60th 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 April 9, 2024

Members Present
Garnet L. Anderson, Ph.D.
Irene Aninye, Ph.D.
Stephen Higgins, Ph.D.
Reshma Jagsi, M.D., D.Phil.
Hendrée Jones, Ph.D.
Thelma Mielenz, Ph.D.
Alexandra Noël, Ph.D.
Yoel Sadovsky, M.D.
Phyllis Sharps, Ph.D. *(virtual)*
Melissa Simon, M.D.
Kimberly J. Templeton, M.D. *(virtual)*

ORWH Leadership Present
Janine A. Clayton, M.D., FARVO, Director
Vivian Ota Wang, Ph.D., FACMG, CGC, Deputy Director
Victoria Shanmugam, MBBS, MRCP, FACR, CCD, Director, NIH Office of Autoimmune Disease Research (OADR-ORWH)
Elizabeth Barr, Ph.D., Associate Director for Interdisciplinary Research
Chyren Hunter, Ph.D., Associate Director for Basic and Translational Research
Samia Noursi, Ph.D., Associate Director for Science Policy, Planning, and Analysis
Xenia Tigno, Ph.D., Associate Director for Careers

Other NIH Leadership Present
Monica M. Bertagnolli, M.D., NIH Director
Lindsey A. Criswell, M.D., M.P.H., D.Sc., Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Tara Schwetz, Ph.D., NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives and the Director of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
Alison Cernich, Ph.D., Deputy Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Other U.S. Government Guests
Carolyn Mazure, Ph.D., Chair, White House Initiative on Women's Health Research

Call to Order

Vivian Ota Wang, Ph.D., FACMG, CGC, ACRWH Executive Secretary and ORWH Deputy Director, called the hybrid meeting to order at 9:32 a.m. Committee members introduced themselves. Dr. Ota Wang acknowledged retiring members Reshma Jagsi, M.D., D.Phil.; Yoel Sadovsky, M.D.; and Kimberly Templeton, M.D., for their service. She also welcomed pending new members Ayush Giri, Ph.D.; Aza Nedhari, M.S.; Ighovwerha Ofotokun, M.D.; and Fatima Stanford, M.D. ACRWH members unanimously approved the minutes of the 59th ACRWH meeting on October 18, 2023.

Dr. Ota Wang requested comments on the draft *NIH-Wide Strategic Plan for Research on the Health of Women, 2024–2028*. ACRWH members suggested adding (1) musculoskeletal health (e.g., osteoporosis) as an important topic; (2) support for women in the late career stage, as they become invisible when they should be rising to leadership positions; (3) creation of common data elements, especially for career transitions, under Goal 2: Data Science and Management; and (4) adding Category 1 and/or Category 2 studies, in addition to pragmatic studies, under Goal 5: Community Engagement.

Vote: Dr. Ota Wang called for a vote to approve the draft *NIH-Wide Strategic Plan for Research on the Health of Women, 2024–2028,* as written. It was accepted with 10 votes in favor and 1 abstention.

ORWH Director's Report

Dr. Ota Wang introduced Janine A. Clayton, M.D., FARVO, Director, ORWH, who delivered the Director's report. Dr. Clayton recognized Lindsey A. Criswell, M.D., M.P.H., D.Sc., Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) who was in attendance.

Opening Remarks. Dr. Clayton stated that it was her pleasure to report to the ACRWH on ORWH's work in collaboration with NIH Institutes, Centers, and Offices (ICOs). Noting that ORWH is a data-driven organization, she reported on recently published data about women and alcohol. Women have been reported to experience a greater increase in alcohol use issues than men for more than 20 years. Before the COVID pandemic (2003–2018), alcohol-involved suicide significantly increased for all women 18 years and older, whereas a significant increase among men occurred only among those aged 35–64. During the pandemic, data from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) showed a reduction in the average number of drinks per day for men and a stable pattern of consumption for women. Data from the U.S. Centers for Disease Control and Prevention (CDC) also revealed that deaths due to excessive alcohol use increased among women by 34.7% between 2016–2021, compared to 26.8% among men. These differences illustrate the importance to disaggregate the data analysis by sex/gender to identify sex differences and enable appropriate targeting of intervention strategies.

ORWH and NIH Update. Dr. Clayton welcomed two new members of the ORWH senior leadership team: Victoria Shanmugam, MBBS, MRCP, FACR, CCD, the new Director of the NIH Office of Autoimmune Disease Research (OADR-ORWH) and Elizabeth Barr, Ph.D., Associate Director of the Interdisciplinary Research Section. She also announced the following new NIH leadership appointments: Tara Schwetz, Ph.D., NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives and the Director of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI); W. Kimryn Rathmell, M.D., Ph.D., Director, National Cancer Institute (NCI); Kathleen M. Neuzil, M.D., Director, Fogarty International Center (FIC) and Associate Director for International Research; Shelli Avenevoli, Ph.D., Acting Director, National Institute of Mental Health (NIMH); Diana Finzi, Ph.D., Acting Associate Director, Office of AIDS Research (OAR) ; Stefan M. Pasiakos, Ph.D., FACSM, Director, Office of Dietary Supplements (ODS); Andrew A. Bremer, M.D., Ph.D., M.A.S., F.A.A.P., Director, Office of Nutrition Research (ONR) ; and Lyric Jorgenson, Ph.D., Associate Director for Science Policy and Director of the Office of Science Policy. Dr. Clayton noted that the number of female NIH Institute/Center (IC) directors now stands at 13, in addition to the new NIH Director Dr. Monica Bertagnolli. Dr. Clayton was excited to report that Dr. Bertagnolli is focused on topics of high relevance to women's health. For example, she has highlighted sex differences about brain function and autoimmune diseases in two of her recent blogs.

Research, Condition, and Disease Categorization (RCDC). NIH is developing a women's health RCDC category that will enable tracking of menopause and other women's health research and reporting of expenditures on research to the public. Other new RCDC terms include Health Disparities and Racial or Ethnic Minority Research, Health Disparities Research, Racial and Ethnic Minority Health Research, Workforce Diversity and Outreach, and Building Research Capacity (at Resource Limited Institutions).

NIH Community Partnerships to Advance Society (ComPASS). Dr. Clayton co-chairs the NIH Common Fund ComPASS initiative that addresses minority health and health disparities using structural interventions. ComPASS aims to (1) develop, share, and evaluate Community-Led Health Equity Structural Interventions (CHESIs) that leverage partnerships across multiple sectors to reduce health disparities and (2) develop a new health equity research model for community-led, multisectoral structural intervention research across NIH and other federal agencies. ComPASS is funded at $200 million dollars for the first five years of its 10-year tenure. Dr. Clayton described three CHESIs to illustrate how the projects strive to achieve the ComPASS goals:

- **Partnership to Optimize Women's Equity in Infant and Maternal Health** by Delta Health Alliance, Inc. is researching ways to address Mississippi's birth and maternal health disparities by providing information and care for participants from pre-pregnancy to postpartum.
- **Humanitarian Health Care Network: Bringing the Most Vulnerable to Care** by Migrant Clinicians' Network, Inc. is testing ways to provide medical care for high-risk children and late-term pregnancy mothers on the Texas border using an interdisciplinary case management system.
- **Puerto Rico Collaborative Advancement of Research, Innovations, Best Practices and Equity for Children, Youth and Families (PR-CARIBE)** by Grupo Nexos, Inc. is enhancing mental health access and educational development at the organizational, community, and government/institutional levels to reduce health disparities.

Policy and Scientific Updates. On November 13, 2023, President Biden announced the first White House Initiative on Women's Health Research at a signing ceremony attended by Drs. Clayton and Bertagnolli. The announcement directed the (1) establishment of an Initiative consisting of executive departments and agencies across the federal government; (2) delivery of concrete recommendations to advance women's health research while addressing health disparities by Initiative members within 45 days; (3) adoption of a targeted, high-impact approach based on priority focus areas where additional investments could be transformative; and (4) participation of the scientific, private sector, and philanthropic communities via new public-private partnerships and engagement of private and philanthropic leaders to drive innovation in the advancement of research on women's health.

