61st Meeting of the National Institutes of Health (NIH) Advisory Committee on Research on Women's Health (ACRWH) Office of Research on Women's Health (ORWH) Bethesda, MD October 8, 2024

Members Present
Garnet L. Anderson, Ph.D.
Irene Aninye, Ph.D.
Arthur Arnold, Ph.D. *(ad hoc)*
Ayush Giri, Ph.D.
Stephen Higgins, Ph.D.
Reshma Jagsi, M.D., D.Phil. *(virtual)*
Hendrée Jones, Ph.D.
Rosalyn E. Maben-Feaster, M.D. *(ad hoc)*
Thelma Mielenz, Ph.D.
Alexandra Noël, Ph.D.
Ighovwerha Ofotokun, M.D.
Phyllis Sharps, Ph.D.
Kimberly J. Templeton, M.D. *(virtual)*

ORWH Leadership Present
Janine A. Clayton, M.D., FARVO,
ORWH Director
Vivian Ota Wang, Ph.D., FACMG, CGC,
ORWH Deputy Director
Victoria Shanmugam, M.D., MBBS, MRCP, FACR, CCD
Director, Office of Autoimmune Disease-ORWH
Sarah Temkin, M.D., FACS
Associate Director for Clinical Research
Xenia Tigno, Ph.D.
Associate Director for Careers

Other NIH Leadership Present
Matthew McMahon, Ph.D.
Director, Small Business Education and Entrepreneurial Development (SEED) Office
Richard Palmer, Dr.P.H., J.D.
Acting Director, National Library of Medicine (NLM) Extramural Programs
Dina N. Paltoo, Ph.D., M.P.H., CPL
Acting Deputy Director, Policy and External Affairs
Bruce J. Tromberg, Ph.D.
Director, National Institute of Biomedical Imaging and Bioengineering (NIBIB)

Other Federal Leadership
Susan Margulies, Ph.D.
Assistant Director, U.S. National Science Foundation (NSF)

Special Guests
Eve J. Higginbotham, M.D., S.M., M.L.
University of Pennsylvania and Chair, National Academies of Sciences, Engineering, and Medicine (NASEM) Consensus Committee on - Chronic Conditions in Women

Call to Order

Vivian Ota Wang, Ph.D., FACMG, CGC, ACRWH Executive Secretary, and ORWH Deputy Director, called the hybrid meeting to order at 9:00 a.m. Dr. Ota Wang acknowledged retiring members Garnet Anderson, Ph.D.; Irene O. Aninye, Ph.D; and Melissa Simon, M.D., M.P.H. She also recognized new members Ayush Giri, Ph.D., and Ighovwerha Ofotokun, M.D., and upcoming members Arthur Arnold, Ph.D.; LaPrincess C. Brewer, M.D., M.P.H.; and Rosalyn E. Maben-Feaster, M.D., M.P.H. She thanked Reshma Jagsi, M.D., D.Phil., and Kimberly J. Templeton, M.D., for their continuing service. ACRWH members introduced themselves. ACRWH members approved the minutes of the 60th ACRWH meeting, held on April 9, 2024, with 10 members in favor.

ORWH Director's Report

Dr. Ota Wang introduced Janine A. Clayton, M.D., FARVO, ORWH Director and NIH Associate Director for Research on Women's Health, who delivered the Director's report. She identified technology and innovation as the theme of the 61st ACRWH meeting. Dr. Clayton introduced Discover **W**omen's **H**ealth **R**esearch (DiscoverWHR), a collaboration between ORWH and the National Library of Medicine (NLM) to create a centralized resource for research on women's health and information that supports NIH-wide efforts to close the gaps in research on women's health across the life course. The resource includes links to open funding opportunities, awarded research projects, recruitment for upcoming clinical trials, recently published literature on NIH-funded research, and patient-friendly summaries of health topics. In its first phase, menopause, polycystic ovary syndrome (PCOS), and selected autoimmune diseases (lupus, rheumatoid arthritis, and scleroderma) are searchable topics.

ORWH and NIH Update. In May 2024, when the *2024–2028 NIH-Wide Strategic Plan for Research on the Health of Women* was issued, Dr. Bertagnolli shared her vision for women's health research in a video titled "Forging into the Future: Research on the Health of Women at NIH and Beyond." During National Women's Health Week (May 12–18, 2024), ORWH and the Office of Disease Prevention (ODP) sponsored "The Future Directions in Menopause Research: Optimizing Midlife Health of Women Roundtable," and Dr. Bertagnolli announced a new Pathways to Prevention initiative on menopause. She also highlighted many topics relevant to women's health research in her Director's Blog, including "Diagnosis and Treatment of Mental Health Conditions During and After Pregnancy is on the Rise, But Disparities Still Exist" (April 18, 2024) and "Maternal Brain Hormone Key to Strengthening Bones Could Help Treat Osteoporosis, Bone Fractures" (August 1, 2024).

In June 2024, Dr. Bertagnolli announced **C**ommunities **A**dvancing **R**esearch **E**quity **for Health** (CARE for Health). NIH is investing approximately $30 million over Fiscal Years (FY) 2024 and 2025 to pilot a primary care research network that integrates clinical research with community-based primary care, particularly in communities historically underrepresented in clinical research or underserved in health care. Researchers will conduct research addressing issues important to diverse communities, reduce burden on providers by using innovative data collection methods, integrate research into the clinical care environment, engender trust in science by addressing community needs, achieve longitudinal collection of clinical data to address health across the lifespan, increase adherence to evidence-based care, and improve the efficiency of care delivery. CARE for Health will help grow an evidence base of research data that contributes to improved patient outcomes, provides communities access to the best available scientific research, and expands opportunities to participate in clinical trials and studies.

Dr. Clayton announced the appointments of two new women leaders at NIH: Geri R. Donenberg, Ph.D., M.P.H., Office of AIDS Research (OAR) Director and NIH Associate Director for AIDS Research, and Annica M. Wayman, Ph.D., M.S., National Center for Advancing Translational Science (NCATS) Deputy Director. This brings the number of women NIH Institute and Center (IC) Deputy Directors to 12; the number of women IC Directors stands at 13 among 27 ICs. Dr. Clayton also welcomed Lucia Hindorff, Ph.D., M.P.H., the new Senior Advisor for Scientific and Organizational Strategy at ORWH.

Women's health research has been on the agenda of NIH Advisory Councils. On May 14, 2024, Dr. Clayton gave a virtual presentation to the NLM Board of Regents that provided an overview of women's health research and activities at NIH. On May 15, 2024, Dr. Clayton addressed the National Institute of Biomedical Imaging and Bioengineering (NIBIB) National Advisory Council for Biomedical Imaging and Bioengineering, covering women and biotechnology careers, women's health, and how the Sex as a Biological Variable (SABV) policy is addressing gaps relevant to women in biotechnology. On June 13,

2024, Dr. Clayton presented during the 128th NIH Advisory Committee to the Director meeting about ORWH programs and activities, current NIH women's health research efforts, and the recent release of the *NIH Fact Sheets on Women's Health Research.* On September 19, 2024, Dr. Clayton presented to the National Institute on Aging (NIA) National Advisory Council on Aging on women's health topics—including midlife women's health, menopause research, and the ORWH menopause and midlife health webpage—and women's health research funding opportunities. ORWH has also actively promoted women's health on the national and global stage. Dr. Clayton was honored during the Society for Women's Health Research Annual Awards event on April 25, 2024. She addressed women's health research during the NIH Patient Engagement Summit on September 11, 2024. Dr. Clayton was also honored to be recognized as a champion of women's health during the Annual Meeting of the Champions of the Global Alliance for Women's Health, World Economic Forum, on September 23, 2024, and she participated in the 9th edition of Science Summit 2024 at the United Nations General Assembly.

Policy and Scientific Updates. Dr. Clayton serves as Co-Chair of **Com**munity **P**artnerships to **A**dvance **S**cience for **S**ociety (ComPASS). ComPASS's goals are to (1) catalyze, deploy, and evaluate community-led health equity structural interventions that leverage partnerships across multiple sectors and (2) develop new research models for community-led, multisectoral structural intervention research across NIH and other federal agencies. This 10-year program has a budget of approximately $200 million for the first 5 years. ComPASS has three initiatives: (1) 25 Community-Led, Health Equity Structural Intervention (CHESI) projects (awarded in 2023) engage communities in research led by community organizations, which work in collaboration with research partners to study ways to address the underlying structural factors within communities that affect health; (2) the ComPASS Coordinating Center (awarded in 2023) provides oversight for the planning, implementation, and evaluation of the ComPASS program; and (3) five ComPASS Health Equity Research Hubs (awarded in 2024) provide localized technical assistance and scientific support for the CHESI projects in collaboration with the coordinating center. The five newly funded ComPASS Hubs are at the University of Mississippi Medical Center; Yale University; University of Maryland, Baltimore; New York University Grossman School of Medicine; and the University of Michigan at Ann Arbor.

