64th 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 7, 2026

Members Present
Garnet L. Anderson, Ph.D.
Irene Aninye, Ph.D.
Arthur Arnold, Ph.D.
Ayush Giri, Ph.D.
Stephen Higgins, Ph.D.
Hendrée Jones, Ph.D.
Rosalyn Maben-Feaster, M.D.
Thelma Mielenz, Ph.D.
Alexandra Noël, Ph.D.
Ighovwerha Ofotokun, M.D. (online)
Phyllis Sharps, Ph.D.

ORWH Leadership Present
Janine A. Clayton, M.D., FARVO, Director; Chair, ACRWH
Cindy Caughman, M.P.H., Acting Deputy Director
Lucia Hindorff, Ph.D., M.P.H., Executive Secretary, ACRWH; Senior Advisor for Scientific and Organizational Strategy
Elizabeth Barr, Ph.D., Associate Director for Interdisciplinary Research
Chyren Hunter, Ph.D., Associate Director for Basic and Translational Research
Victoria Shanmugam, M.B.B.S., M.R.C.P., FACR, CCD, Director, NIH Office of Autoimmune Disease Research in the Office of Research on Women's Health (OADR-ORWH)
Xenia Tigno, Ph.D., Associate Director for Careers

NIH Leadership Present
Nicole C. Kleinstreuer, Ph.D. NIH Deputy Director, Program Coordination, Planning, and Strategic Initiatives; Director, Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
David C. Goff, M.D., Ph.D., Acting Director, National Heart, Lung, and Blood Institute (NHLBI)

Panelists and Keynote Speaker
Chloe E. Bird, Ph.D., FAAAS, FAAHB, Director, Center for Health Equity Research, Tufts Medical Center, and Sara Murray Jordan Professor of Medicine, Tufts University School of Medicine
Lida Chatzi, M.D., Ph.D., Professor of Population and Public Health Sciences, University of Southern California (USC); Director, USC Superfund Research Program, Director, USC Center for Translational Exposomics Research, and Deputy Director, Southern California Environmental Health Sciences Center, USC Keck School of Medicine
Mariana Kaplan, M.D., NIH Distinguished Investigator and Chief, Systemic Autoimmunity Branch, and Deputy Scientific Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Sheida Nabavi, Ph.D., Associate Professor, School of Computing and Engineering, University of Connecticut

Honorable Guest
Vivian W. Pinn, M.D., Founding ORWH Director

Call to Order

Lucia Hindorff, Ph.D., M.P.H., ACRWH Executive Secretary called the hybrid meeting to order at 9:00 a.m. ACRWH members introduced themselves. Dr. Hindorff acknowledged retiring members: Drs.

Higgins, Jones, Mielenz, Noël, and Sharps. Dr. Hindorff also thanked Drs. Anderson, Aninye, Higgins, Jones, Mielenz, Noël, and Sharps for their continued service. The minutes of the June 17, 2025, meeting were approved unanimously with 11 votes in favor.

ORWH Director's Report

ORWH Director and NIH Associate Director for Research on Women's Health and ACRWH Chair, Janine A. Clayton, M.D., FARVO, delivered the ORWH Director's report.

NIH Updates. Dr. Clayton shared a list of 15 new Institute/Center (IC) Directors at NIH; 14 remain in an acting capacity. Nicole Kleinstreuer, Ph.D., formerly Acting Director, Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), is now DPCPSI Director.

RCDC. NIH has recently implemented a change to the Research, Condition, and Disease Categorization (RCDC) reporting system. Starting with Fiscal Year (FY) 2024 expenditures, an automated Women's Health Research RCDC category will increase rigor, accuracy, and analytical capability in the women's health portfolio.

Simplified Review Framework. NIH has revised its review process to address three factors, including 1) the importance of the research, 2) rigor and feasibility (including Sex as a Biological Variable (SABV)), and 3) expertise and resources. The NIH Director's framework for Gold Standard Science underscores SABV as a key aspect of rigor and reproducibility.

New Funding Resource. NIH has introduced a Highlighted Topics (HTs) resource to inform the research community about NIH areas of scientific interest, including new or emerging area, and thereby reduce the effort to search and apply for funding opportunities. ORWH-supported HTs are available on the ORWH Profile page. Applicants are encouraged to apply through an NIH Parent Announcement or other opportunity at Grants.gov.

Events. National Women's Health Research Day is observed annually on January 25th to commemorate the 2016 implementation of the NIH Policy on SABV. On January 20, 2026, ORWH participated in two high-visibility Capitol Hill events in recognition of the 10th National Women's Health Research Day and ORWH's 35th Anniversary: a Congressional Briefing on barriers to women's participation in clinical research, organized by the Society for Women's Health Research (SWHR), and a Friends of ORWH reception. ORWH was well-represented at the Inaugural HHS National Conference on Women's Health on March 11-13, 2026. At the conference, NIH Director Jay Bhattacharya, M.D., Ph.D., and DPCPSI Director Dr. Kleinstreuer, conducted a fireside chat on "Accelerating Transformative Women's Health Research." ORWH staff presented posters on a range of topics, including chronic conditions and chronic disease prevention in women, and SABV's impact on biomedical research.

Scientific Updates. ORWH is delighted to be among the founding funders of the Standardized Organoid Modeling (SOM) Center, a national resource for using cutting-edge technologies to develop standardized organoid-based new approach methodologies (NAMs) that deliver robust, reproducible, and patient-centered research findings and reduce reliance on animal models. The initiative is being launched by DPCPSI in collaboration with multiple ICOs. The Center's goal will be to leverage the latest technologies, including artificial intelligence (AI) and robotics, to enable real-time optimization of organoid protocols. The Foundation for the National Institutes of Health (FNIH) is establishing a NAMs Pilot Project Validation and Qualification Network to support pilot projects.

NAMs lie at the intersection of the NIH-wide Strategic Plan for Research on the Health of Women, NIH, and DPCPSI priorities. In FY 2025, ORWH invested in two NAMs projects, one at Brigham and Women's Hospital to develop an ethically-centered, data-driven multimodal AI tool to predict preeclampsia risk in early pregnancy, and the other at the CFD Research Corporation to develop a uterus-on-a-chip to study microgravity-induced aging in uterine cells and to identify and evaluate therapeutic approaches for stopping, reversing and/or repairing uterine aging. In addition, ORWH invested $4.7 million in a new Technology Development Center at the Massachusetts Institute of Technology to facilitate drug development for gynecological disorders by preparing NAM technologies for rigorous regulatory requirements.

Whole-Person Paradigm Shift. The concept of whole-person health, introduced to ACRWH at the 51st Annual Meeting, is now coming to fruition with the Whole Person Physiome (WPP) Research and Coordination Center (WPP-RCC) at Stanford University, which will coordinate a multi-tier network of collaboration across clinical and scientific researchers to design and curate a WPP-integrated map of the healthy male and female body and transform it into models for analyzing clinical data, shifting the focus from disease to optimal function.

SABV in Action. A collaborative publication between the Specialized Centers of Research Excellence (SCORE) on Sex Differences at Cedars Sinai and the University of Colorado Anschutz Medical Center titled "Sex Differences in Association of Physical Activity With All-Cause and Cardiovascular Mortality" featured SABV in action. It reported that women, compared to men, derived greater gains in all-cause and cardiovascular mortality risk reduction from equivalent doses of leisure-time physical activity. In another example of SABV, researchers in the NIH-supported Nurses' Health Study adopted a multi-omics approach integrating genetic (*APOE4*), metabolomic and dietary data to identify modifiable risk factors for dementia. They found that adherence to the Mediterranean diet is associated with a significantly lower risk of dementia and better cognitive function in men and women.

DiscoverWHR. Discover Women's Health Research (DiscoverWHR) is a centralized resource for women's health research and information from ORWH and the National Library of Medicine (NLM) that supports NIH-wide efforts to close the gaps in women's health across the life course. Many new health topics relevant to women have been added since its inception, bringing the total to 26. Menopause and PCOS have been the most visited topics. The funding page is consistently in the top 5 DiscoverWHR pages, indicating that DiscoverWHR is serving as a trusted information for researchers as well as patients and providers.

