteta, Alfred Kien	Kilimanjaro Christian Medical College	5 D43 TW010138-02	RePORTER Proj Info
2016	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Building Research and Innovation In Nigeria's Science - (BRAINS)	Ogunsola, Folasade Tolulope	University of Lagos-College of Medicine	5 D43 TW010134-02	RePORTER Proj Info
2016	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Partnership for Health Research Training In Kenya (P-HERT)	Wamalwa, Dalton Chekoko	University of Nairobi	5 D43 TW010141-02	RePORTER Proj Info

FY	RFA Title	Title	PI Name	Institution	Grant	RePORTER Project Info.
2016	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Nurture: Research Training and Mentoring Program for Career Development of Faculty at Makerere University College of Health Sciences	Sewankambo, Nelson K	Makerere University	5 D43 TW010132-02	RePORTER Proj Info
2016	Fogarty Global Injury and Trauma Research Training Program (D43)	Biobehavioral Research Approaches to Reduce Effects of Trauma on Mental and Physical Health and Cognitive Outcomes in South Africa	Wyatt, Gail E	University of California Los Angeles	2 D43 TW007278-11	RePORTER Proj Info

Appendix C. Members of the Working Group on Women in Biomedical Careers

FY 15

Co-Chairs

Francis S. Collins, M.D., Ph.D., Director, NIH
Janine Austin Clayton, M.D., Director, ORWH

Institute and Center Directors

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S., Director, NIEHS
Alan E. Guttmacher, Ph.D., Director, NICHD
Patricia Grady, Ph.D., R.N., F.A.A.N., Director, NINR
Story Landis, Ph.D., Director, NINDS
Griffin P. Rodgers, M.D., M.A.C.P., Director, NIDDK

Office of the Director

Lawrence Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH
Kathy L. Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, NIH
Benjamin Butler, J.D., Senior Attorney, Office of General Council (Ex-Officio)
Debra C. Chew, J.D., Director, Office of Equal, Diversity, and Inclusion, NIH
Hannah Valantine, M.D., Chief Officer for Scientific Workforce Diversity, NIH

Intramural Research

Michael Gottesman, M.D., Deputy Director for Intramural Research, NIH
Joan Schwartz, Ph.D., Special Volunteer, Office of Intramural Research
Edward Giniger, Ph.D., Investigator, NINDS
Elaine Ostrander, Ph.D., Chief & Senior Investigator, Cancer Genetics Branch, NHGRI
Kathryn Zoon, Ph.D., Scientific Director, NIAID

Extramural Research

Sally Rockey, Ph.D., Deputy Director for Extramural Research, NIH
P. Kay Lund, Ph.D., Ph.D., Director, Division of Biomedical Research Workforce, Office of Extramural Research, NIH
Judith H. Greenberg, Ph.D., Deputy Director, NIGMS
Pamela Marino, Ph.D., Program Director, Pharmacology, Physiology, and Biological Chemistry Division; Co-Director, Pharmacology Research Associate Program, NIGMS
Belinda Seto, Ph.D., Deputy Director, NEI
Marie Bernard, M.D., Deputy Director, NIA
Susan Shurin, M.D., Deputy Director, NHLBI
Joyce Hunter, Ph.D., Deputy Director, NIMHD

FY 16

Co-Chairs

Francis S. Collins, M.D., Ph.D., Director, NIH
Janine Austin Clayton, M.D., Director, ORWH

Institute and Center Directors

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S., Director, NIEHS
Patricia Grady, Ph.D., R.N., F.A.A.N., Director, NINR
Griffin P. Rodgers, M.D., M.A.C.P., Director, NIDDK
Cathy Y. Spong, M.D., Acting Director, NICHD

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Hannah Valentine, M.D., Chief Officer for Scientific
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Belinda Seto, Ph.D., Deputy Director, NEI
Marie Bernard, M.D., Deputy Director, NIA
Susan Shurin, M.D., Deputy Director, NHLBI
Catherine Spong, M.D., Deputy Director, NICHD
Joyce Hunter, Ph.D., Deputy Director, NIMHD

Appendix D. Aggregate Enrollment Data and Tables

Section 1: Metrics Based on Aggregate Enrollment by Sex/Gender

Table 1A: Total Enrollment for All National Institutes of Health (NIH) Clinical Research from FY 06-16

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2006	14,830,930	9,473,273	63.9	5,172,205	34.9	185,452	1.3	4,120,055	27.8	336,717	2.3	5,353,218	36.1	4,835,488	32.6
2007	17,448,458	10,152,589	58.2	6,887,791	39.5	408,078	2.3	9,000,648	51.6	377,803	2.2	1,151,941	6.6	6,509,988	37.3
2008	15,412,355	9,243,966	60.0	5,991,739	38.9	176,650	1.1	7,507,149	48.7	361,434	2.3	1,736,817	11.3	5,630,305	36.5
2009	19,138,738	11,439,143	59.8	7,570,646	39.6	128,949	0.7	4,830,093	25.2	396,076	2.1	6,609,050	34.5	7,174,570	37.5
2010	23,363,635	13,102,832	56.1	10,044,444	43.0	216,359	0.9	4,440,402	19.0	1,328,551	5.7	8,662,430	37.1	8,715,893	37.3
2011	15,982,456	9,499,682	59.4	6,287,306	39.3	205,468	1.3	4,562,652	28.5	1,210,876	7.6	4,937,030	30.9	5,076,430	31.7
2012	17,655,238	10,071,897	57.0	7,382,884	41.8	200,457	1.1	3,713,994	21.0	1,096,914	6.2	6,357,903	36.0	6,285,970	35.6
2013	17,580,725	9,961,014	56.7	7,397,295	42.1	222,416	1.3	3,522,251	20.0	1,174,274	6.7	6,438,763	36.6	6,223,021	35.4
2014	28,565,995	16,353,416	57.2	11,038,679	38.6	1,173,900	4.1	3,550,006	12.4	429,440	1.5	12,803,410	44.8	10,609,239	37.1
2015	21,453,866	13,278,481	61.9	7,829,861	36.5	345,524	1.6	3,828,704	17.8	280,567	1.3	9,449,777	44.0	7,549,294	35.2
2016	40,327,265	20,983,081	52.0	17,865,381	44.3	1,478,803	3.7	2,985,796	7.4	217,876	0.5	17,997,285	44.6	17,647,505	43.8

Table 1B: Total Enrollment for NIH Clinical Research at U.S. Sites from FY 11-16

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2011	13,470,269	7,974,958	59.2	5,314,952	39.5	180,359	1.3	4,318,845	32.1	1,172,588	8.7	3,656,113	27.1	4,142,364	30.8
2012	15,077,760	8,490,785	56.3	6,408,209	42.5	178,766	1.2	3,471,881	23.0	1,064,581	7.1	5,018,904	33.3	5,343,628	35.4
2013	14,766,330	8,160,136	55.3	6,406,256	43.4	199,938	1.4	3,118,017	21.1	1,100,347	7.5	5,042,119	34.1	5,305,909	35.9
2014	25,209,874	14,395,132	57.1	9,944,895	39.4	869,847	3.5	3,120,777	12.4	335,703	1.3	11,274,355	44.7	9,609,192	38.1
2015	17,212,103	10,529,683	61.2	6,404,104	37.2	278,316	1.6	3,569,721	20.7	209,567	1.2	6,959,962	40.4	6,194,537	36.0
2016	31,325,848	16,594,940	53.0	13,311,968	42.5	1,418,940	4.5	2,722,586	8.7	163,430	0.5	13,872,354	44.3	13,148,538	42.0