Strategic Plan. ComPASS efforts are aligned with Goal 5 in the *2024–2028 NIH-wide Strategic Plan for Research on the Health of Women*. Its five goals include (1) advance research that examines the multiple biological, behavioral, social, structural, and environmental factors that influence the health of women, as well as the intersections of these factors; (2) improve data science and data management practices with innovative research methods, measurements, and cutting-edge technologies to prevent and treat conditions affecting women; (3) foster women scientists' career development and promote scientific workforce training and education that advances the health of women and the science of sex and gender influences; (4) support basic and translational study disease and health preservation in women across the life course; and (5) advance community-engaged science across the research and practice continuum and enhance the dissemination and implementation of evidence-based solutions to improve the health of women.

Sex and Gender Equity in Research. Journal editors and publishers play an important role in women's health research by adhering to the Sex and Gender in Research (SAGER) Guidelines. The World Health Organization has formally adopted the Guidelines, marking a major milestone in their dissemination. The Guidelines have been translated into seven languages, are included on the EQUATOR website, and are listed in NLM's Research Reporting Guidelines. In addition, the *Journal of the National Cancer Institute* (NCI) now outlines guidelines for its editors and authors including how to report all outcomes by sex and/or gender.

Office of Autoimmune Disease Research (OADR-ORWH). OADR-ORWH has published a Request for Information (NOT-OD-24-049) inviting input on a strategic planning process focused on the following key objective areas: (1) research areas that would benefit from cross-cutting, collaborative research; 2) opportunities to advance collaborative, innovative, or interdisciplinary areas of autoimmune disease research; and (3) opportunities to improve outcomes for individuals living with autoimmune diseases, especially health disparity populations and historically underrepresented groups.

NIH Policy on Sex as a Biological Variable. Colleagues in nursing research are disseminating SABV as a policy. For example, a "call to action," titled "Ensuring accountability for consideration of sex as a biological variable in research," was published in *Nursing Outlook* (July–August 2024) with key recommendations to advance generation and dissemination of rigorous research.

Science Update. New research from NCI identified inherited gene variants that may predict the age-related loss of one X chromosome in women, known as mosaic loss of chromosome X (mLOX). This condition is linked to an increased risk of abnormal blood cell proliferation and several health issues, including cancer. These findings could lead to predictive tools for identifying which X chromosome is retained, highlighting the need for further research into mLOX's role in disease risk.

Clinical Trials Website Update. On June 25, 2024, the modernized ClinicalTrials.gov, redesigned by NLM, became the singular website experience for all users. Data disaggregated by sex that clinicians use to make decisions are now available.

White House Initiative on Women's Health Research. On November 13, 2023, a Memorandum on the White House Initiative on Women's Health Research (WHI WHR) was announced. The initiative aims to improve women's health in the United States by accelerating research on the health needs of women across their lifespans. ORWH is honored to serve alongside other NIH Institutes, Centers, and Offices (ICOs) and various federal agencies and offices to transform the research landscape and close gaps to improve the health of women. ORWH submitted robust input from ICO colleagues on NIH priorities and proposed initiatives and policy changes. Signed on March 18, 2024, Executive Order 14120, Advancing Women's Health Research and Innovation directed 11 federal agencies to implement a cross-cutting program to advance new, interdisciplinary women's health research toward transformative research and development in women's health. Dr. Clayton is co-chairing an interagency work group on research and data standards.

Although Executive Order 14120 contains multiple sections, Dr. Clayton emphasized the following four sections: *Section 3. Further Integrating Women's Health Research in Federal Research Programs* to advance system-wide enhancements to business processes to incorporate consideration of women's health across the grant lifecycle; *Section 4. Prioritizing Federal Investments in Women's Health Research*, including an NIH-wide Notice of Special Interest (NOSI; NOT-OD-24-079) to highlight interest and pathways for research on the health of women; *Section 5. Galvanizing Research on Women's Midlife Health*, which includes the Menopause Common Data Elements (CDEs) Working Group that completed an NIH-wide landscape analysis to identify CDE-related gaps and is working toward harmonizing existing and creating menopause CDEs; and *Section 6. Assessing Unmet Needs to Support Women's Health Research*, which is conducting a robust review to assess gaps in federal funding for women's health research and identify necessary changes—whether statutory, regulatory, or budgetary.

In response to Executive Order 14120, NIH is committed to collaborative cross-cutting efforts to advance the health of women's research across the life course. The Seed Fund's efforts will direct key

investments of $200 million in FY2025 to fund new, interdisciplinary women's health research that transcends the traditional missions of the ICs, and the proposed Central Fund effort (pending availability of funds) will accelerate interdisciplinary women's health research by capitalizing on NIH research data assets to address bold research questions to identify and analyze interdisciplinary research questions for developing innovative new diagnostics and treatments. These NIH-wide efforts are overseen by an Executive Committee composed of co-chairs Dr. Clayton, Dr. Lindsay Criswell, the Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and Dr. Diana Bianchi, the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and other IC Directors including from NIA, National Institute on Drug Abuse (NIDA), and National Heart, Lung, and Blood Institute (NHLBI). Further, efforts are under way to align women's health across NIH and federal agencies through collaboration. These efforts include (1) increasing access and collaboration to close research gaps with new women's health research, survey tools, analyses, and insights (e.g., DiscoverWHR, described above); (2) enhancing data collection and transparency in reporting of NIH support of women's health and diseases and conditions with standardized methodology (e.g., Research Condition and Disease Categorization funding on menopause; (3) ORWH and the Centers for Disease Control and Prevention collaborating to develop questions about menopause status, which will be included in the 2025 National Health Interview Survey; and (4) streamlining women's health efforts and amplifying priorities across multiple sectors of the federal government. NIH is also investing in innovative research to address health concerns that are relevant to women. An NIH-wide NOSI on Women's Health Research (NOT-OD-24-079) added 41 new pathways to women's health funding, spanning research grants, career development grants, fellowships, and small business grants. Thirty ICOs are participating, representing more than 175 priority research topics.

ORWH is making it easier to find Notices of Funding Opportunity (NOFOs) from a new ORWH "front door" webpage titled "Women's Health Funding Opportunities." It features more than 160 NOFOs, including 11 ORWH Opportunities and Notices, 112 ORWH Participating Funding Opportunities and Notices, NIH Women's Health Funding Opportunities, and 42 NIH NOFOs.

Innovations in Women's Health Research at NIH. Dr. Clayton highlighted several steps undertaken by NIH to increase innovation in women's health. These included (1) a commitment to increase funding by up to 50% to support small businesses dedicated to research and development in women's health; (2) a partnership with the Small Business Education and Entrepreneurial Development (SEED) Office, which led to ORWH's first participation in the NIH-wide FY25 Omnibus Solicitation for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) (PA-24-245, PA-24-246, PA-24-247, PA-24-248) applications; and (3) the newly released RADx Tech ACT ENDO Challenge, managed by NICHD in partnership with NIBIB, to accelerate the development of innovative, noninvasive technologies to improve the diagnosis of endometriosis, a condition that affects 1 in 10 women. ORWH developed a webinar series for the Small Business Offices in each IC to expand opportunities for women's health innovation among small businesses. The first webinar was held in June 2024, with upcoming webinars scheduled for October 30, 2024, and January 29, 2025.

Providing Resources. In response to the Presidential Memorandum on women's health research, ORWH—in partnership with ODP, NICHD, NIA, and the National Institute of Mental Health (NIMH)—developed the NIH Women's Health Roundtable Series to emphasize priority Department of Health and Human Services (HHS) topics and disseminate information about federally supported research areas. More than 5,400 individuals have attended the series. To date, roundtables have addressed Future Directions in Menopause Research—Optimizing Midlife Health of Women, Endometriosis—Beyond the

Lesion: Charting New Paths, and Maternal Mental Health Research—Elevating Women's Voices to Improve Maternal Mental Health.

Executive Order 14120 also has resulted in disseminating information, funding opportunities, and research partnerships on the health of women. In addition to the new *2024–2028 NIH-Wide Strategic Plan for Research on the Health of Women*, ORWH marked National Women's Health Week with the launch of the *NIH Health of Women of U3 Populations Databook 2024*, *NIH Fact Sheets on Women's Health Research*, the Future Directions in Menopause Research Roundtable, and the 8th Annual Vivian W. Pinn Symposium, which focused on innovations in autoimmune disease research and care.

Biennial Report. Development of the *FY2023–2024 NIH Report of the Advisory Committee on Research on Women's Health: Office of Research on Women's Health and NIH Support for Research on Women's Health* (Biennial Report) has begun. The Biennial Report includes information about programs and initiatives undertaken across NIH ICOs in service of the core mission of ORWH.

Women's Health Research in Institutional Development Award (IDeA) States Programs. To build women's health research capacity in the 23 states and Puerto Rico that receive the least federal funding, ORWH has collaborated since 2020 with the National Institute of General Medical Sciences (NIGMS) to create the first IDeA funding opportunities on women's health. With support from 14 ICOs, ORWH and NIGMS issued NOT-GM-20-017. Awards were given to 15 IDeA states in FY20 and 11 IDeA states in FY21. By FY23, the program grew to 60 grants totaling $16.46 million. To date, 21 IDeA states have received awards. In June 2024, ORWH and NIGMS organized the first "NIH Symposium on Women's Health Research in the IDeA States" to showcase the significant progress made in women's health research in IDeA states. In addition, the first NOSI on Supporting Women's Health Research in IDeA States through Centers of Biomedical Research Excellence (COBRE) was released on October 27, 2022. In FY24, applications were accepted; ORWH co-funded (with NIGMS) the application "Leveraging Big Data to Improve Women's Health" from the University of Kansas, Lawrence.