OWRH Program Updates. ***Women's Health Intramural Innovation Awards***. ORWH, with support from the Director of the NIH Office of Intramural Research (OIR) and the Office of Behavioral and Social Sciences Research (OBSSR), is supporting one-year, proof-of-concept pilot awards on women's midlife health to incentivize interdisciplinary research collaborations across NIH intramural programs. Applications were received from PI teams representing 14 IC intramural programs, with awards given to five teams at eight ICs.

Publications. NIH research on women's health is spotlighted in ORWH's quarterly publication, "Women's Health *In Focus* at NIH." Recent issues have focused on physical activity and data science in women's health. Past issues have addressed topics such as autoimmune disease, chronic debilitating conditions, maternal morbidity and mortality, SABV, and women in the biomedical workforce.

SCORE. The (postponed) 2025 Specialized Centers of Research Excellence (SCORE) on Sex Differences Annual Meeting took place March 17, 2026. On February 20, 2026, a symposium on Sex Differences in

Autoimmune Disease and Immunology of Infectious Disease was held in California. The symposium was a collaborative effort among three SCORE centers.

IDeA States. Over the past six years, ORWH has prioritized building capacity for women's health research through the Congressionally mandated Institutional Development Award (IDeA) Program, establishing the Women's Health Research in IDeA States Program to strengthen biomedical research in historically underfunded states. In close collaboration with NIGMS and 14 additional ICOs, ORWH has supported women's health research across the IDeA states, with NIH awarding 90 administrative supplements totaling $25.6 million from FY 2020–2025 to investigators in 21 of the 23 IDeA states and Puerto Rico and launching two annual symposia beginning in 2024. Through the Centers of Biomedical Research Excellence (COBRE) component, which supports the phased development of innovative biomedical research centers, NIH provided $9.49 million in FYs 2024–2025 to four IDeA institutions—Maternal and Reproductive Community Health Excellence (University of Arkansas for Medical Sciences, co-funded by ORWH), Nutrition and Women's Health (University of Idaho), Sex-Based Precision Medicine (Tulane University of Louisiana), and Leveraging Big Data to Improve Women's Health (University of Kansas, Lawrence, co-funded by ORWH).

OADR-ORWH. The inaugural NIH-Wide Strategic Plan for Autoimmune Disease Research (2025), aligned with OADR-ORWH Congressional Directive 2 to identify emerging areas of innovation and research opportunity, is dedicated to advancing the understanding, diagnosis, and treatment of autoimmune diseases through an interdisciplinary approach. A primary focus is the identification of genetic, environmental, and biological risk factors to enhance disease prevention and early detection strategies, underscoring the importance of developing personalized therapeutic interventions tailored to individual patient profiles. The autoimmune disease community provided invaluable input to the plan.

CDEs. OADR-ORWH mobilized NIH resources to advance the development of Common Data Elements (CDEs) in autoimmune disease research. In collaboration with NLM and the National Institute of Environmental Health Sciences (NIEHS), CDEs for myositis core set activity measures were developed, in part through an OADR-ORWH Intramural Research Award to support high-priority autoimmune disease research.

NOURISH. In September 2025, OADR-ORWH launched a Prize Competition to solicit entries for the Nutrition for OUR Immune System Health (NOURISH): Autoimmunity Challenge. With up to $150,000 in prizes, the purpose of this crowdsourcing competition was to develop a cadre of innovative ideas from interdisciplinary problem solver communities on how to best integrate diet and nutrition studies into autoimmune disease research, identify potential feasible and scalable dietary or nutritional interventions for people living with autoimmune diseases, and create a transformative far-reaching impact across the broad autoimmune disease portfolio. Fifteen winners were announced in March 2026.

Chronic Diseases. In FY 2025, ORWH continued to collaborate with ICO partners to fund investigator-initiated research on chronic diseases in women, including both R01 research project grants and R21 exploratory/developmental grants. ORWH (including OADR-ORWH) and six other ICOs funded 22 awards in FY25; 14 awards were for female-specific conditions. Twelve of these were R01 awards, nine were R21 awards, and one was R56 (high priority, short term project award). Adding these awards to those already funded in FY24, the chronic conditions program grew to $6.8 million in total ORWH funding, and over $20 million in total NIH funding for chronic disease research affecting women.

***Careers*.** The Building Interdisciplinary Research Careers in Women's Health (BIRCWH) is a K12 Mentored Research Career Development Program for Junior Faculty. There are currently 23 active programs across

the country and in its 25-year history, over 840 scholars have been funded at 47 institutions. ICOs contribute over $15 million per year to support BIRCWH; ORWH is thankful to Congress for an additional $10 million appropriated specifically for BIRCWH in FY 2026. A recent independent evaluation of the program concluded that BIRCWH has been transformational and pivotal for scholars' career trajectories: 60% of scholars received funding from at least one award within 5 years of starting BIRCWH; 89% of former scholars stay in research with 86% in women's health research; and 70% hold leadership positions.

Expansion of the BIRCWH program. ORWH is proud to announce its first-ever interagency collaboration with the U.S. Department of Veterans Affairs (VA). Beginning June 2025, four VA Career Development awardees are matched annually to active BIRCWH sites as NIH-VA BIRCWH Scholars. The inaugural cohort onboarded on April 1, 2026, at BIRCWH centers at Johns Hopkins University, Tufts University, the University of California Davis, and Magee-Women's Research Institute. Another strategic partnership between ORWH and the National Science Foundation (NSF) culminated in a Memorandum of Understanding (MOU) between the two agencies to strengthen the workforce focused on women's health research.

AMP® AIM. The Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Diseases (AMP® AIM) program is a collaborative effort between NIH, FNIH, pharmaceutical companies, and non-profit organizations to study the cellular and molecular interactions and pathways that lead to inflammation and autoimmune/immune-mediated diseases. The AMP AIM Team Science Leadership Scholars Program (LSP) further supports investigators to be leaders in women's health research, building on an inaugural cohort of sex scholars with a second cohort of four scholars has been announced.

Re-entry, Re-integration, Retraining (RRR) Supplements Administrative supplements to existing NIH research grants are available to support individuals re-entering the workforce, who are in unsafe work environments due to unlawful harassment, or who wish to expand their skill sets. Over 100 individuals across 23 ICs have been supported (2013-2024). In 2025, program participants reported successful re-entry into the scientific workforce, high levels of job satisfaction and overall wellbeing., and the critical contribution of the program to their career progression.

Research Continuity and Retention Supplements. The ORWH-led research continuity supplement program for first-time RPG or K awardees has supported over 600 early career investigators (K) and first-time research project grant (RPG) investigators across 23 ICs from 2020-2024. These supported investigators, who experienced a qualifying life event like birth of a child or while caregiving, went on to outperform their peers in obtaining subsequent research funding.

DEBUT: Innovative Technologies for Women's Health. ORWH collaborated with the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and VentureWell on the Design by Biomedical Undergraduate Teams (DEBUT) Challenge to develop innovative technology solutions addressing unmet healthcare needs. The 2025 DEBUT Challenge had a record number of participants with 123 teams representing 534 students from 67 universities across 24 U.S. states. ORWH collaborated with NIBIB to sponsor a $15,000 prize for an undergraduate team from Clemson University, for their first of its kind technology solution, *The LidoSound*, that addresses pain and cramping during the insertion procedure for intrauterine devices (IUDs). The 2026 DEBUT Challenge is open until June 5, 2026.

Other Program Updates. ORWH is leading a Pathways to Prevention Workshop: Advancing Research to Improve Health during the Menopausal Transition on April 15-17, 2026. ORWH is also preparing to launch the COMpetency in Menopause & Integrated Therapy (COMMIT) Challenge to identify, amplify,

and reward curricula that comprehensively address the menopausal transition within U.S. health education programs.

Military Women's Health Webinar Series. Women in the military represent a force larger than the entire U.S. Navy. ORWH continues to collaborate with military colleagues on ORWH's Women's Health Webinar Series, a monthly exploration of research topics relevant to military and women's health. Over 1500 individuals spanning different regions and sectors have participated to date. Upcoming webinars are scheduled for the second Thursday of each month. Past webinars are available on the Uniformed Services University (USU) YouTube channel.

