



National Institutes
of Health

The Next Frontier in Women's Health: Harnessing Innovation to Power Interdisciplinary Research

October 29, 2024

Executive Summary

Gaps in research knowledge about biological and social factors contribute to poorer health outcomes at great costs to women and society. For longer, healthier lives, research is needed to address the health needs of women across the life course, from puberty through midlife and menopause and beyond.

On October 29, 2024, leaders from the White House and the National Institutes of Health (NIH) met to discuss advances and future directions for NIH interdisciplinary and innovative research on women's health as part of [Executive Order 14120](#). This workshop showcased how NIH research can advance women's health across the lifespan to fundamentally reshape the care women receive.

Leaders from the White House Gender Policy Council (GPC), the NIH Office of the Director, and NIH Institutes and Centers (ICs) spoke to the importance and value of interdisciplinary research and envisioned the future of research on the health of women. Attendees included representatives from Department of Health and Human Services (HHS) agencies; the National Academies of Sciences, Engineering, and Medicine (NASEM); foundations and community partner organizations; and congressional staffers.

Workshop Themes and Priorities

In response to a new federal focus on women's health in 2024, NIH in partnership with other HHS agencies has accomplished much on research for the health of women. Some of these activities are described in the [Fact Sheet on Advancing Women's Health Research and Innovation](#). Additional coordination and prioritization of women's health research at NIH has been in the areas of:

Meeting the research needs of women. The health of women is complex. A focus on understanding how health events are interrelated across a woman's life course must be considered when designing research studies. For example, cardiovascular research could investigate the relationship between health during pregnancy and later in life, sex differences in cardiovascular disease at midlife, and the mechanisms and consequences of early menopause. The effects of drugs and adverse events could be studied during particularly susceptible windows of the life course, including during pregnancy.

Sex differences throughout the translational research spectrum, from bench to bedside, and the need to contextualize research with factors related to social determinants of health and health disparities call for an interdisciplinary and whole-person approach to research on women's health. For example, the National Institute of Allergy and Infectious Diseases (NIAID) funded basic science research

showing that [teclistamab may be effective for targeting severe autoimmune diseases](#) and lead to new treatment approaches for autoimmune diseases (80% of affected individuals are women). Longitudinal clinical studies funded by the National Institute on Aging (NIA) are explaining variations in women’s midlife experiences, which could identify protective and risk factors for cardiovascular disease and chronic illness later in life.

NIH has worked to expand the scope of research opportunities in women’s health by:

- a. Committing \$200 million in FY25 toward new interdisciplinary research with a central focus on the health needs of women. This effort involves all NIH ICs.
- b. Expanding paths for research applications and identifying more than 175 women’s health priority topics and topics on a wide range of diseases that affect women uniquely, disproportionately, or differently through a first-of-its-kind women’s health funding opportunity ([NOT-OD-24-079](#)). This work involves all NIH ICs.
- c. Developing Discover Women’s Health Research ([DiscoverWHR](#)), a centralized resource for women’s health that simplifies access to NIH women’s health information by patients, caregivers, medical professionals, researchers, and the public—a partnership between the Office of Research on Women’s Health (ORWH) and the National Library of Medicine (NLM).
- d. Dedicating a Pathways to Prevention (P2P) Program—an independent, expert review process—to identify existing research gaps and develop an action plan to advance menopause research and care across the federal government and research community. The program is a partnership among ORWH; the National Cancer Institute (NCI); the National Heart, Lung, and Blood Institute (NHLBI); NIA; the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); and the National Institute of Mental Health (NIMH).

Catalyzing innovation to address women’s health needs. The power of innovation and technology to transform research is manifest in this era of -omics, data, and artificial intelligence. It is crucial to harness these advances toward discoveries that will improve women’s health. In many cases, this innovative interdisciplinary research will cross between and include multiple NIH ICs. For example, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) funded research to evaluate whether the widely used β -blocker atenolol can be “repurposed” for the primary prevention of osteoporosis in postmenopausal women. A new initiative announced by NHLBI will leverage artificial intelligence/advanced analytics for prediction, diagnosis, and treatment of multiple disease areas across diverse populations and the lifespan, with midlife as the starting focus.