Menopause. Within the menopause and midlife domain, ORWH has been actively promoting and addressing menopause as a critical research area and how the interrelated issues of cognitive changes, muscle atrophy, bone loss, cardiovascular disease, metabolic dysfunction, weight gain, anxiety, and hot flashes, are related to chronological or reproductive aging. NIA, NIMH, NHLBI, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) maintain the largest NIH research portfolios on menopause. Dr. Clayton has presented to NIH Advisory Councils such as NIA, NIBIB, NHLBI, NLM, and NIH Advisory Committee to the Director and has participated in a Congressional briefing on menopause and midlife women's health. During the Menopause Society Annual Meeting in September 2024, ORWH staff delivered scientific presentations that highlighted NIH research investments in menopause research. ORWH also supported two travel awards for junior investigators who presented their research during the meeting. ODP is planning its first Pathways to Prevention workshop on the menopausal transition to promote midlife health, identify research gaps, and develop a roadmap for advancing research. Partners include ORWH, NHLBI, NIA, NICHD, NIMH, and NCI. The workshop is tentatively scheduled to take place in late 2025. Dr. Clayton also applauded her colleagues at NIMH, who published a review of mental health research and the menopause transition in the *Journal of Women's Health* (February 2024), highlighting data that show minoritized women are disproportionately affected by depression and other mental health conditions. NIH currently has two NOFOs on mood and psychosis during the menopause transition. Finally, ORWH has collaborated with multiple ICs this year on funding applications related to menopause that were submitted in response to Requests for Applications (RFAs) on Understanding Chronic Conditions Understudied Among Women (RFA-OD-23-014 and RFA-OD-23-

013). In FY2024, ORWH funded two applications: "Regenerative Biomaterial for Combating Genitourinary Syndrome of Menopause" and "Changes in Cardiometabolic Tissue Gene Regulation and Omics Profiles with Menopause."

Sex and Gender. The Galvanizing Health Equity Through Novel and Diverse Educational Resources (GENDER) Research Education Program has recently awarded its second round of R25 grants in collaboration with OAR, NLM, the National Institute of Neurological Disorders and Stroke, and the Sexual & Gender Minority Research Office. The GENDER Research Education Program supports educational activities that enhance and complement the current workforce's skills to address diverse biomedical, behavioral, and clinical research needs. Recipients in 2024 include the University of California Irvine, Loyola University of Chicago, Massachusetts General Hospital, University of Cincinnati, and University of California San Francisco. The first annual GENDER meeting of Principal Investigators (PIs) in September 2024 showcased projects in development. In 2023, ORWH released a NOSI for Research on Gender Measurement (NOT-OD-23-046) in collaboration with nine ICOs to support "Objective 2.2: Develop reliable measures relevant to women's health" in the *2024–2028 NIH-wide Strategic Plan for Research on the Health of Women* that resulted in eight FY23 awards. The grantees' work will be presented in a "Research on Gender Measurement" webinar on November 3.

ORWH has funded an open-access supplement on advancing differences in health outcomes in *Social Science & Medicine* where established and emerging leaders across diverse fields provided a multidisciplinary framework to understand the complex intersections of health research.

ORWH's E-Learning courses continue to attract a diverse audience and widespread participation. Over the past five years, more than 2,800 individuals from 69 countries, primarily women, have enrolled. Popular courses include "Bench to Bedside Immunology" and "SABV and the Health of Men and Women."

Careers. Speakers at the 2024 Specialized Centers for Research Excellence on Sex Differences (SCORE) annual meeting included Victor J. Dzau, M.D., President of the National Academy of Medicine, and Carolyn M. Mazure, Ph.D., Chair of the WHI WHR. During the 2024 Building Interdisciplinary Research Careers in Women's Health (BIRCWH) annual meeting, Abbey Berenson, M.D., M.M.S., Ph.D., Director, University of Texas Medical Branch Center for Interdisciplinary Research in Women's Health, and Nina F. Schor, M.D., Ph.D., NIH Deputy Director for Intramural Research, provided keynote addresses.

ORWH is partnering with NIDKK to award the Advancing Gender Inclusive Excellence (AGIE) Coordinating Center to Virginia Commonwealth University. The AGIE Coordinating Center will develop a research strategy; lead and manage the overall program; serve as a centralized resource hub to collect, store, and disseminate resources and results; develop and implement a communication and dissemination plan; and administer and manage a Pilot and Feasibility Studies program supporting awards to investigate programs addressing systemic gender-based inequities.

Upcoming Events. Dr. Clayton highlighted a workshop on "The Intersection of Regenerative Medicine and Women's Health" on October 1, 2024, co-chaired by Dr. Ota Wang, and the upcoming events: "Small Business Opportunities for Innovative Women's Health Research" on October 30; "Updates on OADR-ORWH Session 5" on November 8; and "OADR-ORWH ScienceTALKS: The Cancer Autoimmune Connection: Decoding the Paradox" on December 5.

Closing Remarks. Dr. Clayton encouraged ACRWH members and others to stay in touch with ORWH through its e-learning courses, publications, and social media.

National Institute of Biomedical Imaging and Bioengineering Director's Report

Dr. Clayton introduced Bruce J. Tromberg, Ph.D., NIBIB Director, whose presentation addressed "Accelerating Innovation and Technology Development in Women's Health through Engineering-Medicine Partnerships." He lauded Dr. Clayton's strong support for technology and noted that she will be the keynote speaker during the Biomedical Engineering Society 2024 Annual Meeting, articulating the medical community's needs to technology providers.

Background. NIBIB was created by an Act of Congress in 2000. Since then, the number of academic biomedical engineering (BME) programs across the country has exploded, with more than 175 accredited BME-related programs and nearly 200 graduate programs at many engineering schools prioritizing human health. Bioengineering is also being incorporated into schools of medicine; for example, the University of Illinois at Champaign and Texas A&M University offer programs that enable students to earn both an M.D. and a master's degree in engineering.

Because NIBIB's total budget is about 1% of total NIH spending, the Institute strives to build partnerships and collaborations with NIH ICOs. During FY19–FY23, NIH awarded approximately $55.6 billion for bioengineering awards with 80% of that amount attributable to NIBIB and the remainder spread among ICs, including NLM, the National Institute on Deafness and Other Communication Disorders, the National Human Genome Research Institute, the National Institute of Dental and Craniofacial Research, NIAMS, and the National Eye Institute. In FY23, NIH invested $7.15 billion in bioengineering research, representing an approximate two-fold increase in funding over 10 years.

NIBIB's mission is to transform, through technology development, science's understanding of disease and its prevention, detection, diagnosis, and treatment. Disease-agnostic, NIBIB is focused on bioengineering and biomedical imaging, informed by data science, modeling, and computation (artificial intelligence [AI] and machine learning [ML]). During FY19–FY23, NIBIB made 6,511 awards related to bioengineering and women's health and women's health technology investments consumed about 8–10% of NIBIB's total budget (approximately $200 million) and 3.4% of all NIH awards related to bioengineering and women's health.

Women in Engineering. An underlying factor driving interest in BME and women's health is the increased numbers of women engineering students and faculty. Between 2005 and 2022, the number of female engineering students receiving degrees in BME increased nearly 4-fold, compared to an approximately 2-fold increase in other engineering departments. In 2022, more than 4 in 10 Ph.D. degrees (44%) and over one-half (53%) of undergraduate degrees in BME were awarded to women. During the same period, female faculty in BME experienced a 3.4-fold increase. Today, 28% of BME faculty are women.

The Design by Biomedical Undergraduate Teams (DEBUT) Challenge exemplifies the interest in women's health within BME. In 2024, NIBIB collaborated with six NIH partners (OAR, NCI, NICHD, NIDDK, the National Institute of Minority Health and Health Disparities, and the National Institute of Nursing Research) and nonprofit partner, VentureWell, to sponsor the DEBUT Challenge with a total prize purse of $160,000 for 16 winning teams. Eighty-five applications from 362 students at 48 universities in 24 states were received. For 2025, the DEBUT Challenge purse has increased to $190,000 with 18 prizes and two new sponsors, including ORWH and NIA.

Point of Care Technologies. In 2007, NIBIB created the Point of Care Technologies Research Network (POCTRN) to develop technologies with clinical applications using a network model. Today, POCTRN

consists of six university partners and a coordinating center. During the COVID pandemic, POCTRN was tapped to support NIH's Rapid Acceleration of Diagnostic Technology (RADx Tech) program to accelerate innovation in the development, commercialization, and implementation of technologies for COVID-19 testing. More than 1,000 applications entered the RADx Tech innovation funnel that was designed to compress the customary technology development timeline from years down to just months. Launched on April 29, 2020, the RADx programs were able to validate, de-risk, scale up, manufacture, and deploy novel tests through a seamless pipeline by fall 2020. More than 1 billion at-home COVID tests were distributed to the public in February 2022 and more than 2.5 billion in all of 2022. This required addressing test performance and developing unique pathways to obtain rapid U.S. Food and Drug Administration (FDA) approvals.