NIH Women's Health Research Roundtables. ORWH continues to offer the Women's Health Research Roundtable Series to bring together multisector perspectives on issues impacting women's health.

E-Learning Course. ORWH will expand its e-learning resources to include "Chronic Conditions in Women: A Practical Guide for Healthcare Providers and Patients." The course will focus on major chronic conditions affecting women, including cardiovascular disease (CVD), diabetes, chronic pain, and autoimmune diseases, among others.

NIH Inclusion Policy Resources and Update. NIH recently updated its Inclusion Policy under NOT-OD-25-131 to align with Executive Order 14168. This does not fundamentally change the policy framework, but reinforces expectations around rigorous inclusion, transparent enrollment reporting, and scientifically justified study design. The NIH Inclusion Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research was also updated to reflect the revised policy. Additionally, ORWH collaborated with the National Center for Advancing Translational Sciences (NCATS) to expand the NIH Trial Innovation Network (TIN) Toolbox for Clinical and Translational Science Award (CTSAs) recipients across the country with tools for study design, recruitment, retention, and informed consent, including the revised NIH Inclusion Outreach Toolkit.

Budget. Dr. Clayton shared a slide depicting ORWH's annual funding history, 1991-2026. After a steady increase in funding in the early years, ORWH experienced 20 years of a relatively flat budget. In FY 2026, Congress appropriated an additional $30 million, bringing the total ORWH budget to $106.48 million, compared to $76.48 million in FY 2025.

Extramural Grant Award Investments. In FY 2025, ORWH made a total investment of $54,230,732 in 185 projects, in collaboration with co-funding ICOs. Twenty-two projects that are part of the BIRCWH program received $14,585,674, or just over one-quarter (26.9%) of ORWH's extramural budget, with significant funding from NIAMS and co-funding from five other ICOs. Nine SCORE projects received $9,376,587 (17.3% of extramural spending) with five co-funding ICOs. Twenty-eight chronic disease awards totaling $7,643,402 (14.1%) were made with co-funding from ten ICOs. OADR-ORWH funded 22 projects at $5,249,500 (9.7%, eight co-funding ICOs). Other expenditures included Sex Differences R01 and Administrative Supplements for $3,845,294 (7.1%, 17 projects, four co-funders) and career programs for $2,514,113 (4.6%, 34 projects, nine co-funding ICOs). Finally, $11,027,162 (20.3%, 45 projects) with 15 ICOs on co-funded projects. In total, ORWH partnered with 21 of the 27 ICOs, with the National Heart, Lung, and Blood Institute (NHLBI) receiving the greatest amount of non-BIRCWH ORWH funding.

Upcoming Events. Dr. Clayton highlighted the following upcoming ORWH events: Pathways to Prevention (P2P) Program Workshop: Advancing Research to Improve Health during the Menopausal Transition (April 15-17), Updates on OADR-ORWH (April 23), 10th Anniversary Vivian W. Pinn

Symposium—From Gaps to Gateways: Advancing Research on Chronic Conditions in Women (May 11), 2026 NIH Sleep and Health of Women (SHOW) Conference (October 16), 65th ACRWH meeting (October 20), SCORE 2026 Annual Meeting (December 2-3), BIRCWH Annual Meeting (December 4), and NIH Women's Health Research Roundtables and Military Women's Health Webinars (ongoing).

Dr. Clayton announced a new DPCPSI/ORWH Research Opportunity Announcement titled Initiative on Computational Modeling of Hormone Homeostasis, which will advance the development of in silico computational approaches that model and simulate human hormone homeostasis, with an emphasis on applicability to sex-specific efficacy and toxicity evaluation of therapeutics. Applicants must submit a Letter of Intent by April 24, 2026.

NHLBI: Advancing Shared Priorities for Improving Women's Health Across the Lifecourse

Dr. Clayton introduced David C. Goff, M.D., Ph.D., Acting Director of the National Heart, Lung, and Blood Institute (NHLBI) who presented the NHLBI Director's update. Dr. Goff introduced Gina Wei, M.D., Ph.D., who is NHLBI's Senior Scientific Advisor for Women's Health. He explained that NHLBI refreshed its strategic vision in 2025; women's health is one of five cross-cutting themes. NHLBI began 76 years ago, around the time of the Framingham Heart Study, in which half the research participants were women. Since then, NHLBI has launched multiple studies on women's health, including the Women's Health Initiative, Chronic Hypertension and Pregnancy Trial (CHAP), and NuMoM2B Heart Health Study, among others. NHLBI has actively collaborated with ORWH over the years, including co-funding of the BIRCWH and SCORE programs.

Women and CVD. Despite improvements in women's health, American women face lower life expectancy and higher rates of cardiovascular disease (CVD) mortality. This is also true for American men, as the U.S. CVD rates are higher than in peer countries. The outlook for the future is not bright: an American Heart Association study projects that women's CVD rates are set to climb across all ages and demographics over the next 30 years. NHLBI is advancing a multi-level approach to optimize women's health across the lifespan:

Children and Adolescents. Researchers are projecting an increase in cardiometabolic risks (especially obesity) among girls aged 2-19 years, with distinct racial/ethnic patterns, that will drive a lifelong disease burden. Increases in obesity are projected to rise among Black girls and adolescents to as high as 40% by 2050, and to about 35% among Hispanic girls/adolescents. Poor diet and inadequate physical activity are projected to continue across all demographic groups.

NHLBI has been testing targeted approaches to obesity in girls and adolescents since the late 1980s. Its research shows that weight gain in girls begins around puberty and is especially challenging for Black girls. The Girls Health Enrichment Multi-Site Study (GEMS) conducted from 1999-2008 showed that interventions could have an impact on diet and cholesterol, but not on weight. Similarly, the Trial on Activity in Adolescent Girls (TAAG) (2000-2008) and the Pathways Study (1993-2004) had some impact on physical activity levels, but little impact on weight. The Healthy Communities Study (2010-2015) found that the most successful programs to reduce weight in adolescent girls were those that embedded a comprehensive approach within a community. More favorable results were reported in a clinical trial that found that family-based treatment in primary care setting can improve weight outcomes for all family members; however, weight gain subsequently increased over time. Similarly, We Can! (Ways to Enhance Children's Activity and Nutrition), a public education campaign for children ages 8–13, focused on healthy weight through improved nutrition, increased physical activity, and reduced screen time. Nonetheless, more effective approaches need to be developed.

Young Adulthood. Suboptimal health in girls persists into young adulthood, affecting pregnancy and offspring. Among 18–20-year-olds, about 30% have two or more chronic conditions and over one-half have one. Hypertension (HTN), obesity, and diabetes carry into pregnancy, increasing risk of adverse pregnancy and maternal outcomes. Black women are at particularly high risk for maternal morbidity and mortality (MMM). NHLBI-supported research is elucidating the mechanisms and predictors of adverse pregnancy outcomes. For example, polygenic risk scores calculated from NuMoms2B data revealed multiple genetic factors that increase the risk for preeclampsia, which could help researchers develop therapeutic drugs to target specific gene changes and help clinicians prescribe treatments for high-risk patients, e.g., a low-dose aspirin regimen has been shown to reduce about 50% of preeclampsia.

NHLBI-supported research has demonstrated that dietary patterns can be leveraged to improve maternal outcomes. For example, women who followed the DASH diet developed by NHLBI had better glycemic control during pregnancy than those who did not. Other NHLBI-supported research has focused on the effectiveness of interventions embedded in the community, including ENRICH: Early Intervention to Promote Cardiovascular Health of Mothers and Children (co-funded with ORWH), focusing on home visits to deliver education on parenting and lifestyle behaviors to new mothers and Community-Implementation Program (CIP)s: an NHLBI-specific Maternal Health-CIP to increase preeclampsia screening and low-dose aspirin use, and an NIH-wide IMPROVE-CIP to implement a hypertension care framework across 19 North Carolina clinics. The CHAP trial's treatment of mild chronic hypertension reduced adverse outcomes (37% to 30%), leading the American College of Obstetricians and Gynecologists (ACOG) to recommend treating to <140/90 mm Hg. Proven interventions to improve maternal health, such as this, are advancing using NIH's Community Engagement Alliance (CEAL) platform, which is launching The **C**hronic **H**ypertension **A**nd **P**regnancy **– G**uideline **U**tilization **I**n **D**ifferent **E**nvironments and **S**ettings (CHAP-GUIDES) program to assess how well the updated CHAP-informed guidelines from ACOG for chronic HTN in pregnancy are being implemented.