On March 18, 2024, President Biden issued an Executive Order on Advancing Women's Health Research and Innovation that will (1) prioritize investments in women's health research, (2) integrate women's health across the federal research portfolio, (3) galvanize new research on women's midlife health, (4) assess unmet needs to support women's health research, and (5) create a dedicated front door for NIH funding opportunities on women's health. Drs. Clayton and Bertagnolli and other NIH Directors and senior staff attended the signing ceremony of this landmark document.

In February 2024, the First Lady Jill Biden, Ed.D., visited the Morehouse School of Medicine to speak at a woman's heart healthy luncheon with former ACRWH member Valerie Montgomery Rice, M.D., FACOG, President and CEO of the Morehouse School of Medicine. On March 20, 2024, Dr. Clayton accompanied Dr. Biden when she visited the North Carolina Research Triangle to disseminate information about the new Executive Order. In her remarks, she called women's health a top priority for the Biden Administration, noting that "so many of us and so many of the women in our lives suffer from health conditions for which we simply don't have the answers or solutions." She announced that NIH will fund $200 million in Fiscal Year (FY) 2025 toward new women's interdisciplinary health research. Seventh Annual Vivian Pinn Symposium speaker Genevieve Neal-Perry, M.D., Ph.D., University of North Carolina at Chapel Hill, commented at the meeting that for many years there has been little funding for

understanding women's health conditions, such as menopause, and that she hopes this new infusion of funds will help change that trend.

Notice of Special Interest (NOSI) on Women's Health Research (NOT-OD-24-079). NIH is issuing a new NOSI to highlight interest in receiving research applications focused on diseases and health conditions that: (1) predominantly affect women; (2) present and progress differently in women; and/or (3) are female-specific. This is the first-ever NOSI in which every IC and multiple NIH Offices have pledged to participate. Linking to all NIH parent funding opportunities, the NOSI spans multiple funding mechanisms, topics, pathways and disciplines to enable investigators to apply for research funding that addresses every aspect of women's health.

Online Harassment. ORWH contributed a sex and gender perspective during a virtual NIH workshop on "Understanding and Addressing the Health Impacts of Online Abuse and Harassment" on December 23, 2023. Over half (54%) of girls aged 15–17 have experienced at least one of six cyberbullying behaviors.

Biennial Report. The newly released *Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2021–2023*, the Biennial Report, details NIH-wide programs and accomplishments that fulfilled ORWH's core mission. This report summarizes NIH-wide activities, for NIH ICs and ORWH for FY 2021–2022. The report addresses the inclusion of women and minorities in clinical research and careers and workforce demographics of NIH employees and grantees. New to this report are five cross-cutting integrative topics: (1) aging, (2) mental health and substance use (opioids/pain), (3) maternal morbidity and mortality (MMM), (4) social determinants of health, and (5) violence. These new topics enable NIH ICOs to provide information in multidisciplinary cross-cutting ways.

Innovation Equity Forum (IEF). The International Innovation Equity Forum (IEF) seeks to create an inclusive, globally focused, and widely accepted opportunity map to advance women's health research and development (R&D). A collaboration between NIH and the Bill and Melinda Gates Foundation led by ORWH on behalf of NIH, the Women's Health Opportunity Innovation Map 2023 describes 50 equitable, high-return opportunities to advance global innovation for women's health, prioritizing resources and efforts according to five criteria: potential for impact, readiness, innovation, importance to women, and equity. Under Research Design and Methodologies, the Map identifies four cross-cutting themes: (1) advance sex- and gender-intentional research and development and analysis in all research stages; (2) promote knowledge- and resource-sharing on preclinical and clinical research modeling landscapes in under-resourced settings; (3) strengthen use of computations and bioinformatics, machine learning, and deep learning approaches; and (4) support in vitro translational model development, such as organoids and organ-on-a-chip systems. The Opportunity Map marks the first step to gather stakeholders in the R&D ecosystem and coalesce around impactful investments and important steps and opportunities needed to improve women's health.

HIV and Women's Health*.* ORWH's signature program in HIV and Women's Health with OAR issued a Request for Information (RFI) on "Research Opportunities Related to HIV and Women's Health" (NOT-OD-24-011). Sixty-nine responses were accepted from October 16 to December 31, 2023, with almost half (43%) from community perspectives and the remainder from researchers. The information received is currently being analyzed.

A position paper outlining a framework for an intersectional, equity-informed, data-driven approach to research on HIV and women, highlighting the HIV and Women Signature Program at NIH, was published in *The Lancet* in February 2024.

A virtual "NIH HIV & Women Scientific Workshop: Centering the Health of Women in HIV Research" will be held on March 21–22, 2024, in collaboration with multiple ICOs, to (1) foster interdisciplinary, intersectional, community-centered knowledge exchange on topics of relevance to HIV and cisgender and transgender women, girls, and gender-diverse people; (2) review the state of the science in HIV and women; (3) highlight modifiable factors, interventions, methods, and challenges to advance health equity for women with, or affected by, HIV; and (4) identify opportunities to advance health research and foster interdisciplinary collaborations on HIV and women.

NIH Office of Autoimmune Disease Research (OADR-ORWH). In FY 2023, OADR-ORWH funded 41 applications from 12 ICOs; 15 extramural co-funding awards; three R56 Bridge funding awards; two Accelerating Medicines Partnership Autoimmune and Immune-Mediated Diseases awards; 10 intramural co-funding awards; five intramural scientific fellowships; and six Exposome in Autoimmune Disease Collaborating Teams Planning (EXACT-PLAN) awards. Upcoming OADR-ORWH events include an OADR-ORWH Science Talk (April 23, 2024) and Updates on OADR-ORWH Session 3 (May 3, 2024). An RFI, "Inviting Input on an NIH-wide Strategic Plan on Autoimmune Disease Research," was also issued; responses are being analyzed.

Dr. Clayton was excited to announce The EXposome in Autoimmune Disease Collaborating Teams PLANning Awards (EXACT-PLAN) (NOT-OD-23-112) developed in partnership with NIAMS and the National Institute of Environmental Health Sciences (NIEHS) along with ICO collaborators. EXACT-PLAN is focused on supporting the design, development, and implementation of a future national, interdisciplinary, collaborative, team science research network to advance the study of the exposome in autoimmune disease by developing a systems-level approach to understand the mechanisms underlying how exposures perturb cellular, organ, and tissue function across autoimmune diseases. The EXACT Network, comprised of six awardees in 2023, is a national research collaborative team that conducts research to discover the environmental exposures that influence disease susceptibility, onset, and outcomes.

New research on autoimmune diseases supported by NIH identified the role that Xist RNA protein complex plays in helping explain why more females suffer from autoimmune diseases. As reported in Cell, new research suggests that Xist molecules have a nefarious ability to encourage the formation of odd clumps of RNA, DNA, and proteins that can in turn trigger strong autoimmune responses.

National Academies of Sciences, Engineering, and Medicine (NASEM) Update. NASEM has several initiatives on women's health and careers. Dr. Clayton highlighted two efforts supported by ORWH: "Framework for the Consideration for Chronic Debilitating Conditions in Women" (anticipated release in summer 2024) and "Caregiving Report Public Release Launch: Policies and Practices for Supporting Family Caregivers Working in Science, Engineering, and Medicine" (launched April 11, 2024). In 2018, NASEM issued a report supported by ORWH on sexual harassment among women in science, engineering, and medicine; Dr. Clayton was a working group member that created this report. Subsequently, the National Institute of General Medical Sciences (NIGMS) issued a NOSI (NOT-OD-21-150) on "Interventions Designed to Change the Culture to Mitigate or Eliminate Sexual Harassment in the Biomedical Research Enterprise." ORWH funded two projects with NIGMS under this NOSI, including

- Indiana CARES (Creating Accountability and Building Relationships to Eradicate Sexual Harassment) at Indiana University-Purdue University at Indianapolis (Principal Investigator: Dr. Margaret S. Stockdale)
- Sexual Harassment Training of Principal investigators (STOP) at Stanford University (Principal Investigator: Dr. Arghavan Salles)

Finally, Dr. Clayton announced two new public NASEM meetings: the Committee on the Assessment of NIH Research on Women's Health (the fourth of four meetings on April 11-12, 2024) that will include presentations by Drs. Tara Schwetz and Carolyn Mazure. A "Workshop: Essential Health Care Services Related to Anxiety and Mood Disorders in Women" is being held on April 29-30, 2024.