NIBIB has used the RADx Tech platform to drive innovation for other health conditions, including women's health issues. For example, NICHD and NIBIB are co-sponsoring the RADx® Tech for Maternal Health Challenge, which is coming to a close after two years of competition. The Challenge dedicated $8 million in cash awards to accelerate the development of maternal health diagnostic devices, wearables, or other remote-sensing technologies for use in maternity care deserts and focused on improving maternal health outcomes during the first year of the postpartum period. Ten projects are currently in the clinical performance assessment phase; awards will be announced soon. In September 2023, NIBIB, NICHD, and the Bill & Melinda Gates Foundation announced the RADx® Tech Fetal Monitoring Challenge to develop innovative and accessible technologies to enable earlier and more accurate diagnosis, detection, and monitoring of fetal health status in low-resource settings and to improve fetal health outcomes during the late antepartum and intrapartum periods of pregnancy. Total prizes in this competition equal $2 million. The competition attracted more than 40 entries. Of those, six teams will advance to the final phase of the competition with winners to be announced later this year. Finally, the RADx® Tech ACT ENDO Challenge, co-sponsored by NICHD, offers $3 million in cash prizes to accelerate the development of noninvasive technologies to improve the diagnosis of endometriosis. Proposed technologies should shorten the time to endometriosis diagnosis; eliminate the invasiveness of current techniques; and/or improve accessibility, safety, convenience, and costs of diagnosis. Applications were due on October 11, 2024.

Engineered Biological Systems. Within this domain, NIBIB addresses therapies and materials. NIBIB supports science that includes engineering an immuno-isolating hydrogel for restoring ovarian endocrine function, developing a liquid crystal elastomer to treat incontinence in women, and creating probiotic-guided CAR-T Therapy (ProCARs) for breast cancer.

Biomedical Imaging. Dr. Tromberg illustrated NIBIB's investment in biomedical imaging by highlighting four innovations for women's health: (1) doppler ultrasound breast cancer imaging; (2) quantitative breast photoacoustic computed tomography (PACT) using AI; (3) low-cost, accessible cervical imaging technologies; and (4) female computational models for a virtual platform to evaluate medical imaging technology, for example, female astronaut models to assess radiation dose in deep space missions.

Summary and Conclusions. Dr. Tromberg emphasized the following key points: (1) bioengineering represents approximately 15% of total NIH spending in 2023 (approximately $47 billion) and is growing; (2) women engineers are the key drivers of BME growth at all levels; and (3) growth continues in purpose-driven bioengineering technologies for women's health (8–10% of the NIBIB budget), driven by contributions from undergrad design challenges and academic innovation/entrepreneurship in the FEMTECH sector. Dr. Tromberg also identified the following challenges for the field: (1) continue to increase the number of women BME faculty (28%) to reflect the number of BME doctoral degrees awarded to women (44%) and the number of Ph.D.'s awarded to women to reflect the percentage of

undergraduate degrees (more than one-half); (2) expand development, validation, and clinical adoption of women's health technologies; and (3) create new opportunities for innovation, commercialization, and Engineering-Medicine Partnerships.

Discussion. The following issues were discussed following Dr. Tromberg's presentation:

- A significant number of women lead BME departments, and many female BME engineers are becoming deans at their universities. Three past presidents of the Biomedical Engineering Society have been women.
- A suggested educational module or outreach to students to inform them of the breadth of women's health issues would be an excellent addition to the undergraduate BME curriculum; Dr. Tromberg will speak to NIBIB staff about developing such a product.
- In the future, because the exposome will become part of electronic health records, there should be a joint effort with the environmental science community to identify measurable aspects of the exposome that could potentially be built into a wearable device.

NIH Supports Innovation in Women's Health

Dr. Clayton introduced Matthew McMahon, Ph.D., SEED Director at NIH. Dr. McMahon noted that NIH's mission is not only to seek fundamental knowledge but also to apply that knowledge to enhance health, lengthen life, and reduce illness and disability. SEED was founded in 2019 in response to an increasing understanding across all ICs that investigators need support to bridge the gap between basic discoveries and the application of that knowledge to improve human health. Staffed with industry veterans and entrepreneurs, half of whom are women, SEED acts as an in-house commercialization or product development service. It also includes an in-house regulatory team to help investigators understand FDA requirements and marketing approvals, as well as the business processes for commercialization. SEED and ORWH have the overlapping goal of applying advances in knowledge to address the challenges to commercializing innovative technologies related to women's health. An integral part of that goal is its intersection with increasing the diversity of the biomedical workforce.

Investment and Product Development in the Women's Health Sector. Dr. McMahon emphasized that today is a time of real opportunity to invest in women's health innovations because the potential market is large, the regulatory environment is conducive, and investors are interested in working in this sector. In 2023, Silicon Valley Bank published four predictions for women's health innovations: growth in nonreproductive focus areas, addressing of unmet needs with life sciences (e.g., clinical research, diagnostic and device development, therapeutics for women), the rise of dedicated women's health funds (more investment in early-stage funding), and venture capital investments shifting toward later-stage product development. The January 2024 World Economic Forum report, "*Closing the Women's Health Gap: A $1 Trillion Opportunity to Improve Lives and Economies*" also identified a tremendous gap in women's health that market forces can address. Science, data delivery, and care investments were mentioned as key factors deserving more attention.

Dr. McMahon also discussed that a tremendous amount of capital from federal and private sources is devoted to women's health products and services, changing the landscape from a decade ago when there was great need but no market opportunity. NIH supports innovation at the point of transition from cutting-edge scientific discoveries to early-stage product development through its NIH Research Evaluation and Commercialization Hubs (REACH) and through America's SEED Fund for small businesses.

NIH Research Evaluation and Commercialization Hubs. REACH helps academic researchers convert their research to marketable products by making their products attractive to investors. REACH provides up to

$100,000 in funding for product validation and assists investigators in managing product development using milestone-based project management. The program also provides entrepreneurial training and mentoring, including personalized feedback from NIH, FDA, the Centers for Medicare & Medicaid Services, the U.S. Patent and Trade Office, and industry veterans. REACH, authorized by Congress in 2011, started with three NIH Centers for Accelerated Innovation, followed by three hubs in 2015 and five more in 2019. In 2023, NIH committed $1 million per year for four years to five new hubs in lesser-served geographic areas that together support academic innovators at more than 75 institutions in 12 states. These hubs serve minority-serving institutions, tribal colleges, technical schools, and community colleges to increase workforce diversity and entrepreneurial literacy. To date, REACH has educated more than 2,800 investigators and supported more than 250 technology development projects.

Small Business Innovation Research/Small Business Technology Transfer. NIH supports product development through its SBIR/STTR program, which is mandated by Congress and encourages investigators to use small businesses to move their products to market. NIH funds this program at approximately $1.48 billion per year (4% of NIH's extramural research budget) and currently supports more than 1,400 small businesses. The NIH SBIR/STTR program is the largest source of early product funding in the United States and does not require entrepreneurs to relinquish ownership of their companies, as venture capitalists often do. In addition to receiving funding, successful small business applicants also gain access to SEED's commercialization assistance. In the women's health arena, NIH funds at least 200 small businesses every year.

Biomedical Workforce Development. There is a congressional mandate to increase women-owned small business funding. SEED trains and supports women innovators and entrepreneurs. Over three-quarters (76%) of women's health companies have at least one female founder. SEED also addresses the needs of underrepresented communities. For example, a Navajo entrepreneur supported by SEED developed a bio-absorbable clip to help patients during spinal surgery; she hired Navajo employees and interns. NIH has devoted about 15% of small business funding to women-owned companies but is committed to doing better.

Discussion. Dr. Clayton moderated a discussion during which the following points were made:

- The process of bringing products that address differences in health outcomes to market faces unique challenges. Innovative solutions to these challenges are being developed by MedTech Color, a joint industry-government group; Women in Biology; Association for Women in Science; and other groups.
- As one strategy to increasing market interest in an area, investigators could develop smaller-scale products with smaller markets and then create a network of small product developers; this approach drives growth for products that have not received market attention.
- Diversity in the innovation workforce must be increased. The new REACH funding opportunity was designed to increase geographic, racial/ethnic, and investigator stage diversity. Each hub has a local advisory committee. NIBIB has several diversity-focused opportunities, including R01s and supplements.
- The expansion of women in the BME field is responsive to a societal need to integrate STEM and altruism.

Panel: Technology, Engineering, and Innovation in Women's Health Research

Dr. Ota Wang introduced Panel Moderator Manu O. Platt, Ph.D., Biomedical Engineering Technology Center Director and NIBIB Scientific Diversity, Equity, and Inclusion Associate Director. Dr. Platt introduced the panel members: Ji-Yong Julie Kim, Ph.D., Co-Director of the Center for Reproductive Science at Northwestern University and Susy Y. Hung Research Professor of Obstetrics and Gynecology,

Division of Reproductive Science in Medicine; Michelle L. Oyen, Ph.D., Associate Professor of Biomedical Engineering, Wayne State University; and Ridhi Tariyal, M.B.A., S.M., Chief Executive Officer and Co-Founder of NextGen Jane.