Middle-aged and Older Women. Women 45+ will bear the greatest burden of cardiovascular risk factors and disease over the next 30 years, with projected increases in cholesterol and obesity and stable hypertension rates. The menopausal transition is associated with an increased risk for adverse CVD outcomes. For example, premature and early menopause substantially increases the risk of a first CVD event before age 60; arterial stiffness accelerates within one year of menopause. Similarly, there are changes in women's gut microbiome and estrobolome during menopause that increase CVD risk.

NHLBI is seeking to help define the links between activity, intensity, and health for older women in the Women's Health Initiative. The WHI Objective Physical Activity and Cardiovascular Health (OPACH) Study found that light physical activity could reduce the risk of both coronary heart disease and CVD. This finding led to the WHI Strong and Healthy Study (WHISH), an ongoing physical activity Intervention trial for CVD prevention in ~50,000 older women to determine if light physical activity can lead to better health outcomes. NHLBI has recently launched an AI-Enabled Precision Health Initiative that links a computational biology strategy with behavior, environmental, -omics, and imaging data. Modular programs within the Initiative will include one on women's health during time of transition (e.g., pregnancy, menopause).

Discussion. Key discussion points included the need for continued work to reduce smoking among women, especially those in rural areas; the need for informed policy to guide decisions about deploying GLP-1 drugs to combat obesity at the population level; and future directions in precision medicine to support heart health, e.g., targeted therapeutics to control cholesterol and hypertension.

Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) Update

Dr. Hindorff introduced Nahida Chakhtoura, M.D., Branch Chief of the Pregnancy and Perinatology Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Dr. Chakhtoura began her presentation by reviewing data that demonstrate that the U.S. consistently underperforms its peers in MMM. She noted that 84% of pregnancy-related deaths are preventable. More than 2.3 million women live in maternity care deserts in the U.S. One in ten births occur in these deserts, but rates are higher in rural areas and among American Indian/ Alaska Native (AI/AN) women. Leading causes of pregnancy-related death include mental health conditions (23%); excessive bleeding (hemorrhage) (14%); cardiac and coronary conditions (13%); infection (9%); thrombotic embolism (blood clot) (9%); cardiomyopathy (9%); and hypertensive disorders of pregnancy (7%).

IMPROVE is an NIH-wide effort, co-led by NICHD, the National Institute of Nursing Research (NINR), and ORWH, to reduce preventable causes of MMM; address disparities in maternal health outcomes; expand implementation of evidence-based maternal health care practice before, during, and after pregnancy; build research capacity in community-based organizations; promote access to maternal health care with innovative technology; and enable real-world research with electronic health record standards. IMPROVE programs include Connectathon to develop electronic health record standards for pregnancy to enable real-world research; dissemination and implementation science to promote policy and practice interventions across pre-pregnancy, prenatal, and postpartum care; RADx Tech for Maternal Health to develop technology-based home or point-of-care diagnostics to extend care to maternal care deserts; Connecting the Community for Maternal Health Challenge to build effective research infrastructure and capacity in communities; Community Implementation Program to support community partnerships to enable adoption and integration of interventions that are effective into community settings; and Centers of Excellence to develop, implement, and evaluate community-tailored interventions to address health disparities in maternal health.

RADx® Tech for Maternal Health Challenge. To address the problem of severe maternal morbidity (SMM) in maternity care deserts, IMPROVE leveraged NIH's Rapid Acceleration of Diagnostics Technology (RADx Tech) "innovation funnel" to speed innovation in point-of-care and home-based diagnostic technologies that can predict or diagnose risk for SMM/MM and empower postpartum individuals with actionable health information on when additional care is needed. Six Grand Prize winners were announced, and three have received FDA clearance, including a wireless wrist monitor to evaluate cardiovascular health, a rapid, point-of-care diagnostic for postpartum hemorrhage, and a remote monitoring system for home or point-of-care settings.

Capacity Building in the Community. IMPROVE's Connecting the Community for Maternal Health Challenge sought to encourage community-based and advocacy organizations to develop research infrastructure and capabilities by offering a total prize of ~$3 million along with non-monetary incentives, such as mentoring and proposal writing assistance. Final winners were announced in September 2024. Nurturely of Eugene, Oregon, received first place for a project to test the effect of an infant carrying intervention on lactation and postpartum depression among Black parents. Central Jersey Family Health Consortium of North Brunswick, New Jersey, received second place for its project to develop a data-driven tool to identify maternal risk factors and pregnancy outcomes. Six projects tied for third place.

Implementation Science to Improve Maternal Health. The IMPROVE Community Implementation Program (IMPROVE-CIP) supports the dissemination of evidence-based maternal health interventions

across four sites, including programs focused on doula-supported care, kinship-based support in the Ho-Chunk (Winnebago) Tribe, expanded use of low-dose aspirin and hypertension management, and group prenatal care for people with opioid use disorder.

Centers of Excellence. The IMPROVE Maternal Health Research Centers of Excellence aim to reduce maternal morbidity and preventable mortality by partnering with communities affiliated with 12 Research Centers across the country, supported by a Data and Innovation Hub and an Implementation Science Hub. The Research Centers address multiple conditions (including anemia, preeclampsia, hypertension, gestational diabetes, postpartum hemorrhage, substance use and mental health) across gestational timepoints and diverse populations. They address novel strategies such as community health workers, incorporating doulas into health systems, home visiting programs, applying AI and machine learning to electronic medical records, and integrated care models. A robust training component expands the future workforce, including simulation training for emergency room providers to provide evidence-based care to mothers with complications.

Key accomplishments of the IMPROVE Maternal Health Data Innovation and Coordination Hub include working with NLM to develop and share of CDEs for maternal health research to create standardized language across the field. The AMETHIST program at the University of Pennsylvania provides training to build national capacity in implementation science for maternal health to reduce the evidence-to-implementation cycle and train the next generation of scientists.

FY 2025 Activities. In collaboration with the National Center for Complementary and Integrative Health (NCCIH), ORWH and other ICOs, IMPROVE supported Advancing the Science of Complementary and Integrative Health Approaches to Improve Maternal Health Outcomes(R01 Clinical Trial Required) (RFA-AT-25-002) to expand complementary and integrative health investigators within IMPROVE. A Research Opportunity Announcement (ROA) to evaluate CHAPGuides (Chronic Hypertension And Pregnancy-Guideline Utilization In Different Environments and Settings) will assess implementation of ACOG guidelines for chronic hypertension in pregnancy across different healthcare settings and identify differences and gaps in care delivery and outcomes.

Discussion. IMPROVE does not include telemedicine, but there has been some telehealth consulting between the Centers of Excellence and the communities they serve.

NIH Inclusion Report

Juliane Caviston, Ph.D., Health Science Policy Analyst, ORWH, introduced Dawn Corbett, M.P.H., NIH Inclusion Policy Officer, Office of Policy for Extramural Research Administration, Office of Extramural Research (OER), NIH, who updated ACRWH members on NIH's inclusion results for FY 2025. Ms. Corbett reviewed key milestones in NIH's policies for inclusion in research: women (1986), women and racial/ethnic minorities (1994), children (1998), individuals of all ages (2019), and the July 17, 2025, revision that updates terminology to "sex" and removes "gender," effective August 16, 2025. Current NIH policy requires inclusion of women and racial/ethnic minorities in all NIH-funded clinical research unless justified otherwise, mandates reporting and analysis of these groups in NIH-defined Phase III trials in ClinicalTrials.gov, and requires inclusion across the lifespan unless scientifically or ethically inappropriate. Under the Simplified Review Framework (for due dates after January 25, 2025), inclusion and Phase III design requirements are now evaluated within Factor 2 (Rigor and Feasibility) to underscore their scientific importance. Ms. Corbett's office provides resources, such as tip sheets and case studies, to help investigators meet inclusion requirements. She also noted new federal standards

from OMB requiring combined race/ethnicity reporting, adding Middle Eastern or North African (MENA) as a minimum category, and expanding detailed subgroup reporting.