Table 1C: Total Enrollment for Extramural NIH Clinical Research at U.S. Sites from FY 11-16

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2011	10,853,602	6,961,241	64.1	3,779,319	34.8	113,042	1.0	4,108,737	37.9	1,162,408	10.7	2,852,504	26.3	2,616,911	24.1
2012	11,066,707	6,173,108	55.8	4,770,436	43.1	123,163	1.1	2,089,973	18.9	1,054,158	9.5	4,083,135	36.9	3,716,278	33.6
2013	10,757,737	5,867,799	54.5	4,760,618	44.3	129,320	1.2	1,754,752	16.3	1,088,973	10.1	4,113,047	38.2	3,671,645	34.1
2014	21,897,331	12,126,129	55.4	8,960,001	40.9	811,201	3.7	1,754,275	8.0	324,567	1.5	10,371,854	47.4	8,635,434	39.4
2015	14,149,649	8,427,534	59.6	5,525,413	39.0	196,702	1.4	2,277,591	16.1	199,298	1.4	6,149,943	43.5	5,326,115	37.6
2016	28,125,129	14,418,631	51.3	12,415,288	44.1	1,291,210	4.6	1,377,694	4.9	153,472	0.5	13,040,937	46.4	12,261,816	43.6

Table 1D: Total Enrollment for Intramural NIH Clinical Research at U.S. Sites from FY 11-16

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2011	2,616,667	1,013,717	38.7	1,535,633	58.7	67,317	2.6	210,108	8.0	10,180	0.4	803,609	30.7	1,525,453	58.3
2012	4,011,053	2,317,677	57.8	1,637,773	40.8	55,603	1.4	1,381,908	34.5	10,423	0.3	935,769	23.3	1,627,350	40.6
2013	4,008,593	2,292,337	57.2	1,645,638	41.1	70,618	1.8	1,363,265	34.0	11,374	0.3	929,072	23.2	1,634,264	40.8
2014	3,312,543	2,269,003	68.5	984,894	29.7	58,646	1.8	1,366,502	41.3	11,136	0.3	902,501	27.2	973,758	29.4
2015	3,062,454	2,102,149	68.6	878,691	28.7	81,614	2.7	1,292,130	42.2	10,269	0.3	810,019	26.4	868,422	28.4
2016	3,200,719	2,176,309	68.0	896,680	28.0	127,730	4.0	1,344,892	42.0	9,958	0.3	831,417	26.0	886,722	27.7

Table 1E: Total Enrollment for All NIH-Defined Phase III Clinical Trials from FY 06-16

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2006	499,430	314,066	62.9	179,975	36.0	5,389	1.1	167,624	33.6	27,723	5.6	146,442	29.3	152,252	30.5
2007	591,159	324,694	54.9	249,633	42.2	16,832	2.8	181,625	30.7	79,434	13.4	143,069	24.2	170,199	28.8
2008	792,578	455,612	57.5	319,732	40.3	17,234	2.2	219,673	27.7	79,613	10.0	235,939	29.8	240,119	30.3
2009	652,300	345,748	53.0	276,159	42.3	30,393	4.7	141,892	21.8	65,516	10.0	203,856	31.3	210,643	32.3
2010	769,885	408,181	53.0	330,808	43.0	30,896	4.0	119,103	15.5	62,315	8.1	289,078	37.5	268,493	34.9
2011	584,278	333,293	57.0	222,060	38.0	28,925	5.0	82,315	14.1	26,229	4.5	250,978	43.0	195,831	33.5
2012	603,136	374,819	62.1	197,019	32.7	31,298	5.2	58,916	9.8	10,288	1.7	315,903	52.4	186,731	31.0
2013	691,023	506,732	73.3	179,220	25.9	5,071	0.7	217,869	31.5	12,406	1.8	288,863	41.8	166,814	24.1
2014	797,264	478,222	60.0	314,310	39.4	4,732	0.6	32,310	4.1	4,267	0.5	445,912	55.9	309,951	38.9
2015	1,619,508	1,091,910	67.4	507,561	31.3	20,037	1.2	29,368	1.8	4,267	0.3	1,062,542	65.6	503,294	31.1
2016	2,130,389	1,396,503	65.6	710,818	33.4	23,068	1.1	35,463	1.7	7,480	0.4	1,361,040	63.9	703,338	33.0

Table 1F: Total Enrollment for All NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 11-16

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2011	303,916	160,644	52.9	116,345	38.3	26,927	8.9	64,095	21.1	24,337	8.0	96,549	31.8	92,008	30.3
2012	280,932	146,991	52.3	106,842	38.0	27,099	9.6	48,345	17.2	10,002	3.6	98,646	35.1	96,840	34.5
2013	236,692	137,062	57.9	98,753	41.7	877	0.4	56,821	24.0	12,133	5.1	80,241	33.9	86,620	36.6
2014	254,263	132,354	52.1	121,366	47.7	543	0.2	23,389	9.2	4,282	1.7	108,965	42.9	117,084	46.0
2015	173,640	83,932	48.3	89,228	51.4	480	0.3	17,089	9.8	3,361	1.9	66,843	38.5	85,867	49.5
2016	169,893	83,278	49.0	86,425	50.9	190	0.1	22,733	13.4	6,092	3.6	60,545	35.6	80,333	47.3

Table 1G: Total Enrollment for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 11-16

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2011	293,864	153,306	52.2	113,644	38.7	26,914	9.2	59,915	20.0	24,179	8.2	94,391	32.1	89,465	30.4
2012	270,082	139,811	51.4	104,185	38.6	27,086	10.0	42,375	15.7	9,837	3.6	96,436	35.7	94,348	34.9
2013	226,204	129,126	57.1	96,201	42.5	877	0.4	50,850	22.5	11,972	5.3	78,276	34.6	84,229	37.2
2014	245,611	125,118	50.9	119,950	48.8	543	0.2	17,379	7.1	4,112	1.7	107,739	43.9	115,838	47.2
2015	161,030	74,759	46.4	85,794	53.3	477	0.3	11,067	6.9	3,181	2.0	63,692	39.6	82,613	51.3
2016	158,741	74,969	47.2	83,586	52.7	186	0.1	16,713	10.5	5,911	3.7	58,256	36.7	77,675	48.9

Table 1H: Total Enrollment for Intramural NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 11-16

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2011	10,052	7,338	73.0	2,701	26.9	13	0.1	5,180	51.5	158	1.6	2,158	21.5	2,543	25.3
2012	10,850	8,180	75.4	2,657	24.5	13	0.1	5,970	55.0	165	1.5	2,210	20.4	2,492	23.0
2013	10,488	7,936	75.7	2,552	24.3	0	0.0	5,971	56.9	161	1.5	1,965	18.7	2,391	22.8
2014	8,652	7,236	83.6	1,416	16.4	0	0.0	6,010	69.5	170	2.0	1,226	14.2	1,246	14.4
2015	12,610	9,173	72.7	3,434	27.2	3	0.0	6,022	47.8	180	1.4	3,151	25.0	3,254	25.8
2016	11,152	8,309	74.5	2,839	25.5	4	0.0	6,020	54.0	181	1.6	2,289	20.5	2,658	23.8