The Female Reproductive Microphysiologic System

Dr. Kim, a molecular and reproductive biologist, focused on how she and her colleagues integrate engineering technologies to address the development and growth of uterine diseases. She noted that medicine is failing women because there are no effective treatments for many diseases and conditions that affect women. To ameliorate this situation, medicine needs to apply technologies developed for other fields to the health of women.

Conventional in vitro systems do not accurately represent the complexity of female physiology. Traditionally, researchers have studied one cell at a time in monolayers. However, the ability to study the interactions between multiple cell types in the body is needed. Researchers have used various animal models to study the biology of the body, but no model is perfect for studying human women. The female reproductive system is difficult to model because ethical considerations limit the kinds of studies that can be performed, especially in women who are of reproductive age and/or pregnant. Overall, the challenges to studying reproductive diseases include the lack of in vivo physiological models, overly simplistic in vitro models, complexity of hormones, limited tissue yield, and uniqueness of the human reproductive tract. Identifying better models is important because sex differences exist in drug responses; 8 of 10 drugs pulled from the market produced adverse side effects among women. Most preclinical and clinical research has been conducted with men.

Organs on a Chip. About 10 years ago, NIH created a program with NCATS and the Defense Advanced Research Projects Agency to create a human on a chip, that is, to incorporate the major organ systems of the body in one unit. Investigators participating in the NIH Tissue Chip Consortium created various microphysiological systems of organs of interest and demonstrated physiological functions of the 3D organs, including Evatar, a microfluidic model of the female reproductive tract developed by Teresa Woodruff, Ph.D., of Northwestern University. For Evatar, Dr. Woodruff used a mouse ovary to mimic the human 28-day menstrual cycle, including ovulation, with the ovary producing estrogen and progestin. Evatar demonstrated that such modeling was possible—the tissues were familiar with each other and responded to hormonal secretions—but it was expensive and difficult to use. Therefore, investigators developed a less expensive and easier-to-use model, that is, a "plug and play" platform called LATTICE. This multiorgan in vitro system can study the dynamic interactions of up to eight unique organ cultures, located in wells, which can interact with each other for extended periods of time, currently 28 days. Liquid media support nutrient exchange and waste elimination and enable secreted factors to interact with different tissues via microscale channels. LATTICE is connected to a computer that controls the microfluidic actuation of the system to provide precise media flow from one well to another, enabling the study of interactions between two to four cell types.

LATTICE is a major advancement over current in vitro systems, which can only study two cell cultures simultaneously. It is designed to simulate what happens inside the body so that investigators can analyze, for example, how obesity affects a particular disease; how women metabolize drugs differently than men; or how the initial driver of a disease might eventually impacts multiple organs. Dr. Kim and her colleagues are modeling PCOS, a reproductive disease involving multiple organs, in LATTICE. The causes of PCOS remain unclear; investigators posit that a hyperandrogenic ovary is producing large amounts of testosterone or insuli. To date, Dr. Kim and her colleagues have created a hyperandrogenic ovary to examine what happens downstream when large amounts of testosterone are released.

The LATTICE platform enables researchers to increase complexity but control the parameters so that new scientific questions can be asked. The platform can also be used for drug testing—with multiple organs represented, the side effects of a new drug on different parts of the body can be studied. Drug testing on the Lattice platform enables translation to human health by testing new compounds in the context of sex hormones, mimicking the human body more effectively.

Challenges. Dr. Kim identified several challenges in research with human tissue, such as appropriate physiological cultures; number of cell types in organoids/spheroids; tissue availability tied to surgery schedules; coordinating tissues depending on availability; scalability; and real-time health monitoring. Challenges to commercialization include identifying and documenting demand for the product, enhancing the products usability (simple, inexpensive, plug and play), and finding commercial partners and funders. Dr. Kim concluded by recognizing the substantial market for research and drug testing in women's health, including menopause ($17 billion market), fertility treatment ($23 billion market size), uterine fibroids ($34 billion impact), and endometriosis ($78 billion impact).

Engineering Human Pregnancy in Vitro and in Silico

Dr. Oyen presented on in silico and computational approaches to studying women's reproductive health. She explained that she started her career as an engineer working in orthopedics, a field with mechanical components. One day, she received a call from an obstetrician/gynecologist asking whether she could measure forces, for example, on the uterus. As a result, she completed her Ph.D. examining fetal membranes and discovering numerous opportunities in women's health. Today, she focuses her work on pregnancy and women's health.

Preterm Birth as an Engineering Challenge. Preterm births comprise 10% of all births. Many of the issues associated with preterm births have a mechanical component, including maternal factors (e.g., trauma, uterine rupture, eclampsia/pre-eclampsia, cervical shortening, and dilatation), fetal factors (e.g., polyhydramnios, multiple fetuses), and placental factors (e.g., placental abruption, preterm premature rupture of membranes). Dr. Oyen's primary interests are in the placental factors.

The traditional route to obtain FDA approval for novel drugs and devices is from in vitro testing to preclinical animal studies to clinical trials. In the bipartisan FDA Modernization Act (December 2022), nonclinical tests, including computational modeling, were added to the traditional approval pathway. Today, engineers are using computational models, including machine learning, to transform maternal health. With in silico approaches, engineers strive to build patient-specific computational models based on ultrasound images for real-time clinical decision-making. One approach involves building a digital twin of a human patient, testing different scenarios on the twin, and then modeling clinical strategies for the human patient. For example, the rate of cesarean sections (C-sections) is well over 30% among 100 live births in developed countries, despite no improvement in maternal or fetal mortality recorded above a 19% C-section rate. Defects in C-section scars increase the risk of negative outcomes in future pregnancies, because of an increased risk of scar rupture and implantation at the scar site, leading to ectopic pregnancy or placenta accreta. Dr. Oyen and her Columbia University colleagues have run computational simulations based on ultrasound measurements of C-section scar defects to determine risks of uterine rupture and premature birth in individual patients. Currently, Dr. Oyen's team is working with researchers at University College London, who have collected measurements of C-section scars and defects and related patient outcomes. Dr. Oyen's team is using these data to classify risks, examining how a scar behaves throughout the pregnancy, and comparing images at each trimester in individual patient simulations.

Challenges. Dr. Oyen identified the following challenges occurring at the intersection of pregnancy and engineering: (1) interdisciplinary collaboration is less common in OB/GYN than in other fields; (2) the field needs training image sets for artificial intelligence/machine learning (AI/ML); (3) researchers need an approach to ethically harness the big data "natural experiments" in women's health; (4) human cell sources and consistent biomimetic tissue scaffolds for in vitro studies are needed; and (5) the field needs advances in mechanistic understanding to help shift the benefits of diagnostic advances to better intervention and prevention.

New Insights into Gynecologic Health Through Molecular Uterine Profiling

Ms. Tariyal described NextGen Jane, a menstrual data diagnostic platform. Underlying NextGen Jane is the core thesis that the uterus is a sensitive and responsive organ, especially attuned to changes in its hormone profile. Any hormonal change, no matter how small, should demonstrate biological relevance if it is modeled at a granular level. Shed endometrium (menstrual blood) can be easily accessed to molecularly characterize uterine response. Different hormone contexts will produce different uterine responses. A standardized menstrual data platform will enable uterine profiling at scale. Ms. Tariyal's company received $8 million from NIH to determine whether there is a predictably altered uterine response to endometriosis. In its approach, the company obtained menstrual effluence from used tampons from women with endometriosis and those without it, sampled the effluence over time, subjected it to total RNA bulk sequencing to identify pathogens, and interpreted the results in an RNA abundance interpretation engine. NextGen Jane produced an "EndoScore" that predicts the likelihood of endometriosis.

Studying a complex condition such as endometriosis, however, will require interdisciplinary teams working together. Patients present with self-reported, subjective, common symptoms. Clinical interpretation can also be ambiguous and depends on the specialty and experience of the physician the patient encounters. Although the fundamental understanding of endometriosis has been based on anatomical features (i.e., presence of an endometrioma, superficial lesions, deep infiltrating tissue), Ms. Tariyal proposes that molecular classifications would better inform and drive effective drug development.