FY 2025: Women. **I**n FY 2025, there were 11,048,927 total participants in NIH-funded clinical research. This total was lower than in the two previous years, largely due to the end of large digital health studies. Most participants (8,202,424) were in the U.S., and there were nine times more female-only participants (821,337) than men-only participants (89,251). There were fewer overall participants (720,577) in NIH-Defined Phase 3 clinical trials and almost one-half (46%) were located outside the U.S. Female-only participants (175,002) significantly outnumbered male-only participants (12,250). Overall, women make up more than one-half of all participants in clinical research (58%) and clinical trials (63%) funded by NIH.

FY 2025: Racial/Ethnic Minorities. Members of racial/ethnic minorities comprised 34% of clinical research participants in FY 2025. White (56.2%) was the racial category most frequently represented, followed by Black/African American (14.0%). The race of about one in five participants (20.7%) was unknown/not reported. Non-Hispanic participants (72%) outnumbered Hispanic participants (13%). In NIH-Defined Phase 3 clinical trials in FY 2025, 39% of participants were members of a racial/ethnic minority. Whites represented 64.6% of clinical trial participants; Black/African Americans made up 19.2%. Four out of five clinical trial participants (81%) were non-Hispanic, while 14% identified as Hispanic.

FY 2025: Age. Over half of participants (57%) in NIH-funded clinical research in FY 2025 were adults aged 18-64. Children and adolescents under 18 constituted 17% of clinical research participants, while older adults 65+ represented 8%. The number of those whose age was unknown dropped considerably in FY 2025 compared to the two preceding years.

Open Discussion

Dr. Clayton moderated an open discussion among ACRWH members. Key points included:

- To ORWH's knowledge, NIH is not currently conducting research to identify why the United States underperforms peer nations in MMM. Previous studies conducted by the Fogarty Center sought to better understand the context in which other countries address this issue.
- NHLBI's focus on whole-person health and women's health across the lifespan is much appreciated.
- Dissemination of ORWH's e-learning courses has become more challenging as NIH communication is now more centralized. Where possible, ORWH continues to share information and resources on its website and may consider becoming more proactive about informing professional associations and universities about the availability of its courses. ORWH welcomes suggestions for creating more robust dissemination of these resources from ACRWH members.
- Smoking remains the most preventable cause of death among women in the United States, especially among rural and older women. Smoking is less prevalent among youth, while vaping is becoming more popular. Overall, combustible tobacco poses the greatest threat to health.
- ORWH is expecting to expand BIRCWH this year by supporting more scholars and more states. It is also considering the creation of regional hubs to expand networking across sites.
- Regarding inclusion data, one suggestion is to expand age categories from 65 and older to 65-80 and 80+. Because the data is individual, it can be categorized in multiple ways.
- Organoid research is currently limited to the liver, lung, and intestines, but could be expanded in the future to include other organs, such as the breast and uterus that touch directly on women's health. Some work in this area has begun. Future ACRWH meeting topics should revisit this topic.

- NIH has announced that the number of Notices of Funding Opportunities (NOFOs) will be reduced across the government. Although ORWH supported relatively few NOFOs, it is working with the Office of Extramural Research (OER) and co-funding ICs to ensure that successful ORWH programs remain available to applicants. There is a shift toward investigator-initiated research; the Highlighted Topics can help applicants search for the right opportunities, as can the ICO profiles on the same web pages. Parent funding opportunities can be used to apply for topics in women's health. Whether it's an ORWH-lead or not, women's health will remain a priority for funding.

Oral Comments

Dr. Hindorff acknowledged written comments from the Science Advancement and Outreach Division of the People for the Ethical Treatment of Animals (PETA). She introduced Jessica Kopew, Ph.D., who provided an oral comment on behalf of the Physicians Committee on Responsible Medicine. Dr. Kopew encouraged ORWH to embrace the NIH-wide directive to prioritize human-based research in programs, funding opportunities, and funding decisions, in lieu of animal research.

ORWH 35th Anniversary Commemoration

Welcome and Introduction

Regine Douthard, M.D., M.P.H., Senior Medical Officer at ORWH, and Co-Chair of the 35th Anniversary Planning Committee, welcomed participants to ORWH's 35th anniversary observation on "Advancing the Health of Women through Research and Innovation," and gave a brief overview of the keynote speaker and scientific panel. Dr. Clayton reviewed ORWH's history to show how its mission remains even more relevant today: 1) All women receive evidence-based disease prevention and treatment tailored to their own unique needs, circumstances, and goals; 2) Women are appropriately represented in clinical research populations; 3) Sex is considered at every stage of biomedical research and health care delivery; and 4) All women in scientific career fields are empowered to reach their full potential.

Small Office, Big Impact. A recent analysis of the past 25 years (1999-2024) showed that ORWH has co-funded and partnered with every IC, resulting in 2,094 grants that led to 73,386 publications, which supported 28,467 patent applications and 193 drug licenses. These include drugs that treat conditions that impact women disproportionately or differently, demonstrating direct benefit to patients.

Key Milestones. Key milestones in women's health at NIH include the 1986 NIH Policy on Inclusion of Women in Study Populations; the establishment of ORWH, ACRWH and the Coordinating Committee on Research on Women's Health (CCRWH) as part of the NIH Revitalization Act of 1993; the 1993 expansion of the NIH Inclusion Policy to ensure that women are included in NIH-funded clinical research; the 21st Century Cures Act, which strengthened ORWH's role through annual IC Director consultations with ORWH and the inclusion of women's health priorities in their strategic plans, and the Inclusion Across the Lifespan policy; the 2016 SABV implementation; the 2019 NIH guideline update requiring inclusion of all age groups in NIH-funded clinical research; and the 2023 establishment of OADR-ORWH.

Signature Programs. ORWH has shaped the landscape of women's health research through several signature programs, including BIRCWH (2000); SCORE (2002); NIH's first R01 funding opportunity on sex differences (2019); expansion of the IDeA State Program (2019); and chronic diseases in women (2023).

Amplifying Impact. ORWH serves as a force multiplier by directing strategic focus, identifying knowledge gaps, and expanding the reach of women's health research nationwide. These efforts include

advancing NIH's commitment to rigorous, gold standard science through SABV integration in research; empowering researchers, clinicians, and the public via DiscoverWHR; strategically prioritizing NIH resources through ORWH's first-ever participation in the Small Business SBIR/STTR Omnibus funding opportunity; and investing in New Approach Methodologies (NAMs) to ensure human-based approaches benefit women and incorporate SABV for rigor and reproducibility.

Strengthening the Research Community. Over 35 years, ORWH has led the research community by disseminating trusted information to empower better health for women by developing toolkits to improve recruitment of women, e-courses for patients and providers, and the *In Focus* newsletters; mobilizing national dialogue to advance women's health research via high-impact webinars and research roundtables with partners like the Uniformed Services University to spotlight military women's health and drive cross-sector collaboration; catalyzed innovative interdisciplinary intramural research; and advancing national research priorities in midlife health and menopause through the next Pathways to Prevention program.

Advancing and Sustaining Careers in Biomedical Research. A core part of ORWH's mission is advancing and sustaining the women's health research workforce broadly, and women in science, technology, engineering, and medicine (STEM) more specifically. Through programs like BIRCWH, ORWH has built interdisciplinary pathways for investigators focused on women's health, helping launch independent careers and sustain a vibrant research community. One of ORWH's most important contributions has been addressing real-world barriers to staying in science by spearheading supplements for re-entry, retraining, and continuity during critical life events like childbirth, caregiving, or illness, supporting over 850 researchers to date. Beyond its programs, ORWH has garnered support from IC colleagues to embed workforce considerations into NIH programs and processes, contributing to national discussions on caregiving and STEM careers.