Pathways to Prevention (P2P) Program. P2P provides a structured process to identify research gaps within a topic. In a recent P2P workshop, "Identifying Risks and Interventions to Optimize Postpartum Health," federal partners recommended improving maternal health through a "maternal morbidity and mortality prevention moonshot" featuring adopting a comprehensive, multilevel life course conceptual framework; strengthening maternal health research methods; establishing national prevention, treatment, and policy interventions; and reimbursing evidence-informed clinical approaches. Deliverables included an independent panel report titled *Maternal Mortality: A National Institutes of Health Pathways to Prevention Panel Report*, an independent panel summary, and systematic evidence review titled *An Evidence Map for Social and Structural Determinants for Maternal Morbidity and Mortality*. On April 2, 2024, the Federal Partners Report was issued to facilitate federal agencies' implementation of the recommendations.

Menopause. Dr. Clayton reported several activities related to menopause. First, menopause has been selected as one of the next P2P programs and will kick off with a workshop on the management of menopausal symptoms sponsored by the Office of Disease Prevention (ODP) in partnership with ORWH and NIH ICs. Second, the 2023 Vivian Pinn Symposium focused on "Menopause and Optimizing Midlife Health of Women." Third, on May 16, 2024, ORWH will host "Future Directions in Menopause Research: Optimizing Midlife Health of Women Roundtable" from 11 a.m.–1 p.m. EDT.

Specialized Centers of Research Excellence (SCORE). SCORE on Sex Differences (U54 Clinical Trial Optional) is an ORWH signature program. It is NIH's only center-level sex differences disease-agnostic funding opportunity. Currently, ORWH, in collaboration with 12 NIH IC co-funders, partners with 12 institutions addressing specific women's health topics. For example, the newest SCORE at the Augusta University, co-funded with the National Heart, Lung, and Blood Institute (NHLBI) establishes a Rural, Obese, At-Risk (ROAR) Collaborative Project spanning three universities, four Augusta University Colleges, and ten departments. Dr. Clayton noted that "the interdisciplinary approach represents the hallmark state of the SCORE program on sex differences with real power to address the health of women in very definitive ways that incorporate sex differences as well as the health of women."

Sex and Gender Updates. On November 30, 2023, ORWH hosted the NIH Sex and Gender in Health and Disease Scientific Interest Group program on "Sex as a Biological Variable (SABV) Policy and Sex-Inclusive Research: Making Progress, Taking Stock, and Visioning the Future." In collaboration with the NCI Divisions of Cancer Epidemiology and Genetics and Cancer Biology, ORWH offers a series of virtual workshops on sex and gender differences in cancer. The workshops will present the latest research

findings, identify gaps in knowledge, identify potential collaborative opportunities, and discuss best practices for methodology and reporting. The two remaining series workshops will occur on May 23, 2024 (clinical science) and on June 27, 2024 (population science).

In March 2023, the World Health Organization (WHO) announced the adoption of Sex and Gender Equity in Research (SAGER) guidelines and will begin publishing reports with findings disaggregated by sex and gender, as appropriate. Dr. Clayton served as a panelist at a WHO meeting launching the adoption.

Funding. Dr. Clayton reviewed ORWH's budget history, noting that the ORWH budget was essentially flat until Fiscal Year 2023 when Congress provided an additional $10 million to create the Office of Autoimmune Disease Research (OADR-ORWH). Of the total $77.6 million in the FY23 budget, $15.9 million is allocated for career programs. The largest single component of these career programs, comprising 88% of the careers budget, is ORWH's s Building Interdisciplinary Research Careers in Women's Health (BIRCWH) signature program. BIRCWH is co-funded by the *Eunice Kennedy Shriver* National Institute on Child Health and Development (NICHD) among other NIH ICs and contributes the largest amount of funding as a co-funder of ORWH's external grant programs. If BIRCWH is excluded, the leading co-funders of ORWH initiatives are National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of NICHD respectively. Most of the ICOs co-fund at least one ORWH external research program. ICO support of ORWH signature programs represents complementary efforts to existing ICO leadership and ICO led areas of research.

Careers*.* Dr. Clayton highlighted several ORWH initiatives to support women's career development, including the Team Science Leadership Scholar Program (LSP) in Women's Health, Autoimmune and Immune-Mediated Diseases, a collaboration with NIAMS and the NIH Office of Data Science Strategy, and a pilot program to support and train women's health scholars by helping them acquire and hone team science leadership and mentoring skills that will allow them to become large consortium team leaders. LSP is an initiative of the Accelerating Medicines Partnership in Autoimmune and Immune Diseases (AMP-AIM). In 2023, AMP AIM LSP announced its first cohort of awardees: Sheila Angeles-Han, M.D., M.S.; April Lynn Barnado, M.D., MSCI (former BIRCWH scholar); Monica Guma, M.D., Ph.D.; Sara McCoy, M.D., Ph.D.; Paula Sofia Ramos, M.D., M.Sc.; and Kelly Ruggles, Ph.D., M.S.

Toolkit to Enhance Faculty Gender Diversity. In 2021, ORWH supported a prize competition for enhancing faculty gender diversity and, in June 2022, 10 prize winners and six honorable mentions were announced. A toolkit has been developed to highlight successful strategies, best practices, and interventions submitted to the prize competition and to link these strategies and best practices with evidence of their output, outcomes, and impact. The toolkit is available on the ORWH website.

***Travel Scholarships*.** ORWH is sponsoring travel scholarships for junior and early-stage investigators to attend the annual meetings of the Organization for the Study of Sex Differences (OSSD) (one NIH ORWH Science Policy Scholar Travel Award) and the Menopause Society (two scholarships).

***American Dental Education Association (ADEA*).** ADEA sponsored its 7th International Women's Leadership Conference on March 12–13, 2024. Dr. Clayton reported on ORWH's leadership in women's health research at the meeting.

Upcoming Events. The Eighth Annual Vivian W. Pinn Symposium will be held virtually on May 15, 2024. This year's theme is "Synergy in Science: Innovations in Autoimmune Disease Research and Care" and will be part of a culmination of activities in observation of National Women's Health Week (NWHW). Publications to be released during NWHW 2024 include *NIH Fact Sheets on Women's Health Research*; the *NIH-Wide Strategic Plan for Research on the Health of Women, 2024–2028;* and *U3 Interdisciplinary Research: Bringing Women of Understudied, Underrepresented, and Underreported Populations Databook*.

NIH Inclusion Update

Dr. Juliane Caviston, ORWH, introduced Dawn Corbett, M.P.H., NIH Inclusion Policy Officer, Office of Extramural Research (OER). Ms. Corbett reviewed the following points of the NIH inclusion policies: (1) women and members of racial and ethnic minority groups must be included in all NIH-funded clinical research studies unless there is a compelling rationale for exclusion and (2) individuals of all ages must be included in NIH human subjects research unless there are scientific or ethical reasons not to do so. This policy requires submission of individual-level participant data in progress reports by sex or gender, race, ethnicity, and age at enrollment and annual reporting in the NIH Research, Condition, and Disease Categorization (RCDC) Inclusion Statistics Report.

The NIH Office of Extramural Research (OER) also develops resources related to inclusion. New resources include case studies on inclusion across the lifespan and guidelines on allowable costs related to participant inclusion activities. OER also has collaborated with the U.S. Food and Drug Administration (FDA) and the Clinical Trials Transformation Initiative (CTTI) to identify organizational strategies to support diversity in clinical trials using a maturity model.

Inclusion Data for FY23. More than 28,000 inclusion reports were received by NIH in FY23, including 16,500 studies with enrollment data. Most (14,772) were at U.S. sites. Female-only studies (1,821) outnumbered male-only studies (757) reported. Of 1,187 Phase 3 clinical trial inclusion reports, 792 included enrollment data, mostly in the U.S. There were 121 female-only clinical trials reported compared to 40 men-only trials. Total FY23 enrollment in clinical research studies was 12,258,841 participants with 9,247,082 (75.4%) being U.S. only. FY23 enrollment data in NIH-defined Phase 3 clinical trials was 832,222 (62.1%) U.S.-only participants compared to 315,417 (37.9%) non-U.S.-only participants. In FY23, 56.5% of clinical research participants were female, a pattern that has held steady since FY21. About two-thirds (66.3%) of Phase 3 clinical trial subjects were female in FY23, partly because there were more female-only studies.