Challenges. A major challenge in studying women's bodies is the 28-day cycle in which various hormonal levels fluctuate, providing significant background noise to experiments. There is a narrow window during the first three days of the cycle when woman's body are comparable to each other. In addition, the method for collecting menstrual effluence can pose challenges (i.e., tampon versus pad versus menstrual cup). Ms. Tariyal's company chose a specific tampon to reduce variability and built a system to ensure temperature control during storage and transit. It has since developed a process for easy at-home longitudinal sampling at room temperature, with tampons mailed to the company as late as two weeks after collection. Sample processing and data normalization are complicated and must account for degradation of samples, mucus-filled clotted tissue, and different tampon compositions. Bioinformatic strategies can normalize for these contributors to heterogeneity in the sample, enabling molecular labeling of what was previously subjective labeling (e.g., heavy flow day). Opportunities exist for pre-clinical impact, using patient-derived cells to test different concentrations of drugs to identify the mechanisms of action. There are also challenges in defining a case. Histopathological confirmation of endometriosis is needed for accuracy; if someone had endometriosis three years ago or had surgery but is experiencing a recurrence of symptoms, is she considered an endometriosis case? This patient population is complex, with many comorbidities that add noise to the studies. Similarly, defining a research control participant can also be difficult because of the scarcity of "true endo negatives," that is, women with subclinical endometriosis who do not experience symptoms. Finally, commercialization is

challenged by the diagnostic reimbursement process, lack of effective therapies, difficulties in obtaining funding through traditional private capital, questions about the appropriate call point, and historically greater regulatory burdens for novel sample types.

Adoption of this type of molecular testing will likely increase the cost of patient care. Nonetheless, this research is important because endometriosis affects quality of life for a large number of women. Ms. Tariyal's company is developing a noninvasive diagnostic that could be used to determine whether a therapeutic works.

Discussion: Dr. Platt asked the panelists about protective safeguards for the personal data included in their research. Ms. Tariyal and Dr. Oyen pointed to rigorous informed consent processes and careful data tracking to ensure anonymity. Dr. Platt noted that studying PCOS involves an "N of one." He asked Dr. Kim how her tools can help the patient and provider address this issue. Dr. Kim responded that PCOS has a genetic component; it is possible to obtain a stem cell from a patient with PCOS and transform it into the multiple organ cells needed to study in order to deliver a personalized treatment. Dr. Platt inquired about the type of medical education that would persuade clinicians to adopt this approach. Dr. Kim responded that credible data on outcomes would help to convince clinicians that the technology she described is safe and effective. Dr. Platt asked Dr. Oyen how clinicians would use her engineering analysis. Dr. Oyen responded that her analyses can help determine whether vaginal birth is possible after a C-section. Her goal is to reduce the rate of C-sections in the United States, especially early C-sections that result in preterm births. Dr. Platt asked Dr. Kim and Ms. Tariyal whether commercialization would be easier if their products applied to men. They agreed, noting that having more women investors would be helpful. Questions from ACRWH members addressed the following points:

- Women have many comorbidities, and studying two conditions simultaneously is challenging.
- Women's health issues such as PCOS and endometriosis fall along a spectrum of severity. Development of tools to determine the location of the patient on the spectrum or the specific type of disease is about five years in the future. Among the challenges to building these tools are that existing technologies are not being applied to women's health and that data are not being viewed through an interdisciplinary lens.
- Dissemination of new tools and products requires clinician education and low-cost versions of tools, for example, inexpensive probes for ultrasound imaging at home.
- All students should be provided with information about these tools in the earliest stages of their training.

Transforming Women's Health Through Engineering

Dr. Clayton introduced Susan S. Margulies, Ph.D., Assistant Director of the Directorate for Engineering, U.S. National Science Foundation (NSF). Dr. Margulies's presentation focused on funding deserts and funding collaborations that benefit NSF and NIH. NSF funds all engineering and science topics at the fundamental level to early translation. To accelerate translation from fundamental research to practice, NSF-funded investigators need to find another funding sources to support the next phase of their research. Although NSF is disease agnostic and much of NIH is disease specific, a significant overlap of goals exists where the two agencies can collaborate, including enhancement of the bioengineering workforce.

About NSF. NSF is a $9.06 billion (FY24) independent federal agency created by Congress in 1950 to promote the progress of science, to advance the national health, prosperity, and welfare, and to secure the national defense. Greater than 90% of its funding is dedicated to research, education, and related activities. Each year, NSF's priorities for investment in research and education are guided by the Office

of Science and Technology Policy and the Office of Management and Budget. White House research and development priorities for FY25 include (1) advancing trustworthy AI technology that protects people's rights and safety, and harnessing it to accelerate the nation's progress; (2) leading the world in maintaining global security and stability in the face of immense geopolitical changes and evolving risks; (3) meeting the global climate crisis by reimagining our infrastructures, renewing our relationship with nature, and securing environmental justice; (4) achieving better health outcomes for every person; (5) reducing barriers and inequities; (6) bolstering the research and development and industrial innovation that will build the nation's future economic competitiveness; and (7) strengthening, advancing, and using America's unparalleled research to achieve the nation's great aspirations.

NSF Engineering Goals and Priorities. The mission of NSF's Engineering Directorate is to transform our world for a better tomorrow by driving discovery, inspiring innovation, enriching education, and accelerating access. The directorate's strategic plan will help the nation make significant advances in the following priority areas by 2030: clean energy technology and integrated power systems; climate change adaptation and mitigation; bioeconomy and biomanufacturing; and next-gen microelectronics and wireless. It's four research cross-cutting themes are (1) broadening participation in engineering; (2) equity, justice, and access; (3) sustainable and resilient solutions; (4) pathways to partners for translation.

NSF's Transformational Engineering Impact in Medicine. NSF investments in science have led to the development of messenger RNA vaccines, tissue engineering, magnetic resonance imaging, and digital twin modeling, among other innovations. In biotechnology, NSF investments in molecular biology have led to polymerase chain reaction and Covid-19 tests; tissue engineering to artificial skin; and synthetic biology to precision genome editing and clustered regularly interspaced short palindromic repeats (CRISPR).

Women's Health Research. NSF's investment in women's health is modest, amounting to $17.2 million in FY24. NSF is prioritizing and increasing investments in women's health research by fostering innovation and discovery in women's health; expanding and leveraging data collection and analysis related to women's health; strengthening coordination, infrastructure, and training to support women's health research; and improving women's health across the lifespan. The NSF Engineering Research Visioning Alliance (ERVA) identifies and catalyzes engineering research horizons and priorities for the nation, with stakeholder input from academia, industry societies, investors, government agencies, and the public. In June 2024, ERVA held a visioning event on "Transforming Women's Health Outcomes through Engineering." The conference addressed women's health across the lifespan. Technology areas included AI/imaging, computer modeling, diagnostic technologies and devices, tissue engineering, and microfluidics. The conference report will be available by the end of October 2024. Dr. Margulies noted two other NSF-funded conferences on women's health held in August and September 2024, respectively: (1) "ElevateHER: Engineering Solutions for Women's Health," which was organized by Texas A&M University and the University of Maryland and addressed biomaterials and tissue engineering; biomechanics and mechanobiology; devices, sensors, and photonics; and immuno-engineering and (2) "Using AI to Better Understand Menopause," a collaboration between Columbia University and the University of Colorado that considered state-of-the-art computational approaches and intelligent interactive systems.

In March 2024, NSF announced a funding opportunity (NSF 24-068) for science and engineering on topics of relevance to women's mental and physical health, from the molecular to the ecosystem level, including mechanisms, detection, diagnostics, monitoring, and management of health/disease across all phases of life. Other areas include intersection of gender and other identities; genetic, epigenetic,

biological, economic, societal and environmental determinants; rehabilitation and support technologies; multi-scale models; and research on individuals, populations, generations, and geography.

NSF has large investments in Engineering Research Centers (ERCs) and Industry-University Cooperative Research Centers (IUCRCs), which address priorities that have potential in women's health. ERCs include Advanced Technologies for Preservation of Biological Systems, Cellular Metamaterials, Precise Advanced Technologies and Health Systems for Underserved Populations, and Precision Microbiome Engineering. PIs at IUCRCs must recruit industry partners who contribute $75,000 toward funding pilot projects that lead to full funding. IUCRCs include a Building Reliable Advances and Innovation in Neurotechnology (BRAIN) Center, Center for Data-Driven Drug Development and Treatment Assessment (DATA), Center for Disruptive Musculoskeletal Innovations (CDMI), and Center to Stream Healthcare in Place (C2SHIP).

Smart Health is a long-standing, multidisciplinary collaboration between NSF and NIH to accelerate innovative research that bridges the gap between technological and biomedical research. It uses novel methods to intuitively and intelligently collect, sense, connect, analyze, and interpret data from individuals, devices, and systems to enable discovery and optimize health. NSF 23-614 proposals are due on October 3, 2025.

Most NSF funding is allocated for unsolicited projects. Dr. Margulies highlighted three projects in women's health funded by NSF. The Leading Engineering for America's Prosperity, Health, and Infrastructure (LEAP-HI) Coordinated Advances in Reproductive Engineering for Health Research (CARE4HeR) project, led by researchers at the Virginia Polytechnic Institute and State University, aims to address health care challenges associated with pregnancy and childbirth by integrating novel and transformative approaches in experimental, theoretical, and computational mechanics. State-of-the-art experimental methods are being employed to characterize the mechanical interplay of the uterus, cervix, and vagina, both in vivo and ex vivo, in the murine model. Tissue Engineered Muscle in Microgravity as a Novel Platform to Study Sarcopenia, led by researchers at the Palo Alto Veterans Institute for Research, aims to develop and validate a tissue-engineering model of sarcopenia that can be used to study the progression of muscle deterioration and serve as a useful platform for testing potential treatments in a short time period. Finally, Muyinatu A. Lediju Bell, an investigator at Johns Hopkins University, is enhancing biomedical imaging systems to improve accuracy in imaging skin of all colors, an area where traditional ultrasound imaging fails.