The Vivian W. Pinn Symposium. This annual event honors the founding Director of ORWH, Dr. Vivian W. Pinn, and is held every year during National Women's Health Week. The 10th Anniversary symposium will be on May 11, 2026, and will focus on chronic conditions in women.

Advancing Rigor and Relevance. As ORWH marks its 35th anniversary, it is also marking a fundamental emphasis on rigor and relevance in biomedical research, especially the implementation of SABV.

Opening Remarks from NIH Leadership

Dr. Clayton introduced Nicole C. Kleinstreuer, Ph.D., NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives, and Director of the Division of Program Coordination, Planning, and Strategic Initiatives, (DPCPSI), Office of the Director, NIH. ORWH is one of several Offices within DPCPSI. Dr. Kleinstreuer noted that ORWH is a relatively small office with an outsized impact, serving as a catalyst for coordination, innovation, and strategic investment. Women's health research is a field that cuts across the missions of every IC. As a result, progress in women's health depends on effective agency-wide collaboration, exemplifying DPCPSI's mission to help NIH identify emerging priorities, align resources across ICs, and launch flagship initiatives through coordinated leadership. ORWH is an exemplar of this mission.

Dr. Kleinstreuer highlighted key examples of how ORWH's coordination drives meaningful scientific progress: 1) advancing and codifying SABV through cross-cutting initiatives and policy leadership, aligning with current priorities around rigor, reproducibility, and robustness of science; 2) leading OADR-ORWH to coordinate, develop, and evaluate NIH-wide opportunities to better understand complex

chronic conditions; 3) accelerating innovation in implementation science to deliver scalable, on-the-ground solutions to improve women's well-being; 4) building and sustaining a strong pipeline of investigators through programs such as BIRCWH; 5) ensuring research findings translate into real-world impact by supporting both implementation science-based approaches and evidence-based practices to inform current programs and policies; 6) driving scientific innovation through new approach methodologies (NAMs), including a new program on computational modeling of hormone homeostasis to understand sex specific effects in therapeutics.

On behalf of Dr. Bhattacharya and other senior leadership across NIH and HHS, Dr. Kleinstreuer recognized the ACRWH's tireless efforts to promote women's health research and thanked its members for their contributions. She congratulated ORWH on its 35th year anniversary and its accomplishments over the years.

Keynote Presentation: Advancing Women's Health: ORWH's Role in Transforming Research Gaps into Breakthroughs

Dr. Clayton introduced Chloe E. Bird, Ph.D., FAAAS, FAAHB, Director, Center for Health Equity Research at Tufts Medical Center, and Sara Murray Jordan Professor of Medicine, Tufts University School of Medicine. Dr. Bird began with a brief history on sex and health research before examining the current evidence base on women's health and sex differences in care and whether studying them is cost prohibitive. She then addressed future directions, exploring how to set data-informed priorities and who to stand to benefit from closing existing gaps.

A Brief History of Women and Health Research. In the 1970s, a review of the scientific, ethical, and legal issues affecting the inclusion of women in clinical trials found that research findings often differed by sex were based on a 70kg male norm, and that, following the thalidomide disaster, a 1977 FDA policy recommended excluding women of childbearing potential from Phase I and early Phase II trials. In 1992, Vivian W. Pinn, M.D., ORWH's Founding Director, commissioned the Institute of Medicine (IOM) to assess Ethical and Legal Issues of Including Women in Clinical Studies leading to the 1993 NIH Revitalization Act requiring women's inclusion in clinical trials.

In 1999, with ORWH support, the IOM convened the Committee on Understanding the Biology of Sex and Gender Differences; its 2021 report, Exploring the Biological Contributions to Human Health: Does Sex Matter?, called for research on sex as a biological variable and recommended distinguishing between biological and sociocultural factors. In 2023, Congress mandated an evaluation of NIH women's health research funding, prompting ORWH to task the National Academies to assess the state of women's health research at NIH, identify critical knowledge gaps, assess the level of funding for women's health research, and more. The resulting report, A New Vision for Women's Health Research, reported that over the previous 15 years, 8.8% of NIH funding went to studies answering questions on women's health and outlined a range of investments, restructuring, and policy changes needed to close gaps in the evidence base.

The Present. The clinical evidence base remains disproportionately built on studies of men's health. Without systematically testing for sex differences, science will continue to produce only "good-enough" medicine for women based on flawed assumptions of generalizability – contributing to poorer outcomes, greater disease burden, and underfunding conditions that disproportionately affect women. ORWH has been instrumental in advancing research that disaggregates data and targets studies of sex-specific mechanisms. Nevertheless, despite 35 years of progress, women remain at higher risk for chronic illness, co-occurring disorders, and MMM.

Assessing the Return on Investment (ROI) for Investing in Women's Health. The gaps in the evidence base carry a societal cost in the trillions of dollars yet simultaneously represent a tremendous opportunity for high-impact investment. A 2020 RAND study funded by Women's Health Access Matters (WHAM), Research for Women's Health: Modeling for Societal Impact, modeled the societal impact of doubling one year of women's health research funding, finding significant improvements in health outcomes 30 years into the future, along with substantial cost savings. Using conservative assumptions, RAND's model measured impacts including increased years of life, fewer disease years, and greater caregiver productivity. These impacts can be quantified in terms of costs, such as nursing homes and other health care costs. The model's assumptions were generally conservative; yet many of the results were striking. For Alzheimer's Disease and related dementias, the study found that doubling one-time investment leads to ~4,000 more years of life and ~6,000 fewer years with disease. It also leads to improved quality of life, as measured by ~3,600 fewer years in nursing homes, and nearly 16,000 more quality-adjusted years of life. Fewer nursing home years produced $369 million savings in nursing home costs and $11 million more in other health care costs, as well as a $4 million net impact on caregiver productivity. And the ROI is impressive: An increase of $288 million led to savings of $933 million, a 224% return on investment. The ROI for other diseases was even higher, e.g., a $20 million investment in research on coronary heart disease in women led to $1.9 billion in savings, a 9,500% ROI, while a $6 million investment in rheumatoid arthritis led to $10.5 billion in savings, a 174,000% return.

The model concluded that investment in women's health research produces substantial healthcare cost savings even under conservative health improvement assumptions, and that this modeling approach can and should inform future funding and policy decisions.

The Future. Advancing the next scientific revolution in women's health requires scientists to recognize and systematically address costly knowledge gaps where the existing paradigm is insufficient. The 2025 National Academies of Science, Engineering, and Medicine (NASEM), A New Vision for Women's Health Research, outlines the needed funding and policies to drive this progress. To advance that effort, Dr. Bird and her postdoc, Hamad Al-Ibrahim, have proposed Evidence4All, a data-driven agenda to identify evidence gaps using systematic reviews and data science, map where evidence is thin for women and on sex differences, demonstrate the impact of interventions for prevention and treatment, and create data-informed roadmaps to guide funding and research. An interactive dashboard tracking the intensity of evidence gaps by health condition would support research prioritization, facilitate transparent dissemination of findings to funders, researchers, and policymakers, and offer a scalable model for other disease domains.

Dr. Bird concluded by emphasizing that women's health matters. The current healthcare approach is insufficient, leading to serious consequences for individual lives, public health, and the economy.

Discussion. In response to a question about whether more publications are disaggregating data by sex since the introduction of SABV in 2016, Dr. Bird commented that only half of the studies in ClinicalTrials.gov include disaggregated data. There remains a long way to go.

Panel: Cutting Edge Advances in Women's Health

Welcome and Introduction

Rajeev K. Agarwal, Ph.D., ORWH SCORE Program Officer and Co-Chair of the 35th Anniversary Planning Committee, welcomed participants and introduced Ayush Giri, Ph.D., ACRWH member and Associate Professor/Associate Director of the Center for Research on Women's Health at Vanderbilt University Medical Center, who moderated the panel presentations. Dr. Giri introduced the three panelists:

Mariana Kaplan, M.D., NIH Distinguished Investigator, Chief of the Systemic Autoimmunity Branch, and Deputy Scientific Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); Lida Chatzi, M.D., Ph.D., Professor of Population and Public Health Sciences, Director of the USC Center on Translational Exposomics Research and the USC Superfund Research Program, as well as Deputy Director of the Southern California Environmental Health Sciences Center at the University of Southern California, Keck School of Medicine; and Sheida Nabavi, Ph.D., Associate Professor, Computational Genomics and Biomedical Imaging Lab (CompGBI), School of Computing and Engineering, University of Connecticut.