Aggregate Enrollment of Race and Ethnicity: Clinical Research

Table 2A: Total Enrollment and Minority Enrollment for all NIH Clinical Research From FY 06–16

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2006	14,830,930	6,388,316	43.1
2007	17,448,458	5,216,434	29.9
2008	15,412,355	4,412,106	28.6
2009	19,138,738	5,783,543	30.2
2010	23,363,635	7,510,763	32.1
2011	15,992,456	6,488,223	40.6
2012	17,655,238	6,446,175	36.5
2013	17,580,725	6,687,678	38.0
2014	28,565,995	9,582,978	33.5
2015	21,453,866	8,602,086	40.1
2016	40,327,265	14,987,425	37.2

Table 2B: Total Enrollment and Minority Enrollment for NIH Clinical Research at U.S. Sites from FY 11–16

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2011	13,470,269	4,390,764	32.6
2012	15,077,760	4,332,559	28.7
2013	14,766,330	4,322,007	29.3
2014	25,209,874	6,607,207	26.2
2015	17,212,103	4,778,010	27.8
2016	31,325,848	11,179,772	35.7

Table 2C: Total Enrollment and Minority Enrollment for Extramural NIH Clinical Research at U.S. Sites from FY 11–16

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2011	10,853,602	3,746,667	34.5
2012	11,066,707	3,634,100	32.8
2013	10,757,737	3,666,833	34.1
2014	21,897,331	6,173,549	28.2
2015	14,149,649	4,421,098	31.3
2016	28,125,129	10,770,168	38.3

Table 2D: Total Enrollment and Minority Enrollment for Intramural NIH Clinical Research at U.S. Sites from FY 11–16

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2011	2,616,667	644,097	24.6
2012	4,011,053	689,459	17.2
2013	4,008,593	655,174	16.3
2014	3,312,543	433,658	13.1
2015	3,062,454	356,912	11.7
2016	3,200,719	409,604	12.8

Table 2E: Total Enrollment for All NIH Clinical Research Racial Categories from FY 10–16

Fiscal Year	Total Enrollment	No. Protocols	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2010	23,066,878	11,547	7,453,008	32.3	361,229	1.6	2,133,596	9.2	2,949,614	12.8	150,866	0.7	15,278,117	66.1	358,946	1.6	1,864,520	8.1
2011	15,974,162	11,289	6,484,399	40.6	360,626	2.3	2,351,721	14.7	2,112,553	13.2	47,794	0.3	9,154,454	57.3	349,281	2.2	1,597,733	10.0
2012	17,648,075	10,757	6,442,925	36.5	335,460	1.9	2,157,236	12.2	2,140,641	12.1	56,721	0.3	9,070,528	51.4	355,539	2.0	3,551,950	20.0
2013	17,578,991	10,570	6,686,903	38.0	371,013	2.1	2,474,126	14.1	2,266,772	12.9	43,589	0.2	9,450,454	53.8	209,669	1.2	2,763,368	15.7
2014	28,565,295	10,074	9,582,434	33.5	271,211	0.9	3,330,083	11.7	3,406,343	11.9	97,329	0.3	17,602,822	61.6	370,181	1.3	3,487,326	12.2
2015	21,453,866	11,082	8,602,086	40.1	488,167	2.3	3,403,915	15.9	2,546,765	11.9	40,321	0.2	10,367,705	48.3	339,308	1.6	4,267,685	19.9
2016	40,327,265	13,070	14,987,425	37.2	618,188	1.5	4,466,346	11.1	4,502,686	11.2	261,649	0.7	19,893,061	49.3	875,399	2.2	9,709,936	24.1

Table 2F: Total Enrollment for all NIH Clinical Research Ethnic Categories FY 10–16

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2010	18,962,836	82.1	1,958,060	8.5	2,175,982	9.4
2011	12,687,228	79.4	1,641,383	10.3	1,645,551	10.3
2012	12,091,772	68.5	1,778,148	10.1	3,778,155	21.4
2013	12,895,326	73.4	1,798,501	10.2	2,885,164	16.4
2014	23,270,093	81.5	2,442,998	8.6	2,852,204	10.0
2015	15,298,198	71.3	2,332,328	10.9	3,823,340	17.8
2016	26,831,115	66.5	4,841,284	12.0	8,654,866	21.5

Table 2G: Total Enrollment for All NIH Clinical Research at U.S. Sites Racial Categories from FY 11–16

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	Black/ African American	% Black/ African American	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2011	13,452,391	4,387,041	32.6	153,066	1.1	1,234,591	9.2	1,610,345	12.0	47,247	0.4	8,731,310	64.9	325,613	2.4	1,350,219	10.0	1,350,219	10.0	1,350,219	10.0
2012	15,070,597	4,329,309	28.7	123,329	0.8	1,033,995	6.9	1,665,516	11.1	56,474	0.4	8,598,595	57.1	329,050	2.2	3,263,638	21.7	3,263,638	21.7	3,263,638	21.7
2013	14,764,596	4,321,232	29.3	136,416	0.9	1,008,180	6.8	1,765,689	12.0	41,242	0.3	9,035,020	61.2	190,838	1.3	2,587,211	17.5	2,587,211	17.5	2,587,211	17.5
2014	25,209,174	6,606,663	26.2	187,224	0.7	1,289,490	5.1	2,790,849	11.1	89,184	0.4	17,212,956	68.3	339,596	1.3	3,299,875	13.1	3,299,875	13.1	3,299,875	13.1
2015	17,212,103	4,778,010	27.8	139,377	0.8	970,862	5.6	1,672,975	9.7	31,675	0.2	9,950,746	57.8	288,773	1.7	4,157,695	24.2	4,157,695	24.2	4,157,695	24.2
2016	31,325,848	11,179,772	35.7	321,625	1.0	2,395,431	7.7	3,249,188	10.4	252,436	0.8	19,415,746	62.0	829,095	2.7	4,862,327	15.5	4,862,327	15.5	4,862,327	15.5

Table 2H: Total Enrollment for all NIH Clinical Research at U.S. Sites Ethnic Categories FY 11–16

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2011	10,765,968	80.0	1,151,089	8.6	1,535,334	11.4
2012	10,115,385	67.1	1,263,122	8.4	3,692,090	24.5
2013	10,639,126	72.1	1,313,858	8.9	2,811,612	19.0
2014	20,332,636	80.7	2,082,077	8.3	2,794,461	11.1
2015	11,678,565	67.9	1,834,210	10.7	3,699,328	21.5
2016	23,183,045	74.0	4,373,479	14.0	3,769,324	12.0

Table 2I: Total Enrollment for Extramural NIH Clinical Research at U.S. Sites Racial Categories from FY 11–16