NSF also supports education and workforce development, including grants to enhance engineering curricula and the development of undergraduate research opportunities. A partnership between NSF and the Lemelson Foundation supports innovation in the curriculum, including sustainability and resilience, which can infuse enthusiasm for women's health early in the training process.

Next Steps. NSF's goal is to catalyze purposeful partnerships between NSF and NIH in women's health. NSF analyzed all publications from 2010 to the present (21,710 publications) that acknowledged both the Engineering Directorate and NIH as funders. Overall, collaborations between NIH and the directorate have nearly doubled over the past 10 years with NIGMS, NIBIB, NCI, and NHLBI most often represented in these studies.

Dr. Margulies identified three avenues for NSF and NIH to collaborate to synergize research, especially in women's health. The NSF-NIBIB funding opportunity "Biomedical Research Initiative for Next-Gen BioTechnologies - SynBio Control" (BRING SynBio; NSF 24-603) is designed to advance synthetic and engineering biology research and translation of findings into early-stage biomedical technologies and allows investigators to submit a single proposal to both agencies for two phases of research. These

proposals are due on December 4, 2024. The planned NSF–NIBIB Industry-University Cooperative Research Center on Biomedical Imaging will develop, test, validate, and disseminate novel, dynamic, and tissue-mimicking optical imaging phantoms. Finally, research on the environment and human health will provide data on women's health in the face of disasters.

Discussion: In response to a question from Dr. Clayton about the barriers to NSF and NIH collaboration, Dr. Margulies explained that collaborative mechanisms are needed at the NIH IC Director level and that she and Dr. Tromberg have discussed this barrier. Dr. Clayton will follow up with Dr. Margulies with information about which ICs most support women's health research.

Update on NASEM Report: *Advancing Research on Chronic Conditions in Women*

Dr. Clayton introduced Eva J. Higginbotham, M.D., S.M., M.L., former Vice Dean of Inclusion, Diversity, and Equity at the University of Pennsylvania, Senior Fellow at the Leonard David Institute of Health Economics, Professor of Ophthalmology at the Schele Eye Institute, Perelman School of Medicine, University of Pennsylvania, and Chair of NASEM's ad hoc Committee on a Framework for the Consideration of Chronic Debilitating Conditions in Women. Dr. Higginbotham thanked ORWH for its sponsorship of the Committee and recognized Committee members, including ACRWH member Arthur Arnold, Ph.D.

Dr. Higginbotham reviewed the charge to the Committee: (1) describe current evidence and gaps in the science on chronic conditions in women; (2) assemble evidence-based findings on chronic debilitating conditions in women, including the influence of social determinants of health; and (3) produce a report that describes current gaps. Based on ORWH's framework that includes more than 40 conditions and Committee member expertise, the Committee selected conditions to review that are illustrative of female-specific and gynecologic conditions and that predominantly impact or affect women differently. The former category includes endometriosis/dysmenorrhea/chronic pelvic pain, uterine fibroids, infertility, vulvodynia, pelvic floor disorders (including urinary incontinence and pelvic organ prolapse), and menopausal symptoms (including exogenous hormone use). The latter category includes autoimmune diseases (systemic lupus and multiple sclerosis), musculoskeletal (osteoporosis, sarcopenia), neurocognitive (Alzheimer's Disease), pain disorders, cardiometabolic disease, mental health conditions, and infectious diseases.

Conceptual Framework. The Committee's conceptual framework addresses three major categories: Female-specific and Gynecologic Conditions That Lead to Significant Morbidity; Chronic Conditions That Predominantly Impact or Affect Women Differently; and Accumulation of Multiple Chronic Conditions. The Committee examined various research areas, including impact/burden, pathophysiology, prevention, diagnosis, and treatment/management. The Committee considered all stages of the translational research spectrum, from basic science to population health research, and how findings may translate into interventions within the health care system. The framework also highlights the life course and the influence of structural and social determinants of health related to sex and gender. In addition, the Committee identified essential factors necessary for understanding chronic conditions in women throughout their lives, including stages across the life course and how sex, gender, biology, social, and environment factors affect the manifestation and trajectory of chronic conditions. Finally, factors specific to aspects of the health care system, such as access to care, are noted.

Definitions. The Committee adapted the HHS definition of chronic conditions in women: "conditions that last one year or more and require ongoing medical attention or limit self-care, independent living, social interactions, or quality of life." The Committee chose to remove the word "debilitating," because

it may negate the experiences of women who live with chronic conditions and have developed coping mechanisms that help them function more fully. The Committee defined "woman" as any individual who considers themselves to be a woman or was assigned female sex at birth and noted that biological differences are generally classified as sex differences, whereas those associated with the social environment are considered gender differences. The Committee stressed the importance of distinguishing between social and structural determinants of health. Structural determinants are the "macrolevel factors, such as laws, policies, and social norms that shape the distribution of social determinants of health across and within social groups." The Committee explicitly identifies such factors as sexism, homophobia/heterosexism, racism, and ageism. Social determinants are the conditions in which people are born, grow, work, play, worship, live, and age and the wide forces and systems shaping these conditions.

Conclusions and Recommendations. The Committee identified 10 overarching conclusions and 18 recommendations. The Committee called on NIH and others to support research on chronic conditions in women and noted that the recommendations comprise a research agenda. The Committee identified key research gaps that NIH and other relevant funding agencies should support to advance the understanding of chronic conditions in women: (1) the impact of chronic conditions on women, (2) understanding the biology and pathophysiology of chronic conditions in women, (3) female-specific factors in the development of chronic conditions, (4) health outcome differences and life experiences, (5) diagnosis and treatment, (6) multiple chronic conditions, and (7) inequities and women-centered research. The categories of recommendations are summarized briefly below; the text of the Recommendations and additional details may be found in the Report.

Recommendation 1: The Impact of Chronic Conditions on Women
Chronic conditions continue to have a significant impact in women. Limited data hinders understanding and underreporting promotes inaccurate findings.

Recommendation 2: The Biology & Pathophysiology of Chronic Conditions in Women
Some progress has been made in understanding pathophysiology and biologic mechanisms, but further progress is needed.

Recommendation 3: Female-Specific Factors and Chronic Conditions
Reproductive milestones that impose dramatic changes in a woman's body and functioning can influence the risk of developing certain chronic conditions across the life course.

Recommendations 4–6: Disparities & Life Experiences
Structural and social determinants of health influence the development, progression, and management of chronic conditions in women.

Recommendation 7: Diagnosis and Treatment in Women
Women tend to develop multiple chronic conditions across the life course. Standardized definitions and diagnostic approaches are lacking for multiple chronic conditions.

Recommendation 8: Multiple Chronic Conditions
Women tend to develop multiple chronic conditions across the life course. Standardized definitions and diagnostic approaches are lacking for multiple chronic conditions.

Recommendation 9: Inequities & Women-Centered Research

A health equity lens is important for improving health care access, care, and outcomes, including patient-centered outcomes in women.

Recommendation 10: Inequities and Women-Centered Research
Women-centric research strategies can help ensure that research activities address the unique health needs of women leading to more effective and equitable health outcomes.

Summary. The Committee's research agenda, as outlined in its recommendations, aims to bridge gaps in the scientific understanding of the etiology of chronic conditions over the life course and the interface of biological and social factors that influence their trajectory. Ultimately, research outcomes would lead to greater diagnostic rigor, better data on the impact of these conditions, and more effective therapeutic interventions and woman-centered care.

Discussion. Dr. Clayton acknowledged Dr. Temkin, who served as ORWH's lead for the report. She moderated a discussion in which the following points were raised:

- Chapters 8–9 in the report discuss the challenges posed by multiple conditions and clinical translation. Learning health systems and interdisciplinary engagement are two potential strategies for improving the management of multiple conditions. Improved billing systems are also needed; for example, Medicaid's shift to value-based care reimburses providers for their outcomes.
- Prioritization of which conditions to study (e.g., prevalence, impact on the woman, mortality) starts with basic science, where identification of biomarkers could aid prevention and diagnosis. The current report is a follow-up to a 2001 ORWH workshop report. Since 2001, scientists have developed a greater understanding of sex differences and diseases that predominantly affect women at the basic biological level, such as new sex-related factors that are not yet understood in animal research. For example, there are reports of a new concept of a molecule on the X chromosome that is thought to balance male and female attributes, although it has specific effects in women.
- Clinical practice guidelines should be constantly tested and reevaluated as more is learned about the pathophysiology of these chronic diseases. Improvement will come from standardizing treatment and facilitating transdisciplinary work to provide more patient-centered care. Although basic science and clinical practice are the two pillars of clinical guidelines, Dr. Higginbotham is pinning her hopes for the future more fully in the basic science realm.