Rewiring Immunity: The Metabolic Control of Autoimmune and Chronic Inflammatory Diseases

Dr. Kaplan provided an overview of autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) – which progress through stages from genetic and environmental susceptibility to a preclinical phase marked by aberrant immune responses and subclinical autoantibody formation, to clinical disease characterized by acute flares, remission, and potential chronic complications including CVD, bone problems, fibrosis, and/or cancer. Dr. Kaplan noted autoimmune diseases are disproportionately prevalent in women with well documented immune responses across the lifespan. SLE, for example, primarily affects women of childbearing age. While SLE involves chronic immune activation and loss of tolerance, immune cell function is not simply binary – it is governed by the metabolic pathways that fuel it. Understanding the relationship between immunity and metabolism, known as immunometabolism, is key to understanding disease mechanisms.

Immunometabolism. Immunometabolism is the intersection of metabolic programs inside immune cells that fundamentally shape their function. Normally, immune cells switch between glycolysis and oxidative phosphorylation to balance rapid defense vs. sustained regulation. In autoimmunity, however, these pathways become pathologically reprogrammed: immune cells become overly dependent on glycolysis, fueling persistent effector T and B cell activation; mitochondrial function declines, generating excess reactive oxygen species (ROS) and energy imbalance that amplifies inflammation; and lipid metabolism defects alter membrane structure and immune receptor signaling. Key metabolic regulators like mTOR and AMPK become dysregulated, tipping the balance toward inflammation rather than immune restraint. Importantly, regulatory T cells lose metabolic fitness, impairing their suppressive function and contributing to loss of tolerance. Thus, in autoimmunity, metabolic pathways don't just support immune response, they become reprogrammed in ways that sustain inflammation and weaken regulation.

Translational Implications. Altered immunometabolism affects immune cell plasticity, treatment response, and tissue repair, potentially serving as both a biomarker and therapeutic target. There are existing therapeutic agents targeting immunometabolism, such as metformin, mTOR inhibitors, and antioxidants. Emerging targets include NAD^+/Sirtuins, glycolysis blockers, and mitochondrial modulators. The role of PPAR-gamma agonists has also been tested. However, longer and larger studies are needed.

Immunometabolism in Menopause. The estrogen decline in menopause alters the immune–metabolic balance. Inflammation increases, due to a shift toward pro-inflammatory cytokines ("inflammaging"); mitochondrial efficiency drops; women experience a redistribution of adipose tissue due to altered lipid metabolism and insulin resistance; and immune cells favor glycolysis over oxidative phosphorylation, driving chronic low-grade inflammation. These factors contribute to autoimmunity, osteoporosis, metabolic syndrome, and increased CVD risk.

Future Directions. Future directions in immunometabolism research include integrating multi-omic and metabolic profiling into clinical trials, developing sex-specific immunometabolic diagnostics, and applying AI and machine learning to classify metabolic immune endotypes.

Summary and Conclusion. Dr. Kaplan summarized the key points in her presentation: 1) Immune metabolism is a modifiable layer of immune regulation; 2) Aberrant immunometabolism contributes to autoimmunity and inflammation; 3) Sex-based differences in metabolism may help explain disease bias and outcomes; and 4) Therapeutic metabolic reprogramming is a promising frontier.

Assessing the Impact of PFAS and Microplastics Exposures on Women's Health, Reproductive Health, and Across the Life Span

Dr. Chatzi explained that many common health conditions, including metabolic disorders, cardiovascular disease, and reproductive health outcomes, are increasingly linked to environmental factors.

PFAS. PFAS, a class of over 10,000 synthetic "forever chemicals," are widely encountered in contaminated drinking water, nonstick cookware, waterproof textiles and clothing, food packaging, and personal care products. Their impact on women's health is pronounced, with exposure associated with a range of endocrine and metabolic outcomes across the life course. During reproductive years, PFAS exposures have been linked to reduced ovarian reserve, delayed conception, and low birth weight and preterm birth. In childhood and adolescence, associations have been observed with metabolic dysfunction and dyslipidemia, and early markers of insulin resistance. In adulthood, links extend to cardiovascular and neurodegenerative diseases, as well as cancer.

Prenatal PFAS Exposure. Prenatal PFAS exposure has been consistently associated with increased risk for childhood metabolic syndrome, microbiome and metabolic alterations, and childhood obesity. Critically, hundreds of industrial chemicals and pollutants are known to cross the placenta, exposing the fetus during critical stages of development as shown through an analysis from the ECHO project.

Metabolic Outcomes in Childhood and Adolescence. The metabolic effects of PFAS exposure persist beyond prenatal stages, with childhood and adolescence exposure linked to increased dyslipidemia and insulin resistance across multiple cohorts and ethnic populations, elevating risk for type 2 diabetes. A study by Jesse Goodrich, Ph.D., at Dr. Chatzi's center showed that youth PFAS exposure is associated with dysregulated glucose metabolism, with effects significantly stronger in girls and potentially driven by changes in B-cell function. Another study from Emily Beglarian, MPH, at Dr. Chatzi's center showed that PFAS exposure was associated with reduced bone mineral density in adolescence and young adulthood, especially among girls. Early bone deficits may increase the risk of osteoporosis later in life, particularly in women.

PFAS Health Outcomes in Adults. Adult PFAS exposure has been associated with metabolic disease, cardiovascular disease, liver injury, and liver cancer across multiple prospective studies. A recent study at Dr. Chatzi's center showed that high exposure to PFNA, a specific PFAS compound, is associated with increased risk of endometrial cancer. Higher exposure to other PFAS, such as PFDE and PFUA, has also been linked to melanoma.

*Gaps and Limitations in Current Knowledge***.** Key limitations persist in current PFAS research: exposure is typically measured at a single time point, failing to capture changes in exposure over time; animal models do not fully replicate human disease; and in vitro studies use only single cell types, limiting insight into complex biological systems. Current research does not adequately integrate data from in vitro, in vivo, and human studies, and the combined effects of PFAS mixtures remain poorly understood even though real-world exposures invariably involve mixtures.

To address these limitations, Dr. Chatzi's center has developed a translational, solution-oriented research framework linking population-level findings to mechanistic investigation. The approach pairs comprehensive longitudinal human studies with in vitro experiments using 3D organoids exposed to physiologically relevant PFAS doses, providing causal context and mechanistic interpretation. The overarching goals are to prevent PFAS-related liver disease and inform policy regulations and community-engaged interventions. In one experimental study, Dr. Chatzi and her colleagues used multi-donor 3D liver spheroids and scRNA-seq to study PFAS impact on liver metabolism, exposing the spheroids to PFHpA for seven days, and then analyzing the activation/inhibition of pathways that are part of the natural evolution of non-alcoholic fatty liver disease (NAFLD). They found that spheroids exposed to PFAS mixtures, which had shown a strong upregulation of gene expression and hepatotoxicity, exhibited a remarkable downregulation one week after PFAS removal, as well as a drastic reduction in cancer-related events and an increase in lipid and carbohydrate metabolic events. These findings suggest a likely normalization of hepatic functions.

Dr. Chatzi's center includes a Community Engagement Core that works closely with the community to bridge the gap between research and real-world application.

Clinical Action. The 2022 NASEM Guidance on PFAS Exposure, Testing, and Clinical Follow-up defines exposure thresholds to inform clinical decision-making and preventive strategies: moderate exposure warrants targeted screening(e.g., lipid monitoring, pregnancy-related risk assessment, and cancer screening), while higher exposure calls for more proactive monitoring including thyroid function , kidney and testicular cancer surveillance, and dyslipidemia prioritization.