NIH has worked collaboratively to catalyze innovation in women’s health by:

- a. Increasing investments in private-sector innovations in women’s health through the competitive [Small Business Innovation Research](#) and [Small Business Technology Transfer Programs](#)—a partnership among all NIH ICs, the Food and Drug Administration, and the Centers for Disease Control and Prevention.
- b. Launching the Rapid Acceleration of Diagnostics Technology ([RADx® Tech](#)) [ACT ENDO](#) “innovation funnel” program to develop new, noninvasive technologies for diagnosing endometriosis—a partnership between NICHD and the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

Advancing cross-cutting policies to strengthen women’s health research.

Policies requiring the inclusion of women in clinical research and accounting for [Sex as a Biological Variable \(SABV\)](#) have been foundational in ensuring research rigor and reproducibility and identifying key sex influences on health processes and outcomes. NIH has taken additional actions to ensure that women’s health is being considered at every step in the research process. These actions, taken in collaboration with NIH ICs, include:

- a. Developing women’s health data standards and common data elements for menopause, to enable researchers to more easily share and combine data across research studies and improve the quality of women’s health research.
- b. Leveraging the NIH funding process (application, peer review, grant implementation) to ensure women’s health and potential sex and gender differences are appropriately considered throughout the grant lifecycle.

NIH has and will continue to advance innovative interdisciplinary women’s health research across the NIH ICs. Improved research quality and data standards will promote the advancement of the lifespan approach to women’s health and generate a robust evidence base to address disparities in women’s health across a broad range of health and disease conditions and scientific topics. As science advances and gains continue, NIH is poised to respond to a range of innovative, scalable endeavors in research on women’s health as they arise.

The Next Frontier in Women's Health: Harnessing Innovation to Power Interdisciplinary Research

October 29, 2024
1:00–3:30 p.m.

Welcome

Jennifer Klein, Director, White House Gender Policy Council

Ms. Klein opened the meeting by thanking NIH leaders for the agency's longstanding commitment to improving women's health through research and innovation. As the world's largest funder of biomedical research, NIH plays a critical role in improving our understanding of conditions that affect women uniquely, disproportionately, and differently and in improving women's health and lives.

However, despite tremendous progress, we know too little about how to prevent, diagnose, and treat many health conditions that affect women. To close research gaps and drive discovery, the President and First Lady launched the White House Initiative on Women's Health Research in November 2023. In March 2024, the President signed Executive Order 14120, which directs the most comprehensive set of executive actions ever taken to improve women's health research. So far, progress includes NIH's commitment in fiscal year (FY) 2025 to invest \$200 million in new interdisciplinary women's health research, as well as work to build on its policy on sex as a biological variable (SABV). These actions build on the work of many workshop attendees, who will discuss their progress and how it supports research to improve the health and lives of women.

Prioritizing Women's Health Research from the White House

Carolyn Mazure, Ph.D., Chair, White House Initiative on Women's Health Research

Dr. Mazure provided an overview of the scope of the White House Initiative on Women's Health Research and the response and momentum it has created.

The goal of the Initiative is to fundamentally change the way women's health research is approached and funded. Although meaningful progress has been made in the last two decades, women have historically been underrepresented in health research. Much remains to be done to gather data on women's health, study SABV, and address health conditions that occur disproportionately or differently in women. Although women live longer than men, they spend almost 25% more time in poor health.

To pioneer the next generation of discoveries to close research gaps, President Biden asked each member of the White House Initiative on Women's Health Research how existing federal funding can better support women's health and how policy and programmatic change can advance women's health. The Initiative, co-led by the White House Gender Policy Council and the Office of the First Lady, includes the Departments of Health and Human Services, Defense, Veterans Affairs, and Agriculture, as well as the Environmental Protection Agency and National Science Foundation. Based on input from

numerous stakeholders, the President then signed Executive Order 14120. In addition to driving actions, the Executive Order reiterates the administration's commitment to addressing health disparities. The Executive Order directs agencies and departments to take several steps:

- Integrate women's health research across the research portfolio by developing and strengthening research and data standards that enhance the study of women's health within agencies and across funding opportunities.
- Prioritize investments in women's health research by promoting collaborative, interdisciplinary research; generating federal funding opportunities and facilitating potential applicants' access to information about them; and driving innovation and commercialization to support research translation.
- Galvanize research on the understudied area of women's midlife health and launch a comprehensive research agenda on menopause, conditions that often increase in midlife, and conditions that are more likely during or after menopause.
- Regularly assess unmet needs in women's health by evaluating gaps in federal funding and identify changes to address the needs.