Concept Clearance: Funding Opportunity to Support Research on Chronic Female-Specific and Gynecologic Conditions

Dr. Ota Wang introduced Dr. Temkin, who presented the concept for a new funding opportunity to support research on female-specific conditions. The funding opportunity will invite research projects that improve prevention, diagnosis, early detection, and treatment interventions for female-specific and gynecologic chronic conditions. The anticipated award project period is five years; funding and number of awards is contingent upon NIH appropriations for meritorious awards.

Background. ORWH held the "Advancing NIH Research on the Health of Women: A 2021 Conference" on October 20, 2021, to evaluate research and identify priorities to advance the study of women's health in response to congressional concern about rising rates of debilitating chronic conditions in women. As part of this activity, ORWH staff categorized chronic conditions into those that are female specific; those that are more common in women or carry higher morbidity for women; those that occur in both sexes but may be understudied in women; and those with higher mortality for women. For each category, staff compared FY20 spending on the condition with disability-adjusted life years (DALYs) for

women in 2019. They found that the proportion of spending was not well aligned with the burden of disease among women. In 2023, Dr. Temkin and colleagues published a paper in *BMC Women's Health* that made the following key points: (1) multiple opportunities exist to align the NIH research agenda with the health needs of women; (2) integration of sex as a biological variable across the life course, including during key hormonal transitions, is critical; and (3) it is important to understand how social determinants of health influence the health of women differently.

Another key output of the 2021 Conference was the creation of the NASEM study described above. Addressing female-specific and gynecologic conditions, it is known that (1) female-specific and gynecologic conditions cause significant morbidity; (2) patients are often reluctant to discuss symptoms related to the female reproductive tract; (3) delays to diagnosis are common; (4) differences in health outcomes are significant; and (5) the contribution to multimorbidity is rarely measured. A second output of the 2021 Conference were RFAs on Understanding Chronic Conditions Understudied among Women (RFA-OD-23-013 and RFA-OD-23-014 for R21 and R01 grants, respectively). Dr. Temkin announced that in FY24 ORWH funded 21 awards through these mechanisms in collaboration with NICHD, NHLBI, NIA, NCI, NIAMS, and NIDDK. These awards cover a range of conditions, including menstruation, menstrual bleeding, vaginal toxicity, PCOS, endometriosis, adenomyosis, cervical dysplasia, and pubovisceral muscle enthesis injury.

NIH spending on women's health was approximately $4.6 billion in FY23, or about 10% of total NIH spending. Research on female-specific conditions represents about 12% of that 10%, or about 1% of total spending. Ovarian and cervical cancers were the two women's health conditions that received the most funding.

Dr. Temkin summarized the concept noting that female-specific conditions are highly prevalent, understudied, cross multiple IC priorities, reflect significant health-related disparities, have unknown interactions with other chronic conditions, and provide an opportunity for NIH-wide collaboration.

Discussion. Drs. Sharps and Mielenz were discussants for the concept. Dr. Sharps commented that the research is highly relevant and timely. Women are living longer, and scientists do not yet understand the mechanisms of naturally occurring transitions during the aging process or the long-term effects of female-specific conditions on aging women. Further, vulnerable populations of women experience heavier burdens for these diseases because of biological and environmental factors. The impact of these conditions on women's quality of life is also important to examine. Thus, both qualitative and quantitative research designs are needed. The research also provides an opportunity for clinician education to improve women's experiences in health care settings. Dr. Mielenz inquired whether someone with a female-specific condition and low back pain would be eligible for the proposed research. Dr. Temkin responded that the rationale for focusing only on female-specific conditions is that they have historically been understudied, despite emerging new opportunities at NIH. Other discussion points in response to ACRWH member questions included the following:

- "Female-specific" does not include pregnancy alone because the criteria for chronic conditions specify that a condition lasts for more than one year. However, research on pregnancy's impact on the long-term condition of cardiovascular disease would meet the criteria.
- Applications can address multiple comorbidities, for example, the interaction of endometriosis and autoimmune disease.
- The concept should include clinical research.

Vote. The concept for the "Advancing Our Understanding of Female-Specific and Gynecologic Chronic Conditions" was approved with 11 votes in favor, 0 rejections, and 0 abstentions.

Concept Clearance: NIH Exceptional Research Scientist Award

Xenia Tigno, Ph.D., Associate Director for Careers, ORWH, introduced Carolyn J. Bondar, Ph.D., Program Officer in the Careers Section, ORWH, who presented the concept for a new NIH Exceptional Research Scientist Award. Its objective/purpose is to encourage development of stable research career opportunities for exceptional nontenured scientists positioned to make outstanding contributions to NIH-funded biomedical, clinical, behavioral, or social science research programs over a five-year award period. Available funding and anticipated number of awards are contingent upon NIH appropriations.

Team science has demonstrated its value in increasing impact and innovation and improving productivity. However, the increasing reliance on team science has highlighted the importance of nontenured researchers with extensive experience to provide continuity, stability, and detailed scientific knowledge. Support for nontenured, nontraditional PI roles is needed to attract and retain exceptional research scientists. Women are overrepresented in the nontenured professional research workforce.

Background. Strategic Goal 3 in the *2024–2028 NIH-wide Strategic Plan for Research on the Health of Women* calls for fostering women scientists' career development and promoting scientific workforce training and education that advances the health of women and the science of sex and gender influences. Specifically, Objective 3 addresses support and development of programs to recruit, support, retain, facilitate re-entry of, and advance women at all stages of their research careers, from early career to leadership positions, especially mid-career scientists. Recommendation 3.1 of the *NIH Advisory Committee to the Director Working Group on Re-envisioning NIH-supported Postdoctoral Training* report calls for increased support for a research professional career track that would improve the sustainability and health of the biomedical system by expanding the academic job pool, retaining talented scientists in academic research, maintaining institutional knowledge, providing mentorship and training, and building research enterprises and capacity.

Purposes. The purposes of this concept are to (1) improve the sustainability and health of the biomedical system by supporting research scientists, such as lab scientists, core scientists, and clinician scientists; (2) enhance the professional standing and recognition of exceptional research scientists; and (3) provide autonomy, career development opportunities, and career continuity by supporting salary, travel funds, and protected time.

Application Requirements. This concept does not propose new research. Instead, the following requirements must be met: (1) the application must specify research programs, collaborations, role, and importance of the applicant's participation in advancing NIH-funded research programs; (2) applicants must demonstrate relevant scientific skills, expertise, and success via relevant publications, conference proceedings, and/or awards; (3) applicants must be a full-time nontenured research scientist/nontraditional PI; and (4) the application must include a career development plan with an institutional letter of commitment and supporting letters of recommendation to demonstrate leadership and collegiality.

Other Programs Supporting Research Professionals. Created in 2016, NCI's Research Specialist Award provides salary and travel support for laboratory scientists, core scientists, and clinician scientists. More than 150 awards have been made with a 19% award rate, similar to an R01. The NIH Research Software Engineer Award, launched in 2024 by the Office of Data Science Strategy, provides salary and travel support for Research Software Engineers.

Discussion. Drs. Aninye and Templeton served as discussants for this concept. Dr. Aninye commented that this concept provides an excellent opportunity for nontenured scientists to build their careers. She asked whether scientists outside academia were eligible to apply. Dr. Bondar responded that the concept should target individuals from institutions beyond large universities. Dr. Templeton agreed the concept was extremely important, noting that women are less likely than men to receive tenure. She asked whether a way exists to enforce protected time because women are often burdened by service expectations and suggested that a mentor might help to address this issue. Dr. Bondar replied that ORWH will consider that point. Additional discussion points included the following:

- The concept is not limited to women
- No data from other NIH programs are available to document women's application success rates.
- The award will be renewable.
- At present, the percentage of time to be covered by the award is not specified.
- The institutional letter of support should demonstrate that the institution will support the applicant's career development plan.
- The applicant's career development plan may include becoming a tenure-track scientist.
- The concept is open to researchers at all levels of experience.
- Applicants may propose a new area of research to pursue, which will be reviewed and considered.

Vote. The concept of an "NIH Exceptional Research Scientist Award" was approved with 11 votes in favor, no rejections, and 0 abstentions.

Open Discussion

Dr. Ota Wang moderated an open discussion in which the following comments were made:

- The broader scope of a chronic conditions concept should be more expansive and should not be narrowed to female-specific conditions for addressing women's health in the long term. Maintaining an inclusive and broad approach to eligible chronic conditions beyond female-specific conditions is important.
- Disaggregation of results by sex in preclinical studies is currently governed by NIH's SABV policy. The policy's provisions could be strengthened by requiring that sex differences be addressed in a study's Data Management and Sharing Plan.

Closing Statement

The next meeting will be on April 8, 2025. Dr. Clayton adjourned the meeting at 4:18 p.m.

Certification

We certify that the contents above are accurate and complete.

Janine A. Clayton -S Digitally signed by Janine A. Clayton -S Date: 2025.06.16 13:05:52 -04'00'

Janine Austin Clayton, M.D., Director
Office of Research on Women's Health

Date _____

VIVIAN OTA WANG -S Digitally signed by VIVIAN OTA WANG -S Date: 2025.06.16 11:43:58 -04'00'

Vivian Ota Wang, Ph.D., Executive Secretary
Advisory Committee on Research on Women's Health

Date June 16, 2025