Trends in enrollment by race have been fairly steady over the past three years. In FY23, the largest percentage of clinical trial participants were White (45.7%), followed by Black/African American (18.8%), and Asian American (11.3%), American Indian (2.8%), and Native Hawaiian (0.3%). The percentage for "unknown or not reported" was 18.4%. Over this time period, the percentages for White, American Indian, and "unknown or not report" increased, while the percentage for Native Hawaiians decreased. Racial/ethnic enrollment patterns in clinical trials are more variable over time because of the smaller number of studies. The enrollment of Hispanic participants increased slightly from 10.2% in FY21 to 11.7% in FY23. Hispanic enrollment in NIH-defined Phase 3 clinical trials declined from 31.2% in FY21 when a single large study that enrolled many Hispanic participants was not reported, to 15.9% in FY23. The Office of Management and Budget (OMB) has announced new racial/ethnic categories that NIH will adopt over the coming years.

Inclusion across the lifespan data has been reported since 2019. Most clinical research participants are adults, representing 46.8% of enrollees in FY23. The enrollment levels of children and older adults fluctuates each year. In FY23, the ages of 31.3% of enrollees were not reported.

Discussion. The following issues were discussed following Ms. Corbett's presentation.

- Principal Investigators may report by sex or gender and the Office of Extramural Research (OER aggregates the data for reporting purposes. This approach is currently under discussion.
- NIH ICs have sought to increase diversity; the NIH Community Engagement Alliance (CEAL) and the Trial Innovation Network (TIN) are models. TIN has developed accessible resources.
- Compliance with disaggregating data has increased because of increased awareness among NIH program officers who are notified by OER when compliant analyses are not reported.
- OMB's new racial/ethnic guidelines will require disaggregation of data by subgroups within the Asian population, as well as other racial/ethnic categories. A write-in option also allows for participants to report their self-inferred racial/ethnic identification. NIH and other federal agencies have 18 months to implement the new guidelines.
- Pregnant and lactating women are not specifically identified in inclusion reports. Women of childbearing years may not be excluded from studies, and outreach must address all groups. Pregnancy data are only required for exclusion purposes.

Open Discussion

Dr. Clayton facilitated an open discussion among ACRWH members in which the following comments were made. One ACRWH member recommended adding congenital and pregnancy syphilis as an important topic in women's health. It was noted that ORWH is exploring with the National Institute of Allergy and Infectious Diseases (NIAID) and other NIH ICs how to identify the most important research questions for this topic and the types of activities that ORWH might undertake.

Introduction of the NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives

Dr. Clayton introduced Tara Schwetz, Ph.D., NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives and the Director of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI. Dr. Schwetz shared her career and provided an overview of DPCPSI's activities. She discussed how DPCPSI is poised to address the health of women by identifying and catalyzing research to identify gaps and opportunities to foster collaboration, developing methods to enable research goals, and serving as a testbed for strategies to improve the health of the nation. Dr. Schwetz identified several new and ongoing NIH activities to support women's health, including the Coordinating Committee on Research on Women's Health (CCRWH), ORWH's career development programs, the new NOSI on women's health research, the President's Executive Order on Women's Health Research, and the new P2P menopause initiative.

Enhancing Community Engagement at ORWH

Dr. Ota Wang introduced Elizabeth Barr, Ph.D., Associate Director of Interdisciplinary Research, ORWH, who introduced a new initiative in community engagement at ORWH.

Dr. Barr described the background of community engagement in health research as "the process of working collaboratively with and through groups of people affiliated by geographic proximity, special interest, or similar situations to address issues affecting the well-being of those people." She reported that the benefits of community engagement include increased and expanded recruitment and retention,

improved research quality, enhanced research effectiveness, increased trust in research, demonstration of respect for the community, and increased uptake of research findings. She noted that ORWH currently solicits lived experience, patient testimonies, and advocacy perspectives informally through ad hoc efforts, for example, hosting listening sessions at the U.S. Conference on HIV and AIDS. ORWH also issues RFIs on specific topics. Dr. Barr stated that although these engagements are integral to ORWH planning and programs, they are difficult to sustain without a systematic approach and supportive infrastructure.

To meet the need for sustained community partnership and ensure responsiveness to and input from the women ORWH serves, ORWH proposes the establishment of a standing ACRWH community engagement subcommittee to be comprised of patients and community members. This subcommittee will elicit regular, ongoing, community- and patient-focused input into ORWH programs and priorities. Potential deliverables may include community-focused health information (e.g., webinars, factsheets, FAQs) about women's health topics.

Dr. Barr reported that multiple community engagement efforts are in place across NIH. In 2023, ORWH engaged in a series of meetings with these community engagement efforts to understand best practices and lessons learned. She identified two key learnings that emerged from these consultations: (1) Compensation for community members' time and expertise is an essential element of community engagement structures and (2) Clarity of purpose, scope, and expectations are critical elements of successful community engagement structures. Initial internal dialogues should ascertain what will be asked of community members (e.g., quantity of participation, type of feedback) and what should (and should not) be expected from ORWH (e.g., implementation of input, development of materials).

Dr. Barr described a phased approach to building a subcommittee in which eight members (nominated and self-nominations) join each year and serve three-year terms, with an optional fourth year, resulting in a final membership of 32 members that will ideally reflect a diversity of perspectives that includes disease-agnostic characteristics (e.g., adolescent girls, rural women) and disease-specific experiences (e.g., autoimmune diseases, endometriosis). She noted that not all perspectives will necessarily simultaneously be represented. The subcommittee would meet quarterly. Next steps included solicitation of members (May 2024), review of nominations by ORWH and the CCRWH (June 2024), conversations with nominees (July 2024), invitations to the first round of members (August 2024), planning of first meeting (September 2024), and convening of first meeting in conjunction with the 61st ACRWH meeting (October 2024).

Discussion. Dr. Ota Wang opened the floor for questions and discussion. The following key discussion points were made.

- Members of the subcommittee should reflect a balance of members speaking from their experiences as individuals; research or advocacy experience is not required.
- A phased approach to establish the subcommittee may ease the process of recruiting new members by self-nomination. Other NIH programs have recruited via *Federal Register* notices.
- The opportunity exists to build the subcommittee as most appropriate, for example, the subcommittee could meet prior to each ACRWH meeting. Meetings could be virtual or hybrid. The subcommittee may choose one individual to serve as a liaison with ACRWH.
- The Patient-Centered Outcomes Research Institute (PCORI) emphasizes stakeholder engagement and may offer valuable guidance to ORWH on its community engagement efforts.

NIH Director's Report

Dr. Clayton introduced Monica M. Bertagnolli, M.D., the 17th Director of NIH, and her presentation "Toward Evidence-Based Health Care for Women and for All." Dr. Bertagnolli introduced herself, tracing her lifepath from a Wyoming ranch, medical school at the University of Utah, to training in surgery at Brigham and Women's Hospital. Her journey continued to New York-Presbyterian, Harvard Medical School, and the Dana-Farber Cancer Institute before she became Director of the NIH National Cancer Institute (NCI). She reported being diagnosed with early-stage breast cancer with an excellent prognosis, thanks to treatment research conducted by NIH. Her experiences have provided her a powerful sense of the transformative power of research, coupled with an understanding of the need for access to health care based on her early life experiences in rural Wyoming.

Dr. Bertagnolli's Vision for NIH. Dr. Bertagnolli reported disturbing trends in the health of the U.S. population. Life expectancy among Americans declined from 2014 to 2017, dropped significantly during the pandemic, and is currently below that of other industrialized nations. Health care expenditures in the U.S., however, are high. She highlighted that the same population subgroups that experience the greatest health problems are not only disproportionately affected by the same issues that have caused a decline in Americans' life expectancy but are also underrepresented in clinical research. Conversely, the biomedical field is not effectively harnessing research data. In oncology, for example, she discussed that a review of National Comprehensive Cancer Network (NCCN) guidelines in 2019 showed little to no change over the past decade in the nature of evidence used to develop clinical care guidelines, with only 7% of recommendations supported by randomized controlled trials. The great majority were derived from level 2 evidence, generally provided by observational trials or earlier phase randomized trials.

Dr. Bertagnolli outlined guiding principles and discussed specific research and health care issues.