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2011	10,835,724	3,742,944	34.5	127,914	1.2	1,182,405	10.9	1,295,314	12.0	42,554	0.4	6,986,561	64.5	178,911	1.7	1,022,065	9.4	
2012	11,059,544	3,630,850	32.8	96,939	0.9	969,446	8.8	1,340,160	12.1	50,939	0.5	6,736,548	60.9	181,044	1.6	1,684,468	15.2	
2013	10,756,003	3,666,058	34.1	108,611	1.0	877,176	8.2	1,425,734	13.3	35,395	0.3	7,116,662	66.2	180,878	1.7	1,011,547	9.4	
2014	21,896,631	6,173,005	28.2	160,605	0.7	1,222,199	5.6	2,592,096	11.8	83,039	0.4	15,636,146	71.4	328,422	1.5	1,874,124	8.6	
2015	14,149,649	4,421,098	31.3	112,119	0.8	931,086	6.6	1,481,082	10.5	26,466	0.2	8,593,188	60.7	278,313	2.0	2,727,395	19.3	
2016	28,125,129	10,770,168	38.3	293,887	1.0	2,352,180	8.4	3,028,871	10.8	247,061	0.9	18,012,861	64.1	817,320	2.9	3,372,949	12.0	

Table 2J: Total Enrollment for Extramural NIH Clinical Research at U.S. Sites Ethnic Categories FY 11–16

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2011	8,715,026	80.4	1,044,252	9.6	1,076,446	9.9
2012	8,047,787	72.8	1,128,442	10.2	1,883,315	17.0
2013	8,478,293	78.8	1,166,466	10.8	1,111,244	10.3
2014	18,702,141	85.4	1,952,648	8.9	1,241,842	5.7
2015	10,250,999	72.5	1,745,814	12.3	2,152,836	15.2
2016	21,757,302	77.4	4,265,923	15.2	2,101,904	7.5

Table 2K: Total Enrollment for Intramural NIH Clinical Research at U.S. Sites Racial Categories from FY 11–16

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2011	2,616,667	644,097	24.6	25,152	1.0	52,186	2.0	315,031	12.0	4,693	0.2	1,744,749	66.7	146,702	5.6	328,154	12.5
2012	4,011,053	698,459	17.4	26,390	0.7	64,549	1.6	325,356	8.1	5,535	0.1	1,862,047	46.4	148,006	3.7	1,579,170	39.4
2013	4,008,593	655,174	16.3	27,805	0.7	131,004	3.3	339,955	8.5	5,847	0.1	1,918,358	47.9	9,960	0.2	1,575,664	39.3
2014	3,312,543	433,658	13.1	26,619	0.8	67,291	2.0	198,753	6.0	6,145	0.2	1,576,810	47.6	11,174	0.3	1,425,751	43.0
2015	3,062,454	356,912	11.7	27,258	0.9	39,776	1.3	191,893	6.3	5,209	0.2	1,357,558	44.3	10,460	0.3	1,430,300	46.7
2016	3,200,719	409,604	12.8	27,738	0.9	43,251	1.4	220,317	6.9	5,375	0.2	1,402,885	43.8	11,775	0.4	1,489,378	46.5

Table 2L: Total Enrollment for Intramural NIH Clinical Research at U.S. Sites Ethnic Categories FY 11–16

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2011	2,050,942	78.4	106,837	4.1	458,888	17.5
2012	2,067,598	51.5	134,680	3.4	1,808,790	45.1
2013	2,160,833	53.9	147,392	3.7	1,700,368	42.4
2014	1,630,495	49.2	129,429	3.9	1,552,619	46.9
2015	1,427,566	46.6	88,396	2.9	1,546,492	50.5
2016	1,425,743	44.5	107,556	3.4	1,667,420	52.1

Aggregate Enrollment of Race and Ethnicity: Clinical Research

Table 3A: Total Enrollment and Minority Enrollment for All NIH Defined Phase III Clinical Trials from FY 06–16

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2006	499,430	167,446	33.5
2007	591,159	244,932	41.4
2008	792,578	270,899	34.2
2009	652,300	291,949	44.8
2010	769,885	447,187	58.1
2011	584,278	347,770	59.5
2012	603,136	396,714	65.8
2013	691,023	526,422	76.2
2014	797,264	627,456	78.7
2015	1,619,508	1,492,248	92.1
2016	2,130,389	1,992,237	93.5

Table 3C: Total Enrollment and Minority Enrollment at U.S. Sites for Extramural NIH Defined Phase III Clinical Trials from FY 11–16

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2011	293,864	72,819	24.8
2012	270,082	77,371	28.6
2013	226,204	76,030	33.6
2014	245,611	92,457	37.6
2015	161,030	66,176	41.1
2016	158,741	68,176	43.0

Table 3B: Total Enrollment and Minority Enrollment at U.S. Sites for All NIH Defined Phase III Clinical Trials from FY 11–16

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2011	303,916	76,415	25.1
2012	280,932	81,420	29.0
2013	236,692	79,608	33.6
2014	254,263	95,934	37.7
2015	173,640	70,361	40.5
2016	169,893	72,318	42.6

Table 3D: Total Enrollment and Minority Enrollment at U.S. Sites for Intramural NIH Defined Phase III Clinical Trials from FY 11–16

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2011	10,052	3,596	35.8
2012	10,850	4,049	37.3
2013	10,488	3,578	34.1
2014	8,652	3,477	40.2
2015	12,610	4,185	33.2
2016	11,152	4,142	37.1

Table 3E: Total Enrollment for All NIH-Defined Phase III Clinical Trials Racial Categories from FY 11–16

Fiscal Year	Total Enrollment	No. Protocols	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2011	583,119	579	347,757	59.6	26,035	4.5	179,062	30.7	89,538	15.4	1,043	0.2	213,182	36.6	7,668	1.3	66,591	11.4
2012	603,136	548	396,714	65.8	28,352	4.7	214,542	35.6	96,158	15.9	967	0.2	182,936	30.3	6,398	1.1	73,783	12.2
2013	691,023	570	526,422	76.2	26,834	3.9	341,188	49.4	110,861	16.0	595	0.1	173,672	25.1	3,500	0.5	34,373	5.0
2014	797,264	525	627,456	78.7	30,119	3.8	409,983	51.4	135,630	17.0	490	0.1	184,372	23.1	3,697	0.5	32,973	4.1
2015	1,619,508	498	1,492,248	92.1	124,444	7.7	976,701	60.3	360,471	22.3	300	0.0	124,641	7.7	2,113	0.1	30,838	1.9
2016	2,130,389	574	1,992,237	93.5	150,019	7.0	1,037,057	48.7	772,419	36.3	320	0.0	139,940	6.6	2,096	0.1	28,538	1.3

Table 3F: Total Enrollment for All NIH-Defined Phase III Clinical Trials Ethnic Categories for FY 11–16

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2011	465,714	79.9	71,998	12.3	45,407	7.8
2012	477,908	79.2	78,797	13.1	46,431	7.7
2013	608,564	88.1	71,744	10.4	10,715	1.6
2014	703,877	88.3	77,152	9.7	16,235	2.0
2015	1,457,366	90.0	154,371	9.5	7,771	0.5
2016	1,941,923	91.2	181,121	8.5	7,345	0.3

Table 3G: Total Enrollment for All NIH-Defined Phase III Clinical Trials at U.S. Sites Racial Categories from FY 11–16