Microplastics. In parallel with PFAS, micro- and nanoplastics are emerging as a significant threat to women's health. These particles have now been detected in human tissues, including the placenta, blood, and ovarian tissue, raising concerns about direct biological effects. They have broad effects spanning immune disruption, inflammation, oxidative stress, and organ-specific impacts in the liver, heart, and brain. However, human data remain limited, and studies in women and early life are urgently needed.

The Exposome Framework. Moving forward, advancing women's health will require a shift toward an exposome framework that captures the totality of environmental exposures across the life course. There is a need to integrate multi-omics approaches, develop biomarkers of exposure, and link these data to longitudinal cohort studies.

The Role of AI in Advancing Women's Health through Data Science and Innovation

Dr. Nabavi addressed how AI and data science are transforming women's health by addressing longstanding research and care gaps. AI's ability to learn complex patterns from large, heterogeneous datasets makes it well-suited for conditions like CVD, pregnancy complications, and menopause, which often present differently in women. AI can support personalized diagnosis even in under-resourced healthcare settings and enables continuous monitoring by integrating data from electronic health records (EHRs), imaging, and wearable devices. From a data science perspective, AI spans the full spectrum of biomedical data: medical imaging, genomics, clinical records, and wearable sensor data; its real power emerges when these modalities are integrated, so that scientists can model health holistically, and not in isolation.

Early Detection, Diagnosis, and Risk Prediction. AI has already shown impact in early detection of breast cancer, gynecologic cancers, CVD, endometriosis, and Polycystic Ovary Syndrome (PCOS), conditions frequently underdiagnosed in women. AI enables scalable screening, risk prediction, and decision support across imaging, genomics, and physiological signals. For example, recent work from Dr.

Nabavi's lab illustrates that comparing current and prior breast exams over time, mimicking how radiologists review multiple images over time, improves early detection and reduces unnecessary recalls and false positives. Integrating imaging with clinical and genomic data further allows AI to uncover biologically meaningful risk factors and disease trajectories. A critical principle throughout is that AI should augment, not replace, clinical expertise. Human-in-the-loop systems allow clinicians to evaluate, trust, and refine AI outputs, while models learn from real world feedback; this is essential for safe and responsible deployment.

AI allows researchers and clinicians to move toward more personalized medicine. For example, drug dosages and therapies can be targeted based on women's biology. AI can detect thousands of adverse reactions from EHRs and trials by pharmacovigilance algorithms and can predict sex-specific drug responses by AI-based pharmacogenomics. AI can also help automate CVD screening via wearable devices for analyzing physiological data to detect abnormalities and predict risk.

Maternal and Reproductive Health. In maternal and reproductive health, AI supports fertility treatment, IVF success, pregnancy monitoring, and early detection of serious conditions like preeclampsia and postpartum depression. Menopause is another historically overlooked area. AI-powered symptom tracking and risk modeling support personalized interventions for osteoporosis, dementia, sleep, and metabolic health during aging.

Patient Empowerment and Innovation. AI also empowers patients directly through mobile apps, telemedicine, and virtual assistants reducing stigma, increasing health literacy, and expanding access for women in remote or underserved communities. FemTech represents a rapidly growing ecosystem of AI-driven solutions addressing areas long neglected by traditional healthcare, including cycle and fertility tracking, wearable physiological monitoring, remote pregnancy monitoring, virtual care platforms for fertility and menopause, and smart pelvic health devices. Importantly, these tools do more than serve consumers—they generate data that can inform broader scientific discovery.

Present Challenges/Future Directions. Despite progress, challenges remain, including biased datasets, privacy concerns, unequal access, lack of transparency, and model robustness. Addressing these challenges requires ethical frameworks, regulatory oversight, and interdisciplinary collaboration. The future lies in holistic, fair, and clinically integrated AI systems, including multi-modal data fusion, global health equity, fairness auditing, scalable infrastructure, and embedding AI into clinical workflows.

Discussant Presentation

Dr. Giri summarized the panel presentations and addressed epigenetic changes in pregnancy. Differential methylation at CpG sites across the genome is associated with adverse maternal-fetal outcomes including preterm birth, pre-eclampsia, and low birth weight. However, significant knowledge gaps remain, as most studies only capture methylation changes at birth—precisely when many of these adverse events happen. Thus, there is a need for longitudinal human observational studies measuring epigenetic changes early and across multiple pregnancy checkpoints, alongside animal studies examining tissue-specific changes across key gestational changes. Such studies can inform disease etiology and tissue-specific mechanisms; more clearly delineate temporality and potentially cause and effect; identify epigenetic markers as early predictors of adverse outcomes; develop drugs targeting the expression of specific genes; identify the path of environmental toxicant exposures (PFAS and microplastics) to epigenetic changes to pregnancy outcomes; and improve post-partum recovery.

Panel Q&A

Dr. Giri conducted a Q&A session with the three panelists. Key points included:

- Promising metabolic targets currently in clinical trials for SLE and RA are still in the stage of pilot studies, e.g., an ongoing trial on N-acetylcysteine among lupus patients that has produced promising biomarker data, as well as studies with metformin that suggest some beneficial effects on clinical markers of the disease and how immune cells were rewired to look more normal. In a study at NIH, scientists are looking at a nicotinamide adenine dinucleotide (NAD)- boosting approach which in theory should have no significant side effects. Beyond that, there is a myriad of potential targets, and the key question will be cost versus benefit versus potential effects on antimicrobial responses.
- AI might be incorporated into these approaches by helping to integrate and harmonize all the data that is being collected. AI's ability to integrate huge amounts of high-dimensional data, such as genomics data, shifts the focus of research to knowledge discovery via data mining.
- The key biological pathways involved in microplastics are unknown because the research is at an early stage. Further, microplastics are not just one group of chemicals, but a mixture of chemicals. Therefore, some of the effects may come from plasticizers like bisphenol A and phthalates, while others may come from other chemicals included in the microplastics matrix.
- For PFAS, researchers have identified systemic effects, including increased inflammation and immunosuppression, based on human epidemiological studies and mechanistic models. Other identified changes include oxidative stress, changes in PPR gamma, and changes in biosynthesis. However, PFAS affects every single tissue and organ in the human body. Thus, they may have different mechanisms depending on the target organ.
- In light of data privacy issues in the age of AI, policy measures that can be preemptively adopted in the context of women's health may include adoption of a European model that creates sanctions and costs for violating individual patient privacy, rather than trying to gatekeep in ways that the technology is rapidly outpacing.
- The greatest challenges posed by AI include the fact that the field is moving so quickly that it is impossible for scientists to keep up. There are opportunities to enhance the new methods being developed to ensure that AI findings are accurate, e.g., systematic review and meta-analysis; these new methods need to be compared to traditional methods to validate their results. Finally, a major challenge for computational scientists is learning to explain or interpret their models to clinicians and biologists to build trust in these AI findings.

Closing Statement

Dr. Clayton thanked Dr. Vivian W. Pinn, the Founding Director of ORWH, for her trailblazing efforts in advancing women's health. Since 2013, ORWH activity has produced $610,461,673 in grant funding; 2,200 research projects; 1,460 clinical trials; 650+ patents; 190+ Drug Licenses (1999-2024); 65,000+ journal articles published; 3,000+ participants in e-learning courses; 10,960+ In Focus downloads (since 2019); and 55+ countries reached with DiscoverWHR (since 2024). She concluded by noting that science, technology, innovation, and rigorous research can improve the health of women by discerning clinically relevant sex influences, enabling personalized and predictive medicine, informing evidence-based care, applying NAMs to accelerate progress, and leveraging computational approaches and. ORWH has successfully made the case that a comprehensive view of women's health considers the whole person and takes the broader life course perspective in its view.

Dr. Clayton thanked Dr. Hindorff for her leadership, Drs. Douthard and Agarwal, for organizing the 35th anniversary symposium, and the entire ORWH staff for their efforts. She also thanked the ACRWH members for their service and said she looked forward to seeing them in person at the 65th ACRWH meeting on October 20, 2026. Dr. Clayton adjourned the meeting at 4:17 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: 2026.06.10 10:44:08 -04'00'

Janine Austin Clayton, M.D., Director
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Date 06/10/2026

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Advisory Committee on Research on Women's Health

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