Guiding Principles. To respond to these challenges, NIH is adopting the following guiding principles:

- Our work is not finished when we deliver scientific discoveries; our work is finished when all people are living long and healthy lives.
- NIH research encompasses the laboratory, the clinic, and the community. Fundamental science remains critical. NIH must be more effective in communicating what is learned.
- Progress is accelerated when advanced scientific methods, such as new data analytics, are applied to data that includes everyone, and when new discoveries are rapidly and equitably adopted in clinical care. To realize the potential of new technologies, NIH must invest in a new and secure data sharing structure.

What NIH Should Do. NIH needs to make evidence-based health care available to all by:

- Connecting research to primary care to optimize outcomes for patients. This includes (1) meeting people where they already receive care to better engage underrepresented communities in research, (2) increasing research capabilities and efficiency with innovative study designs that address common health issues, (3) providing prevention and implementation relevant to individual communities, (4) using electronic health records to respectfully engage people in research with their permission, and (5) rapidly disseminating evidence to guide patient and provider decisions.
- Expanding use of biomedical research data use to inform new research and improve health outcomes by integrating data from basic and social science research, public health, and clinical care.

- Employing a federated architecture for data sharing and use by increasing capacity for data hosting, enabling low-cost access to data using open-industry data standards, supporting broad access to advanced analytics and computational power, and providing education and workforce development.

Federal Support for Women's Health Research. On March 18, 2024, President Biden signed an Executive Order that laid out a vision for women's health research. A particular area of concern has been a lack of research on women's midlife health including menopause, cardiovascular health, and autoimmune issues. She noted that women's health is one of five cross-cutting themes in the *NIH-Wide Strategic Plan for Fiscal Years 2021–2025*, highlighting its importance.

Maternal Morbidity and Mortality (MMM). MMM is a challenging issue with a disturbing number of deaths postpartum due to depression, hypertension, and other issues. She noted that MMM varies by groups with rural, older, and minority women facing particular risks. An NIH clinical trial in Pakistan demonstrated that nonclinical providers using a cognitive behavioral therapy–based intervention were able to reduce women's postpartum depression by two-thirds or more, suggesting a promising strategy for providing mental health care in low-resource settings.

Dr. Bertagnolli shared that nearly seven million women in the U.S. have no or limited access to maternity care including a high number of maternal health care deserts across the country in rural areas and low-income communities. She reported that NIH's Improving Maternal health and Pregnancy Outcomes for Everyone (IMPROVE) initiative supports research to reduce preventable causes of maternal deaths and improve health for women before, during, and after pregnancy. This effort includes a special emphasis on health disparities and populations that are disproportionately affected. The IMPROVE-Community Implementation Program (CIP) supports community-engaged implementation research to address factors that contribute to MMM. Also, the NIH Community Engagement Alliance CEAL is a research network designed to work with communities and community-based organizations to identify promising engagement and outreach practices that communicate trustworthy, science-based information to communities experiencing health disparities. CEAL began as a COVID initiative and has now expanded to address maternal health inequity in the primary care setting through the CEAL Primary Care Research Network (CEAL-CAREnet).

Midlife and Transition into Older Age. Dr. Bertagnolli also discussed the Women's Health Initiative (WHI), ongoing since 1991, that is part of NIH/NHLBI's longstanding commitment to women's health, with a goal of preventing chronic disease among older women. A 2021 WHI study, for example, demonstrated that light physical activity is associated with a reduced risk of heart disease.

The Impact of Research. There is promising research on reducing pain from endometriosis, a condition that affects one in ten women. Dr. Bertagnolli reported an NIH study that found that a repurposed drug—NSAID fenoprofen—alleviated pain and inflammation in a rodent model of endometriosis. This is an example of how a small NIH study can have a large impact on women's health.

Dr. Bertagnolli discussed that autoimmune diseases comprise the third most prevalent disease category, surpassed only by cancer and heart disease. As many as four out of every five people with these diseases are women. She reported that Stanford University researchers found that this increased prevalence could be explained in part by X-chromosome inactivation and overproduction of an X-chromosome specific protein that may lead to autoimmune disorders. Specifically, molecules called Xist are encoded on the X chromosome, but only when there are two X chromosomes, something most females have. Xist

molecules can encourage the formation of odd clumps of RNA, DNA, and proteins that can trigger strong autoimmune responses. This important discovery could have implications for the early detection, treatment, and prevention of autoimmune diseases, with implications for other diseases that impact women.

Discussion: Dr. Clayton facilitated an open discussion among ACRWH members in which the following key points were made.

- Tobacco smoking remains a key public health issue and has an impact on health disparities. Providers are often not proactive in addressing smoking, even though effective interventions exist. Dr. Bertagnolli noted that the CEAL Primary Care Network could provide a setting in which to implement tobacco-related interventions.
- Metastatic cancer in older minority women has not yet been impacted by effective treatments. Dr. Bertagnolli observed that fundamental research and health service delivery research are the great levelers where the health of everyone can be addressed.
- Women's health conditions should not compete against one another for funding, and more funding is needed to address all these conditions. The NIH Director stated that NIH is working diligently to eliminate silos across ICs and to identify common drivers of diseases, such as inflammation, metabolic syndrome, or genetics. The National Library of Medicine (NLM) will serve as the focal point for bringing NIH research into one place.
- Confidence and trust in science is an issue. Dr. Bertagnolli concurred, noting that NIH seeks to earn trust by (1) asking what people need rather than NIH dictating what it thinks they need and (2) sharing data, including allowing people control over their own data.
- Maternal health care deserts are often characterized by a lack of health care providers who focus on women and a lack of training opportunities in maternal health. Dr. Bertagnolli responded that several programs at NIH enable research in overlooked areas (e.g., the Institutional Development Award [IDeA] states seek to build research capacity, including three that focus on women's health; CEAL is a collaboration across several NIH ICs that offers training and workforce development programs in under-resourced areas). The sites for the CEAL Primary Care Network have not yet been selected but are expected to be in health care deserts, and will include providers who provide continuity of care, including OB/GYNs, pediatricians, and mental health clinicians.
- There is a lack of high-quality data and a need for new data analytic tools. NIH envisions NLM as the focal point for data sharing where people can obtain guidance in accessing datasets on specific topics. This cloud-based environment will provide data analytics and allow researchers to generate hypotheses and encourage collaboration with other individuals who are interested in the topic. All research resources on the topic could be identified, including the ability to launch new clinical trials.
- Other conditions that could be considered relevant to the health of midlife and older women include inflammation and lack of physical activity due to joint pain and osteoarthritis. Osteoarthritis research should be a priority topic. Dr. Bertagnolli concurred. In the Helping to End Addiction Long-Term (HEAL) initiative, osteoarthritis is a significant area of focus in reducing opioid use for pain.
- Although each NIH IC has a specific focus and mission, NIH seeks to eliminate silos across the agency to support examining common underlying issues that impact women's health. She noted that the NIH ICs will continue to maintain their own networks for clinical trials.
- There is a need for specialty care.

- By the time minority women are able to receive primary care for their health problems, it is often too late. Dr. Bertagnolli responded that NIH and CDC are exploring ways to work in the community to address minority women's health needs.

White House Women's Health Research Initiative Update

Dr. Clayton introduced Carolyn Mazure, Ph.D., Chair of the White House Initiative on Women's Health Research, Professor in Women's Health Research and in Psychiatry and Psychology at Yale University, and former ACRWH member. The White House Initiative was launched in November 2023 by President Biden in close collaboration with the White House Council on Gender Policy. As President Biden stated, its goal is to "fundamentally change how we approach and fund women's health research."

Dr. Mazure reported that although there has been some meaningful progress in women's health research, providers still lack tools to diagnose and treat the diseases that affect women only, disproportionately, or differently. She stated that the President sought to close existing research gaps by mandating that, within 45 days, nine agencies within the U.S. Department of Health and Human Services (HHS) and the Departments of Defense (DoD) and Veterans Affairs (VA) examine their research portfolios and decide how they can increase women's health research, both internally and externally.

Dr. Mazure noted that First Lady Dr. Jill Biden is leading the Initiative. She and Dr. Mazure traveled the country touring research laboratories and inviting researchers to describe the questions they are trying to answer. Dr. Mazure reported that the Initiative's staff will also engage in listening sessions with a wide array of stakeholders between November 2023 and March 2024. She shared that recurring themes that emerged from these efforts include (1) addressing health disparities, including in clinical trial participation and, especially, retention; (2) increasing interdisciplinary collaborations to address complex health questions that can only answered by multiple disciplines; and (3) addressing the delay in translating critical research findings into the marketplace.