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2011	302,987	76,403	25.2	3,390	1.1	7,720	2.5	27,134	9.0	1,014	0.3	204,315	67.4	6,142	2.0	53,272	17.6	
2012	280,932	81,420	29.0	3,397	1.2	5,504	2.0	34,495	12.3	943	0.3	176,627	62.9	6,396	2.3	53,570	19.1	
2013	236,692	79,608	33.6	1,868	0.8	5,302	2.2	45,303	19.1	553	0.2	166,186	70.2	2,963	1.3	14,517	6.1	
2014	254,263	95,934	37.7	5,129	2.0	4,150	1.6	58,170	22.9	457	0.2	173,719	68.3	3,053	1.2	9,585	3.8	
2015	173,640	70,361	40.5	1,996	1.2	7,632	4.4	41,046	23.6	268	0.2	114,014	65.7	1,742	1.0	6,942	4.0	
2016	169,893	72,318	42.6	1,259	0.7	19,470	11.5	29,367	17.3	276	0.2	110,836	65.2	1,973	1.2	6,712	4.0	

Table 3H: Total Enrollment for All NIH-Defined Phase III Clinical Trials at U.S. Sites Ethnic Categories for FY 11–16

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2011	230,759	76.2	34,308	11.3	37,920	12.5
2012	205,055	73.0	34,255	12.2	41,622	14.8
2013	200,126	84.6	26,015	11.0	10,551	4.5
2014	214,559	84.4	28,814	11.3	10,890	4.3
2015	150,486	86.7	20,845	12.0	2,309	1.3
2016	144,849	85.3	21,801	12.8	3,243	1.9

Table 3I: Total Enrollment for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites Racial Categories from FY 11–16

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2011	292,935	72,807	24.9	3,092	1.1	7,451	2.5	24,435	8.3	1,011	0.3	197,742	67.5	6,131	2.1	53,073	18.1
2012	270,082	77,371	28.6	3,091	1.1	5,207	1.9	31,609	11.7	938	0.3	169,553	62.8	6,377	2.4	53,307	19.7
2013	226,204	76,030	33.6	1,554	0.7	5,001	2.2	42,994	19.0	547	0.2	158,999	70.3	2,942	1.3	14,167	6.3
2014	245,611	92,457	37.6	4,788	1.9	3,868	1.6	55,899	22.8	451	0.2	168,262	68.5	3,016	1.2	9,327	3.8
2015	161,030	66,176	41.1	1,537	1.0	7,340	4.6	38,110	23.7	261	0.2	105,555	65.6	1,705	1.1	6,522	4.1
2016	158,741	68,176	43.0	859	0.5	19,172	12.1	26,438	16.7	271	0.2	103,776	65.4	1,924	1.2	6,301	4.0

Table 3J: Total Enrollment for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites Ethnic Categories for FY 11–16

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2011	221,136	75.5	33,942	11.6	37,857	12.9
2012	194,915	72.2	33,657	12.5	41,510	15.4
2013	190,444	84.2	25,325	11.2	10,435	4.6
2014	206,640	84.1	28,202	11.5	10,769	4.4
2015	138,597	86.1	20,303	12.6	2,130	1.3
2016	134,461	84.7	21,238	13.4	3,042	1.9

Table 3K: Total Enrollment for Intramural NIH-Defined Phase III Clinical Trials at U.S. Sites Racial Categories from FY 11–16

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2011	10,052	3,596	35.8	298	3.0	269	2.7	2,699	26.9	3	0.0	6,573	65.4	11	0.1	199	2.0	
2012	10,850	4,049	37.3	306	2.8	297	2.7	2,886	26.6	5	0.0	7,074	65.2	19	0.2	263	2.4	
2013	10,488	3,578	34.1	314	3.0	301	2.9	2,309	22.0	6	0.1	7,187	68.5	21	0.2	350	3.3	
2014	8,652	3,477	40.2	341	3.9	282	3.3	2,271	26.2	6	0.1	5,457	63.1	37	0.4	258	3.0	
2015	12,610	4,185	33.2	459	3.6	292	2.3	2,936	23.3	7	0.1	8,459	67.1	37	0.3	420	3.3	
2016	11,152	4,142	37.1	400	3.6	298	2.7	2,929	26.3	5	0.0	7,060	63.3	49	0.4	411	3.7	

Table 3L: Total Enrollment for Intramural NIH-Defined Phase III Clinical Trials at U.S. Sites Ethnic Categories for FY 11–16

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2011	9,623	95.7	366	3.6	63	0.6
2012	10,140	93.5	598	5.5	112	1.0
2013	9,682	92.3	690	6.6	116	1.1
2014	7,919	91.5	612	7.1	121	1.4
2015	12,610	94.3	542	4.3	179	1.4
2016	10,388	93.2	563	5.1	201	1.8

Aggregate Enrollment: Sex/Gender by Race and Ethnicity for NIH Clinical Research

Table 4A: Minority Enrollment by Sex/Gender for All NIH Clinical Research from FY 11–16

Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2011	Female	4,018,450	62.3	9,499,682	42.3
	Male	2,430,139	37.7	6,287,306	38.7
	Unknown	39,634	0.6	205,468	19.3
2012	Female	3,742,903	58.1	10,071,897	37.2
	Male	2,661,413	41.3	7,382,884	36.0
	Unknown	41,859	0.6	200,457	20.9
2013	Female	3,861,247	57.7	9,961,014	38.8
	Male	2,767,206	41.4	7,397,295	37.4
	Unknown	59,225	0.9	222,416	26.6
2014	Female	5,264,659	54.9	16,353,416	32.2
	Male	3,899,441	40.7	11,038,679	35.3
	Unknown	418,878	4.4	1,173,900	35.7
2015	Female	5,255,224	61.1	13,278,481	39.6
	Male	3,175,954	36.9	7,829,861	40.6
	Unknown	170,908	2.0	345,524	49.5
2016	Female	8,226,149	54.9	20,983,081	39.2
	Male	6,649,220	44.4	17,865,381	37.2
	Unknown	112,056	0.8	1,478,803	7.6

Table 4B: Minority Enrollment by Sex/Gender for All NIH Clinical Research at U.S. Sites from FY 11–16

Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2011	Female	2,744,151	62.5	7,974,958	34.4
	Male	1,625,743	37.0	5,314,952	30.6
	Unknown	20,870	0.5	180,359	11.6
2012	Female	2,423,584	55.9	8,490,785	28.5
	Male	1,882,114	43.4	6,408,209	29.4
	Unknown	26,861	0.6	178,766	15.0
2013	Female	2,316,451	53.6	8,160,136	28.4
	Male	1,961,559	45.4	6,406,256	30.6
	Unknown	43,997	1.0	199,938	22.0
2014	Female	3,534,913	53.5	14,395,132	24.6
	Male	2,946,342	44.6	9,944,895	29.6
	Unknown	125,952	1.9	869,847	14.5
2015	Female	2,737,095	57.3	10,529,683	26.0
	Male	1,921,639	40.2	6,404,104	30.0
	Unknown	119,276	2.5	278,316	42.9
2016	Female	5,855,133	52.4	16,594,940	35.3
	Male	5,256,810	47.0	13,311,968	39.5
	Unknown	67,829	0.6	1,418,940	4.8

Table 4C: Minority Enrollment by Sex/Gender for Extramural NIH Clinical Research at U.S. Sites from FY 11–16

Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2011	Female	2,478,812	66.2	6,961,241	35.6
	Male	1,254,173	33.5	3,779,319	33.2
	Unknown	13,682	0.4	113,042	12.1
2012	Female	2,128,669	58.6	6,173,108	34.5
	Male	1,480,077	40.7	4,770,436	31.0
	Unknown	25,354	0.7	123,163	20.6
2013	Female	2,050,457	55.9	5,867,799	34.9
	Male	1,582,377	43.2	4,760,618	33.2
	Unknown	33,999	0.9	129,320	26.3
2014	Female	3,294,588	53.4	12,126,129	27.2
	Male	2,762,889	44.8	8,960,001	30.8
	Unknown	116,072	1.9	811,201	14.3
2015	Female	2,545,119	57.6	8,427,534	30.2
	Male	1,761,708	39.9	5,525,413	31.9
	Unknown	114,271	2.6	196,702	58.1
2016	Female	5,623,816	52.2	14,418,631	39.0
	Male	5,083,588	47.2	12,415,288	40.9
	Unknown	62,764	0.6	1,291,210	4.9

Table 4D: Minority Enrollment by Sex/Gender for Intramural NIH Clinical Research at U.S. Sites from FY 11–16

Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2011	Female	265,339	41.2	1,013,717	26.2
	Male	371,570	57.7	1,535,633	24.2
	Unknown	7,188	1.1	67,317	10.7
2012	Female	294,915	42.2	2,317,677	12.7
	Male	402,037	57.6	1,637,773	24.5
	Unknown	1,507	0.2	55,603	2.7
2013	Female	265,994	40.6	2,292,337	11.6
	Male	379,182	57.9	1,645,638	23.0
	Unknown	9,998	1.5	70,618	14.2
2014	Female	240,325	55.4	2,269,003	10.6
	Male	183,453	42.3	984,894	18.6
	Unknown	9,880	2.3	58,646	16.8
2015	Female	191,976	53.8	2,102,149	9.1
	Male	159,931	44.8	878,691	18.2
	Unknown	5,005	1.4	81,614	6.1
2016	Female	231,317	56.5	2,176,309	10.6
	Male	173,222	42.3	896,680	19.3
	Unknown	5,065	1.2	127,730	4.0

Table 4E: Minority Enrollment by Sex/Gender for All NIH-Defined Phase III Clinical Trials from FY 11–16

Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2011	Female	214,756	61.8	333,293	64.4
	Male	130,546	37.5	222,060	58.8
	Unknown	2,468	0.7	28,925	8.5
2012	Female	273,477	68.9	374,819	73.0
	Male	118,517	29.9	197,019	60.2
	Unknown	4,720	1.2	31,298	15.1
2013	Female	416,971	79.2	506,732	82.3
	Male	105,242	20.0	179,220	58.7
	Unknown	4,209	0.8	5,071	83.0
2014	Female	392,878	62.6	478,222	82.2
	Male	230,310	36.7	314,310	73.3
	Unknown	4,268	0.7	4,732	90.2
2015	Female	1,030,479	69.1	1,091,910	94.4
	Male	442,084	29.6	507,561	87.1
	Unknown	19,685	1.3	20,037	98.2
2016	Female	1,323,770	66.5	1,396,503	94.8
	Male	645,583	32.4	710,818	90.8
	Unknown	22,884	1.2	23,068	99.2

Table 4G: Minority Enrollment by Sex/Gender for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 11–16

Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2011	Female	43,996	60.4	153,306	28.7
	Male	28,356	38.9	113,644	25.0
	Unknown	467	0.6	26,914	1.7
2012	Female	45,421	58.7	138,811	32.7
	Male	31,432	40.6	104,185	30.2
	Unknown	518	0.7	27,086	1.9
2013	Female	48,209	63.4	129,126	37.3
	Male	27,802	36.6	96,201	28.9
	Unknown	19	0.0	877	2.2
2014	Female	49,653	53.7	125,118	39.7
	Male	42,725	46.2	119,950	35.6
	Unknown	79	0.1	543	14.5
2015	Female	32,534	49.2	74,759	43.5
	Male	33,493	50.6	85,794	39.0
	Unknown	149	0.2	477	31.2
2016	Female	30,878	45.3	74,969	41.2
	Male	37,279	54.7	83,586	44.6
	Unknown	19	0.0	186	10.2

Table 4F: Minority Enrollment by Sex/Gender for All NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 11–16

Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2011	Female	46,895	61.4	160,644	29.2
	Male	29,040	38.0	116,345	25.0
	Unknown	480	0.6	26,927	1.8
2012	Female	48,783	59.9	146,991	33.2
	Male	32,106	39.4	106,842	30.0
	Unknown	531	0.7	27,099	2.0
2013	Female	51,289	64.4	137,062	37.4
	Male	28,300	35.5	98,753	28.7
	Unknown	19	0.0	877	2.2
2014	Female	52,725	55.0	132,354	39.8
	Male	43,130	45.0	121,366	35.5
	Unknown	79	0.1	543	14.5
2015	Female	35,848	51.0	83,932	42.7
	Male	34,362	48.8	89,228	38.5
	Unknown	151	0.2	480	31.5
2016	Female	34,156	47.2	83,278	41.0
	Male	38,140	52.7	86,425	44.1
	Unknown	22	0.0	190	11.6

Table 4H: Minority Enrollment by Sex/Gender for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 11–16

Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2011	Female	2,899	80.6	7,338	39.5
	Male	684	19.0	2,701	25.3
	Unknown	13	0.4	13	100.0
2012	Female	3,362	83.0	8,180	41.1
	Male	674	16.6	2,657	25.4
	Unknown	13	0.3	13	100.0
2013	Female	3,080	86.1	7,936	38.8
	Male	498	13.9	2,552	19.5
	Unknown	0	0.0	0	0.0
2014	Female	3,072	88.4	7,236	42.5
	Male	405	11.6	1,416	28.6
	Unknown	0	0.0	0	0.0
2015	Female	3,314	79.2	9,173	36.1
	Male	869	20.8	3,434	25.3
	Unknown	2	0.1	3	66.7
2016	Female	3,278	79.1	8,309	39.5
	Male	861	20.8	2,839	30.3
	Unknown	3	0.1	4	75.0

Table 4I: Enrollment for All NIH-Defined Clinical Research, Sex/Gender by Race and Ethnicity for FY 15–16

Year	Sex/Gender	American Indian/ Alaska Native	Asian	Black/ African	Black/ African	Native Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Not Hispanic	Hispanic	% Reported/ Not Reported	%	Unknown/ Not Reported	%						
2015	Female	335,667	2.5	2,040,978	15.4	1,608,128	12.1	21,923	0.2	6,233,178	46.9	201,505	1.5	2,837,102	21.4	9,335,593	70.3	1,419,208	10.7	2,523,680	19.0
	Male	151,039	1.9	1,221,664	15.6	921,259	11.8	18,216	0.2	4,108,592	52.5	136,328	1.7	1,272,763	16.3	5,871,732	75.0	902,099	11.5	1,056,030	13.5
	Unknown	1,461	0.4	141,273	40.9	17,378	5.0	182	0.1	25,935	7.5	1,475	0.4	157,820	45.7	90,873	26.3	11,021	3.2	243,630	70.5
2016	Female	389,643	1.9	2,485,827	11.9	2,521,038	12.0	138,585	0.7	10,747,619	51.2	444,496	2.1	4,255,873	20.3	14,525,927	69.2	2,615,657	12.5	3,841,497	18.3
	Male	226,085	1.3	1,941,315	10.9	1,958,484	11.0	122,760	0.7	9,095,492	50.9	427,976	2.4	4,093,269	22.9	12,070,643	67.6	2,177,329	12.2	3,617,409	20.3
	Unknown	2,460	0.2	39,204	2.7	23,164	1.6	304	0.0	49,950	3.4	2,927	0.2	1,360,794	92.0	234,545	15.9	48,298	3.3	1,195,960	80.9