Dr. Mazure said that, in response to these learnings, the First Lady announced the Advanced Research Projects Agency for Health (ARPA-H)'s first-ever Sprint for Women's Health, with a commitment of $100 million. ARPA-H's specialty is to convene problem-solvers on an issue and then take their solution to the marketplace. ARPA-H's statement on the new initiative noted that few of the current tools to improve women's health are affordable, available in the marketplace, or easy to use. ARPA-H wants to change that landscape.

Dr. Mazure reminded ACRWH members that, during his State of the Union address on March 8, 2024, President Biden called on Congress to make a bold, transformative investment of $12 billion in women's health as part of his FY25 budget request. Two primary goals were part of that request: (1) a Central Fund for Women's Health at NIH to advance interdisciplinary research, bringing together ICs to answer important questions that do not fit within specific IC mandates and (2) a nationwide network of research centers of excellence and innovation in women's health, building on the successes of the SCOREs.

Dr. Mazure discussed other activities that are occurring as the White House works with Congress to ensure this investment. First, NIH is launching a new NIH-wide effort to close gaps in women's health research across the lifespan, which will initially be supported by $200 million from NIH beginning in FY25. Second NIH will establish an initiative on biomarker discovery and validation to improve the ability to prevent, diagnose, and treat conditions that affect women uniquely, such as endometriosis; launch its first-ever Pathways to Prevention series on menopause and the treatment of menopausal symptoms; and kick off an effort to identify and develop new common data elements related to women's health.

Third, the National Science Foundation is calling for new research and education proposals related to women's health. Fourth, DoD and VA are launching a new Women's Health Research Collaborative to improve health outcomes for women Veterans and Servicewomen. Fifth, the Centers for Medicare & Medicaid Services (CMS) is taking steps to ensure that new medical services and technologies work well in women before being covered through Medicare. Finally, sixth, the Centers for Disease Control and Prevention (CDCP) is expanding training in women's health research and public health surveillance to OB-GYNs, nurses, and advanced practice nurses.

Dr. Mazure concluded her presentation by noting that on March 18, 2024, President Biden signed an Executive Order on Advancing Women's Health Research and Innovation to address the need for further action to support women's health research. Research gaps are most prominent for minority and older women.

Discussion: Dr. Clayton discussed the following points with Dr. Mazure:

- An NIH 45-day sprint to assess women's health research portfolios and propose new approaches ended on December 28, 2023; Dr. Biden was briefed on December 31.
- Researchers and the scientific community have been hugely enthusiastic in response to the Initiative.
- Developing new common data elements (CDEs) for women's health research, if done well, will have a significant impact on the creation of a federated data system. CDEs will provide the opportunity to characterize studies, establish cross-agency understanding of what research is being funded by whom, and improve analysis and meta-analysis of data.
- The next step in advancing the Initiative is to ensure implementation of the Executive Order. A Working Group chaired by Drs. Clayton and Mazure will create an inter-agency agreement across important areas. In addition, the Initiative is working with Congress (e.g., providing briefings to its members).
- The White House Initiative and Executive Order represent a real commitment to improving the health of the nation.

Panel: Middle-Life Health of Women and Menopause

Dr. Ota Wang introduced panel moderator Chhanda Dutta, Ph.D., Chief of the Clinical Gerontology Branch, Division of Geriatrics and Clinical Gerontology, National Institute on Aging (NIA. Dr. Dutta introduced the panel members: Roberta Diaz Brinton, Ph.D., Director, Center for Innovation in Brain Science, University of Arizona Health Sciences; Sherri-Ann Burnett-Bowie, M.D., M.P.H., Associate Professor of Medicine, Harvard Medical School; and Howard Neil Hodis, M.D., Professor of Cardiology; Medicine, Population, and Public Health Sciences, and Molecular Pharmacology and Toxicology, and Director of the Atherosclerosis Research Unit at the University of Southern California.

Women and Alzheimer's Disease Risk Begins in Midlife During the Menopausal Transition: Implications for Prevention and Treatment

Dr. Brinton's journey studying Alzheimer's disease (AD) began with a woman with AD. This experience prompted her to ask why women face a two-fold greater risk for developing the disease. Dr. Brinton's preclinical research suggested that women develop AD not because they live longer but because of changes in their brains that start during menopause.

She described menopause, like adolescence, as a neurological transition. With this transition, a decline in glucose metabolism in the brain is coupled with a rise in variability of neurological function during

perimenopause that later stabilizes. Menopause is characterized by symptoms such as hot flashes, among others, which occur in 80% of women. These symptoms reflect the changes that are occurring in the brain during the menopausal transition from early chronological to endocrinological to late chronological phases.

The brain is a glucose-dependent organ, and estrogen regulates about 20-25% of its glucose metabolism. Loss of estrogen during the menopausal transition activates a starvation response that prompts the brain to find an alternative auxiliary fuel in addition to ketone bodies that are generated by astrocytes using the brain's white matter. A midlife reprogramming in the female brain during the menopausal transition is characterized by reduced glucose metabolism and by an early but short-lived rise in the use of amino acids as an auxiliary fuel at the cost of synaptic neural development. This is followed by a significant rise in fatty acid β metabolism in the brain, which is associated with a change in the mitochondrial phenotype from a highly efficient estrogenic profile to a less efficient one, paralleled by a rise in ketone bodies. During the catabolism of white matter to generate ketone bodies, myelin debris is generated, which is taken up on the plasma membrane of the brain's microglia. As this happens, the researchers observed a response that is consistent with an autoimmune response of the brain can be observed. This observation is consistent with the fact that 95% of all people who develop the autoimmune disease muscular sclerosis (MS) past the age of 50 are women.

Thus, two processes occur—the metabolic reprogramming and the immune activation—during the menopausal transition. Finally, there is activation of the adaptive immune system. Each of these systems are consistent with a profile in AD. Research also has shown that vasomotor symptoms (i.e., the hot flash) are likely due to activation of the microglia that act as neutrophils in the brain where they have respiratory bursts to destroy a foreign body (usually myelin debris). Thus, the hot flash is due to inefficient mitochondria and then a proton leak within the brain that is generating heat and is associated with white matter loss.

Dr. Brinton's research team and colleagues found that–consistent with the discovery data described above—during menopause, there is reduced glucose metabolism in the temporal cortex, the precuneus cortex, and the frontal cortex, all brain regions that are involved in AD. Looking at changes in brain structure via magnetic resonance imaging (MRI), the researchers found significant changes in the brain's white matter. Further, these changes in glucose metabolism and in white matter volume during the menopausal transition is associated with the classic markers of AD, that is, the deposition of beta-amyloid plaque in the brain.

Hormone Replacement Therapy (HRT). Because these changes are triggered by loss of estrogen, does HRT affect the risk of developing AD? Research has shown that the risk of a women who uses HRT developing a neurodegenerative disease is reduced by 50% or more. The longer HRT is used, the more the risk is reduced. However, timing matters. HRT is normally given to reduce menopausal symptoms when the symptoms are experienced in the early chronological phase in the transition. What impact does that have on the next endocrinological phase or the late chronological phase? Biological systems that are activated in the brain during these phases are quite different. This may be one of the reasons for the great controversy around HRT and its outcomes. Eighty percent of women elect not to use HRT with fear of developing breast cancer as an overriding reason for this decision.

To promote brain health, Dr. Brinton and her team sought to link HRT to breast health. The research team developed an intervention, PhytoSERMS, that targets estrogen receptor β in the brain. Estrogen receptor β is a very effective receptor that promotes glucose metabolism, reduces inflammation,

sustains estrogen activity, and is particularly important because it inhibits breast cancer cell development, proliferation, and migration/invasion. Researchers conducted a Phase 1b/2a clinical trial of three plant-based molecules that activate estrogen receptor β to determine safety and optimal dosing. Two Phase 2 clinical trials are now under way, one targeting the decline in brain glucose metabolism to determine whether PhytoSERMS reduce the decline, thereby allowing the brain to sustain its white matter integrity and potentially prevent AD, and the other targeting relief from hot flashes.