Table 4J: U.S. Site Enrollment for All NIH-Defined Clinical Research, Sex/Gender by Race and Ethnicity for FY 15–16

Year	Sex/Gender	American Indian/ Alaska Native	Asian	Black/ African	Black/ African	Native Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Not Hispanic	Hispanic	% Reported/ Not Reported	%	Unknown/ Not Reported	%						
2015	Female	77,316	0.7	486,480	4.6	1,014,430	9.6	17,560	0.2	5,995,456	56.9	170,724	1.6	2,767,717	26.3	7,038,343	66.8	1,061,863	10.1	2,429,477	23.1
	Male	61,139	1.0	387,265	6.1	647,034	10.1	13,934	0.2	3,933,519	61.4	116,610	1.8	1,244,603	19.4	4,601,030	71.9	763,233	11.9	1,039,841	16.2
	Unknown	922	0.3	97,117	34.9	11,511	4.1	181	0.1	21,771	7.8	1,439	0.5	145,375	52.2	39,192	14.1	9,114	3.3	230,010	82.6
2016	Female	170,089	1.0	1,215,536	7.3	1,766,063	10.6	133,979	0.8	10,458,864	63.0	419,271	2.5	2,431,138	14.7	12,337,045	74.3	2,277,211	13.7	1,980,684	11.9
	Male	150,345	1.1	1,176,880	8.8	1,465,554	11.0	118,154	0.9	8,909,182	66.9	406,946	3.1	1,084,907	8.2	10,656,205	80.1	2,050,381	15.4	605,382	4.6
	Unknown	1,191	0.1	3,015	0.2	17,571	1.2	303	0.0	47,700	3.4	2,878	0.2	1,346,282	94.9	189,795	13.4	45,887	3.2	1,183,258	83.4

Table 4K: U.S. Site Enrollment for NIH-Defined Extramural Clinical Research, Sex/Gender by Race and Ethnicity for FY 15–16

Year	Sex/Gender	American Indian/ Alaska Native	Asian	Black/ African	Black/ African	Native Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Not Hispanic	Hispanic	% Reported/ Not Reported	%	Unknown/ Not Reported	%						
2015	Female	62,779	0.7	467,259	5.5	906,697	10.8	14,802	0.2	5,329,797	63.2	164,671	2.0	1,481,529	17.6	6,305,607	74.8	1,016,538	12.1	1,105,389	13.1
	Male	48,437	0.9	366,769	6.6	566,869	10.3	11,493	0.2	3,242,671	58.7	112,251	2.0	1,176,923	21.3	3,911,121	70.8	721,054	13.1	893,238	16.2
	Unknown	903	0.5	97,058	49.3	7,516	3.8	171	0.1	20,720	10.5	1,391	0.7	68,943	35.1	34,271	17.4	8,222	4.2	154,209	78.4
2016	Female	155,236	1.1	1,194,455	8.3	1,631,811	11.3	131,140	0.9	9,756,913	67.7	412,432	2.9	1,136,644	7.9	11,601,654	80.5	2,221,962	15.4	595,015	4.1
	Male	137,479	1.1	1,154,769	9.3	1,383,500	11.1	115,627	0.9	8,209,142	66.1	402,038	3.2	1,012,733	8.2	9,970,337	80.3	1,999,040	16.1	445,911	3.6
	Unknown	1,172	0.1	2,956	0.2	13,560	1.1	294	0.0	46,806	3.6	2,850	0.2	1,223,572	94.8	185,311	14.4	44,921	3.5	1,060,978	82.2

Table 4L: U.S. Site Enrollment for NIH-Defined Intramural Clinical Research, Sex/Gender by Race for FY 15–16

Year	Sex/Gender	American Indian/ Alaska Native	Asian	Black/ African	Black/ African	Native Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Not Hispanic	Hispanic	%	Unknown/ Not Reported	%							
2015	Female	14,537	0.7	19,221	0.9	107,733	5.1	2,758	0.1	665,659	31.7	6,053	0.3	1,286,188	61.2	732,736	34.9	45,325	2.2	1,324,088	63.0
	Male	12,702	1.5	20,496	2.3	80,165	9.1	2,441	0.3	690,848	78.6	4,359	0.5	67,680	7.7	689,909	78.5	42,179	4.8	146,603	16.7
	Unknown	19	0.0	59	0.1	3,995	4.9	10	0.0	1,051	1.3	48	0.1	76,432	93.7	4,921	6.0	892	1.1	75,801	92.9
2016	Female	14,853	0.7	21,081	1.0	134,252	6.2	2,839	0.1	701,951	32.3	6,839	0.3	1,294,494	59.5	735,391	33.8	55,249	2.5	1,385,669	63.7
	Male	12,866	1.4	22,111	2.5	82,054	9.2	2,527	0.3	700,040	78.1	4,908	0.6	72,174	8.1	685,868	76.5	51,341	5.7	159,471	17.8
	Unknown	19	0.0	59	0.1	4,011	3.1	9	0.0	894	0.7	28	0.0	122,710	96.1	4,484	3.5	966	0.8	122,280	95.7

Table 4M: Enrollment of All NIH-Defined Phase III Trials, Sex/Gender by Race and Ethnicity for FY 15–16

Year	Sex/Gender	American Indian/ Alaska Native	Asian	Black/ African	Black/ African	Native Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Not Hispanic	Hispanic	%	Unknown/ Not Reported	%							
2015	Female	93,335	8.6	665,102	23.3	147	0.0	57,409	5.3	1,050	0.1	20,953	1.9	976,149	89.4	111,166	10.2	4,595	0.4		
	Male	31,021	6.1	293,407	57.8	150	0.0	67,068	13.2	1,061	0.2	9,638	1.9	461,452	90.9	43,057	8.5	3,052	0.6		
	Unknown	88	0.4	18,192	90.8	1,341	6.7	164	0.8	2	0.0	247	1.2	19,765	98.6	148	0.7	124	0.6		
2016	Female	112,730	8.1	712,622	51.0	478,018	34.2	168	0.0	71,582	5.1	1,101	0.1	20,282	1.5	1,260,494	90.3	132,225	9.5	3,784	0.3
	Male	37,084	5.2	302,788	42.6	293,383	41.3	152	0.0	68,354	9.6	992	0.1	8,065	1.1	658,731	92.7	48,676	6.9	3,411	0.5
	Unknown	205	0.9	21,647	93.8	1,018	4.4	4	0.0	3	0.0	191	0.8	22,698	98.4	220	1.0	150	0.7		