Key Points. Dr. Brinton identified the following key points about menopause: (1) Menopause is a neurological transition that can unmask vulnerability to age-associated neurodegenerative disease. (2) The menopausal transition involves both the metabolic and immune systems of the brain. (3) HRT sustains and promotes healthy brain aging but does not reverse disease. (4) Promoting brain and breast health is feasible through estrogen receptor β selective formulation.

***Gaps and Opportunities in Women's Brain Health*.** Dr. Brinton recommended further research into precision hormone therapy to prevent neurological risks and biomarkers of the transition stage beyond clinical symptoms that reflect neurological health or vulnerability.

Impact of the Midlife and Menopause on Bone Health: What We Know, What We Need to Learn
Dr. Burnett-Bowie began by noting that she represents the Study of Women's Health Across the Nation (SWAN), a multi-site longitudinal, epidemiologic study to examine the health of women during their middle years. Her presentation focused on bone health in midlife women, particularly osteoporosis. Osteoporosis is a public health problem. In 2005, there were two million osteoporotic fractures, costing $17 billion dollars. Of these, 70% occurred among women. Almost three-quarters (72%) of the cost was related to hip fractures, constituting 14% of all fractures. In 2025, 3 million fractures are anticipated at a cost of $25 billion per year due to aging of the U.S. population. The greatest rise in fractures and associated costs is anticipated in minority populations, particularly among Hispanic individuals. Data from the WHI indicate that the number of osteoporotic fractures among women exceed those of stroke, invasive breast cancer, and myocardial infarction/cardiovascular disease combined. A study using Medicare data revealed that Black women are more likely to experience mortality, debility, or destitution one year after fracture than White women.

If the goal is to prevent osteoporosis or fractures, two questions must be addressed: How does the midlife/menopause transition impact bone loss? and Are there racial/ethnic differences in fractures and/or bone loss?

The SWAN study started in the early 1990s to develop longitudinal epidemiological data on women's health in midlife and beyond. Between 1996- 1997, 3,302 women were recruited via community-based sampling of zip codes at seven centers across the country. Half of the cohort were White, and the other half were Black, Chinese, Hispanic, or Japanese. The investigators have now completed Visit 17 with the women, achieving 75% retention at Visit 15 (n=2,366).

Bone Density in the SWAN Study. Data on bone density loss and body mass index (BMI) are available from five of the seven SWAN study sites. The investigators observed variation in bone density over time with a large loss associated with the menopausal transition and a subsequent slowdown after that 3- to 4-year window. Although loss occurred across all four groups (Hispanic women were not included in this analysis), Black women experienced significantly less loss of bone density in the lumbar spine during the

menopause transition than did other groups in one 10-year study. An HR-pQCT scan revealed that White women have thinner cortices (edges) for both the radius and the tibia than do Black women.

The SWAN study also found a negative relationship between BMI and bone density loss. Individuals with the lowest BMI had greater bone density loss than those with higher BMI. Black women had the highest BMI at baseline and the least bone density loss. In general, investigators observed average rises in body weight and BMI among study participants over a 15-year period, with steep increases in the proportion of fat mass and decreases in lean mass among White, Black, and Japanese women (data were not available for Latinas), indicating rapid changes in body composition during the menopausal transition. Overall, as lean mass declined, lumbar spinal bone density declined. Hence, a decline in lean mass and an increase in fat mass is associated with an increased likelihood of bone fractures in midlife/menopausal women.

***Preventing Bone Loss in Midlife Women*.** A SWAN study found that leisure-time physical activity (walking) was associated with stable spine and femoral neck bone mineral density over a 17-year period. Study participants with the highest level of activity had the highest bone density. Further, the LIFTMOR (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation) trial (not part of SWAN) showed that high-intensity resistance and impact training improved bone mineral density and physical function in postmenopausal women with osteopenia and osteoporosis. In SWAN studies, higher levels of vitamin D were associated with fewer fractures over time; however, these findings are not consistent with those from the VITAL clinical trial. Various medications investigated over the years have shown either no effect on bone density or an increased risk of fractures (e.g., blood pressure medications). Factors that decrease midlife/menopausal bone loss include age of final menstrual period (more important than chronological age), increased leisure-time physical activity, higher BMI, and higher anti-mullerian hormone (AMH) levels. Factors that increase bone loss in midlife/menopausal women include diabetes mellitus/insulin resistance with the menopause transition, increase in fat mass, higher dietary inflammation index, and higher C-reactive protein (CRP) levels.

Gaps in Knowledge. Researchers continue to seek answers to these questions: How does midlife/menopausal transition bone loss inform bone loss in later years? Can we predict who will fracture or have accelerated bone loss in her 60s, 70s, and 80s based on changes in bone mineral density at midlife and/or changes in other midlife/menopause transition factors, for example, AMH, estradiol, CRP? For a woman who has not fractured but has osteopenia and/or increased fracture risk, when should prescription anti-osteoporosis medication be initiated? And finally, what can be done at midlife to reduce racial and ethnic disparities in mortality, disability, and destitution with fracture?

Timing of Menopausal Hormone Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease

Dr. Hodis noted that cardiovascular disease (CVD) is the leading cause of death in women and that its incidence continues to rise. Most women who die from CVD are postmenopausal. The Framingham Study indicated that the incidence of CVD is higher in postmenopausal women in all age cohorts; for those age 50-64, the incidence is 6.5 times higher. Forty years of observational studies have indicated that women who choose HRT have a reduction in CVD and all-cause mortality. The data from two clinical trials are less positive. These differences in outcomes may be attributed to different sampling characteristics, including age at enrollment, amount of time after menopause that HRT was initiated, presence of menopausal symptoms, duration of therapy, and BMI.

***Timing of Menopausal HRT Hypothesis*.** The effects of menopausal HRT on atherosclerosis and clinical events depend upon when HRT is initiated in relation to menopause and/or age, according to observational, animal, and athero-imaging clinical trials. According to this timing hypothesis, HRT can be effective in preventing morbidity and mortality if started early during menopausal transition.

Prior to emergence of the timing hypothesis, the healthy endothelium hypothesis tried to explain what was thought to be a duality of estrogen and its effects on the natural history of atherosclerosis. Many beneficial effects of estrogen/HRT on atherogenesis were recognized. Somewhere in the early postmenopausal phase (about six years after last menses), the loss of estrogen's beneficial effects could be observed due to methylation of the promoter site estrogen receptor alpha gene. As more years post menopause passed, estrogen was thought to have an adverse or null effect (hence, the duality). The timing hypothesis emerged from a mechanistic understanding of this process derived from clinical trials.

An early study, the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) (2001), demonstrated a significant treatment effect of estradiol on carotid intima-media thickness (CIMT) compared to placebo. Dr. Hodis and his co-investigators also examined the impact of HRT on women with diseased vessels and found no treatment effect. This was the first evidence of the timing hypothesis and showed, in animal studies, that estradiol can prevent new lesion formation, but not progression of disease once lesions have been established. The Early versus Late Intervention Trial with Estradiol (ELITE) was a direct test of the timing hypothesis. In this study, 643 healthy postmenopausal women without preexisting CVD and diabetes mellitus were randomized to oral micronized 17β-estradiol 1 mg/day or a placebo by time since menopause (less than six years [average age 55]) or more than 10 years [(average age 64]). There was a significant treatment effect in the younger women but no effect in the older women, thus validating the timing hypothesis. A similar effect was found for coronary heart disease (CHD) mortality and for all-cause mortality in Cochrane meta-analyses of randomized clinical trials, that is, a significant effect of HRT for younger women closer to menopause and a null effect for older women with more years post menopause. A Danish longitudinal randomized clinical trial of CVD outcomes followed 1,006 women who were recently postmenopausal. It found that after 10 years of randomized treatment, women receiving HRT early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke.

The relative risk of coronary heart disease (CHD following HRT use has been relatively consistent between observational studies and clinical trials, with both showing a reduction in CHD and all-cause mortality. A similar positive result for HRT's impact on all-cause mortality was also shown in the WHI. Similar results were found for AD. There is a five times higher risk of CHD in women 45-74 years old with diabetes, compared to a 2.4 times higher risk in men, according to the Framingham 18-year follow-up study. However, there are fewer cases of new onset diabetes among women using HRT.