Table 4N: U.S. Site Enrollment for NIH-Defined Phase III Trials, Sex/Gender by Race and Ethnicity for FY 15–16

Year	Sex/Gender	American Indian/ Alaska Native	Asian	Black/ African	Black/ African	Native Hawaiian/ Pacific Islander	White	More Than One Race	Unknown/ Not Reported	Not Hispanic	Hispanic	%	Unknown/ Not Reported	%							
2015	Female	1,088	1.3	2,644	3.2	22,134	26.4	134	0.2	53,726	64.0	876	1.0	3,330	4.0	72,052	85.9	10,704	12.8	1,176	1.4
	Male	901	1.0	4,980	5.6	18,840	21.1	131	0.2	60,124	67.4	864	1.0	3,388	3.8	78,133	87.6	10,079	11.3	1,016	1.1
	Unknown	7	1.5	8	1.7	72	15.0	3	0.6	164	34.2	2	0.4	224	46.7	301	62.7	62	12.9	117	24.4
2016	Female	789	1.0	5,499	6.6	16,352	19.6	145	0.2	56,284	67.6	1,031	1.2	3,178	3.8	70,264	84.4	11,363	13.6	1,651	2.0
	Male	468	0.5	13,971	16.2	13,009	15.1	131	0.2	54,548	63.1	939	1.1	3,359	3.9	74,555	86.3	10,424	12.1	1,446	1.7
	Unknown	2	1.1	0	0.0	6	3.2	0	0.0	4	2.1	3	1.6	175	92.1	30	15.8	14	7.4	146	76.8

Table 40: Enrollment for NIH-Defined U.S. Site Extramural Phase III Trials for FY 15–16

Year	Sex/Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2015	Female	727	1.0	2,417	3.2	19,800	26.5	130	0.2	47,794	63.9	847	1.1	3,044	4.1	63,438	84.9	10,272	13.7	1,049	1.4
	Male	805	0.9	4,915	5.7	18,238	21.3	128	0.2	57,597	67.1	856	1.0	3,255	3.8	74,859	87.3	9,971	11.6	964	1.1
	Unknown	5	1.1	8	1.7	72	15.1	3	0.6	164	34.4	2	0.4	223	46.8	300	62.9	60	12.6	117	24.5
2016	Female	476	0.6	5,267	7.0	14,018	18.7	142	0.2	51,166	68.3	996	1.3	2,904	3.9	62,541	83.4	10,917	14.6	1,511	2.0
	Male	383	0.5	13,905	16.6	12,415	14.9	129	0.2	52,606	62.9	925	1.1	3,223	3.9	71,891	86.0	10,309	12.3	1,386	1.7
	Unknown	0	0.0	0	0.0	5	2.7	0	0.0	4	2.2	3	1.6	174	93.6	29	15.6	12	6.5	145	78.0

Table 4P: U.S. Site Enrollment for NIH-Defined Intramural Phase III Trials, Sex/Gender by Race and Ethnicity for FY 15–16

Year	Sex/Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2015	Female	361	3.9	227	2.5	2,334	25.4	4	0.0	5,932	64.7	29	0.3	286	3.1	8,614	93.9	432	4.7	127	1.4
	Male	96	2.8	65	1.9	602	17.5	3	0.1	2,527	73.6	8	0.2	133	3.9	3,274	95.3	108	3.2	52	1.5
	Unknown	2	66.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	33.3	1	33.3	2	66.7	0	0.0
2016	Female	313	3.8	232	2.8	2,334	28.1	3	0.0	5,118	61.6	35	0.4	274	3.3	7,723	93.0	446	5.4	140	1.7
	Male	85	3.0	66	2.3	594	20.9	2	0.1	1,942	68.4	14	0.5	136	4.8	2,664	93.8	115	4.1	60	2.1
	Unknown	2	50.0	0	0.0	1	25.0	0	0.0	0	0.0	0	0.0	1	25.0	1	25.0	2	50.0	1	25.0

Appendix E. 2017 Biennial Advisory Council Reports Certifying Compliance with NIH Policy on Inclusion Guidelines

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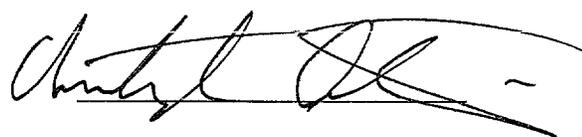
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Signature

Christopher P. Austin, M.D.

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National Center for Advancing Translational Sciences

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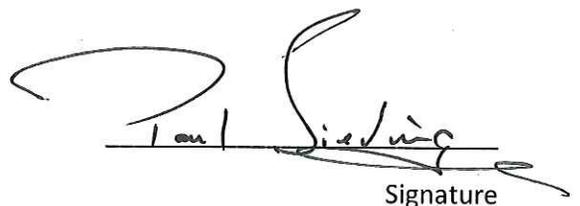
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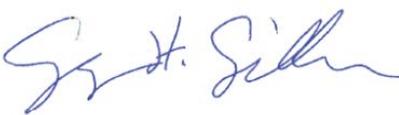


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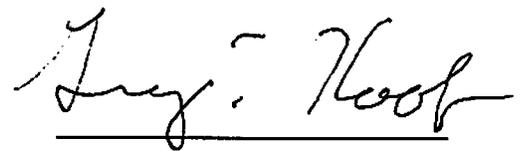
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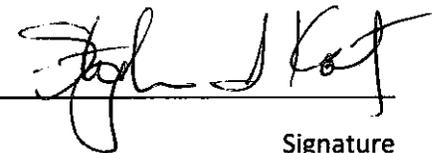
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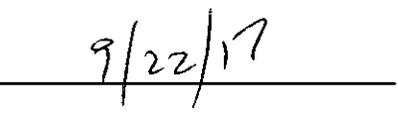
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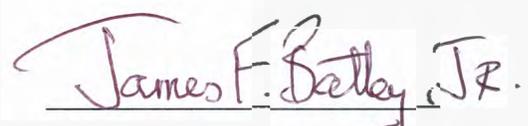
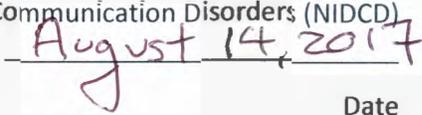
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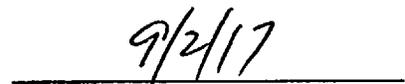
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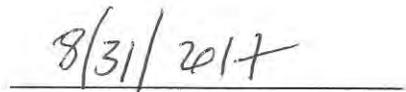
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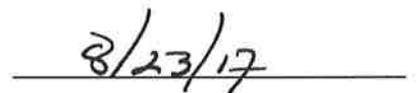
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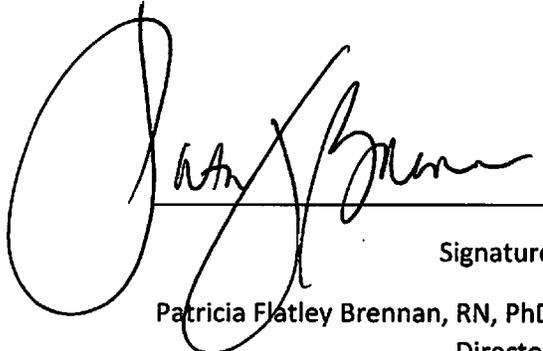
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