Key Points and Future Directions. Dr. Hodis summarized the following key points: (1) CVD is the number one cause of death in women. (2) Postmenopausal women are at an increased risk for CVD. (3) Menopausal HRT is a cost-effective sex-specific therapy that reduces all-cause mortality (including CVD, cancer, dementia/AD), CHD, bone fracture, and new onset diabetes mellitus with rare risks when initiated around the time of menopause. (4) Benefits of menopausal HRT outweigh risks when initiated around the time of menopause.

A promising new approach to advancing postmenopausal prevention therapy is tissue-selective estrogen complex (TSEC), a progestogen-free option for the treatment of estrogen deficiency symptoms in

postmenopausal, non-hysterectomized women. Another important area worth investigating to better understand AD is the vascular response to HRT in the brain.

Discussion: Dr. Dutta moderated a discussion that addressed the following topics.

- The value of HRT to prevent CVD among Black women in terms of the timing hypothesis has not been differentiated from that of other racial/ethnic groups, but larger studies are needed to substantiate this finding.
- The impact of HRT across multiple diseases when administered early enough is significant and can positively change the trajectory of aging. A shared common driver across biological systems is activation of the immune system, first the early innate immune system response and then the adapted immune system.
- HRT appears to work in the opposite direction for breast cancer: An early start to HRT increases breast cancer risk. This makes the decision to use HRT difficult for women.
- Some researchers have considered the role of progesterone in HRT and whether there are differences from a neurological perspective among different types of HRT. With the exception of medroxyprogesterone acetate (MPA), the progesterone in HRT acts to inhibit estrogen action in multiple organs, including the brain. The normal biological pattern has estrogen increasing and then declining, with progesterone then activating. When the HRT follows this natural path, HRT is beneficial. When the HRT is a continuous combination of estrogen and progesterone, the progesterone is inhibitory. MPA, however, drives proliferation of cells in the breast and uterus and relies on cell cycle checkpoint programs. Thus, the type of progesterone used in HRT matters. This is a key area for further investigation, because the data to confirm observations are currently insufficient.
- HRT administered at the time of symptoms has been shown to be helpful in preventing AD, amyotrophic lateral sclerosis (ALS), muscular sclerosis, and Parkinson's disease in women. Research on the impact of HRT initiated later has shown neither benefit nor harm on the risk of developing these diseases.
- Some research on pharmacological breast cancer therapies (e.g., tamoxifen, raloxifene, and aromatase inhibitors) found that aromatase inhibitors and tamoxifen reduced the risk of developing age-associated neurodegenerative diseases at about one-half the impact of estrogen. Raloxifene had less impact because it does not cross the blood–brain barrier.
- Although estrogen may be protective for breast cancer in older women according to a study presented by Dr. Hodis, those effects disappear for women younger than age 60 years. In that study, the reduction from HRT was much more significant for ductal carcinoma in situ (DIS) in the trial. There is a difference of opinion on whether MPA is the bad player in HRT.
- Dr. Criswell noted that this discussion illustrates the complexity of issues and problems that will continue to be encountered in women's health research. For example, bisphosphonates decrease fractures, but reports of rare side effects led to a decline in use and subsequent increase in fractures. The side effects are so rare that they are difficult to study in a rigorous way. At the same time, research has shown that women who experience an osteoporotic fracture are at very high risk for another one. In response, clinical teams have developed fracture liaison services, but they are not currently reimbursable. Developing new drugs to prevent fractures is a long process. This is a common problem that is multi-factorial and illustrates the challenges facing much of women's health research.

Concept Clearance: NIH Office of Autoimmune Disease Research (OADR-ORWH) Notice of Special Interest (NOSI)

Dr. Clayton introduced Dr. Shanmugam, Director of the NIH Office of Autoimmune Disease Research (OADR-ORWH) who presented a concept clearance for a new NOSI on "Building Consensus for Autoimmune Disease-Related Common Data Elements." The NOSI's objective is to generate interest in receiving applications to stimulate development of NIH-endorsed common data elements applicable to autoimmune diseases through convening members of the scientific, clinical, patient, and advocate community to inform discussions.

Background. There are 144 autoimmune diseases that affect various organ systems. These diseases affect 7-8% of the population, impacting approximately 23.5 million Americans. Nearly 80% of people with autoimmune diseases are women. However, the exact prevalence of autoimmune disease in the U.S. is unknown because of a lack of longitudinal data repositories.

NIH-Endorsed Common Data Elements. A CDE is a standardized, precisely defined question, paired with a set of allowable responses, used systematically across different sites, studies, or clinical trials to ensure consistent data collection. Multiple CDEs (from one or more Collections) can be curated into forms. Forms in the NIH Repository might be original or might recreate the format of real-world data collection instruments or case report forms. NIH has endorsed collections of CDEs that meet established criteria. The purpose of this endorsement is to facilitate data-sharing and harmonize CDEs across datasets, in accordance with the 2023 NIH Data Management and Sharing Policy.

There are currently NIH-endorsed CDEs for nine autoimmune diseases. Their number varies from 56 CDEs for multiple sclerosis and 37 for type 1 diabetes to only 1 for uveitis, vasculitis, and vitiligo. Even a common disease such as lupus is associated with only four NIH-endorsed CDEs. The lack of CDEs is difficult to understand given the large number of autoimmune disease registries.

OADR-ORWH. Aligned with the 2022 NASEM Report *Enhancing NIH Research on Autoimmune Disease*, Congress directed NIH to establish the OADR in ORWH. This NOSI responds to four of six OADR mandates: identifying emerging areas of innovation and research opportunity, coordinating and fostering collaborative research across ICs; providing resources to support planning, collaboration and innovation, and developing a publicly accessible central repository for autoimmune disease research.

NOSI. The award period for projects funded under this NOSI is one year. Funding is subject to availability of funds and NIH ICO collaboration, for which there has been an expressed high interest. Examples of high-priority topics include myositis, hidradenitis suppurativa, rheumatoid arthritis, sarcoidosis, scleroderma, systemic lupus erythematosus, uveitis, and vasculitis. Collaborative approaches are encouraged.

Discussion: The following key points were made during the discussion of Dr. Shanmugam's presentation.

- The focus of the proposed work is not only on the diseases themselves, but also on disease processes (e.g., environmental triggers) that cut across different ICO areas and that integrate data across the lifespan.
- Proposed topics are not limited to the diseases identified above as high-priority topics.

Vote: The concept for the OADR-OWRH Notice of Special Interest (NOSI): "Building Consensus for Autoimmune Disease-Related Common Data Elements" was approved with nine votes in favor with no oppositions or abstentions.

Open Discussion

Dr. Clayton facilitated an open discussion in which the following comments were made.

- Today's meeting was excellent.
- Retiring members expressed appreciation for what they have learned from their participation on ACRWH.
- The strategic plan is well written.
- With exciting new ventures, ORWH should not forget issues such as MMM and infant mortality. In fact, ORWH should be commended for sticking with important topics over the long term.
- It may be helpful to have an update on the IMPROVE Centers of Excellence at a future meeting.
- To address issues of women and alcohol cited in the Director's Report, NIAAA and the National Institute on Drug Abuse (NIDA) are focused on alcohol abuse and substance abuse, respectively, among women. Several SCORE programs are addressing this issue.
- Aging women and the impact of caregiving on their health is a topic deserving attention.
- Musculoskeletal issues should be priorities at both ends of the lifespan.
- Disaggregation of data by sex is critical. There has been an increase in disaggregated results for Phase 3 clinical trials, and the sex and gender guidelines have been adopted by many journals. Although ORWH cannot control journal editors, it can continue to work with them to emphasize the importance of disaggregation.
- ORWH should report to ACRWH on the responses to new Notices of Funding Opportunity (NOFOs) like the new NOSI on autoimmune diseases, that is, number of applications, types of research funded.

Closing Remarks

Dr. Clayton adjourned the meeting at 4:18 p.m. The next meeting, scheduled for October 16, 2024, will be a hybrid meeting held at the NIH campus in Bethesda, MD.

Certification

We certify that the contents above are accurate and complete.

Janine A. Clayton -S
Digitally signed by Janine A. Clayton -S
Date: 2024.10.02 16:58:12 -04'00'

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

Date _____

Vivian Ota Wang -S
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Date: 2024.09.27 16:04:26 -04'00'

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

Date _____