Since the Initiative launched, a significant amount of new research funds have been committed to women's health. NIH has committed to launching a new agency-wide effort to close gaps in women's health research, initially supported by \$200 million from the NIH budget in FY25. This work will be co-chaired by five Institute and Center (IC) Directors in addition to the Office of the Director's (OD) Office of Research on Women's Health (ORWH). It is a first step toward a transformative central fund on women's health research at NIH, which the President has called on Congress to provide. Other examples of progress include a \$500 million commitment from the Department of Defense and \$110 million in new awards from the Advanced Research Projects Agency for Health (ARPA-H) to accelerate development of research and translation, which First Lady Dr. Jill Biden recently announced.

Government funding for research is being coupled with actions that affect policy and programs. For example, in collaboration with NIH, the Department of Defense created a new policy on SABV. NIH released a [Notice of Special Interest on Women's Health Research](#) that expanded funding pathways for women's health, created a front door to [NIH Women's Health Funding Opportunities](#), and launched [Discover Women's Health Research \(DiscoverWHR\)](#) a central location for investigators and the public to find information and other research resources related to women's health research. The National Science Foundation and Department of Veterans Affairs released their first-ever calls for research applications focused on women's health. Across Initiative members, new research and data standards will help ensure that women's health is considered at every step in the research process. These and other efforts are discussed during regular meetings of the Initiative's inter-agency working group, co-chaired by Dr. Mazure and

Janine Clayton, M.D., FARVO, Associate Director for Research on Women's Health and Director of the Office of Research on Women's Health at NIH.

Finally, because nongovernment sources of support are essential for growing the pace of discovery and for translating discovery into benefit, the Initiative has engaged the private sector, including philanthropists, private investors, entrepreneurs, and innovators. These stakeholders have shown dramatic new interest in investing in women's health research.

Women's Health: A Pillar of NIH Research

Monica Bertagnolli, M.D., NIH Director

Breakthroughs in biomedical research have benefited countless people, including Dr. Bertagnolli, who is a breast cancer survivor. However, many women are searching for answers to improve their health—for example, to manage chronic pain, postpartum depression, or flare-ups from autoimmune diseases. Women's role in society has changed dramatically in the past 60 years. Overall, women are now more educated, and their economic status has improved. The White House Initiative challenges the research community to expand knowledge of all of the influences on women's health, including social determinants of health, to improve lives.

NIH takes an interdisciplinary, whole-person approach throughout the lifespan. This approach provides a more complete picture of health and allows researchers and clinicians to address needs throughout a woman's lifetime. For example, care during and after pregnancy requires attention to mental health, cardiovascular disease, nutrition, infectious diseases, substance abuse, home safety, and many other issues, and interdisciplinary research is needed to understand how these interconnected factors affect health.

NIH continues to investigate diseases and conditions that are unique to women as well as those that affect women disproportionately or differently. NIH also has renewed its commitment to investing in programs that address health across the lifespan, particularly at the inflection points such as menarche, pregnancy, and menopause. This work must be approached with urgency, and it does not stop with scientific breakthroughs; the care that women receive must be fundamentally reshaped to allow them to live long, healthy lives. Dr. Bertagnolli hoped that today's workshop would help identify renewed priorities for women's health research.

NIH Priorities for FY25 and Beyond

Tara Schwetz, Ph.D., NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives

As Dr. Biden has emphasized, there are gaps in our understanding of the unique challenges facing women across the lifespan as well as the lived experiences of women. NIH supports research in these areas through policies, programs, strategic planning, and collaborations. NIH invests nearly \$5 billion in women's health research per year across all Institutes, Centers, and Offices, and many more of its basic science and clinical studies inform our understanding of women's health.

In addition, NIH has broad impact through its policies. Before ORWH was established in 1990, NIH encouraged the inclusion of women and minorities in NIH-funded clinical research; this inclusion became a requirement as part of the NIH Revitalization Act of 1993. Recent data show that 55% of participants in clinical research are female. NIH also established the landmark SABV policy requiring that sex be considered a biological variable in vertebrate animal studies as well as clinical studies; the Department of Defense has embraced and implemented a similar policy. Finally, the 21st Century Cures Act requires that Phase III clinical trials report results by sex, gender, race, and ethnicity. This requirement led to the creation of NIH's Inclusion Across the Lifespan Policy. Now, inclusion of females in NIH-defined Phase III clinical trials is over 60%.

In FY21, the second [NIH-Wide Strategic Plan](#) was released, which elevates women's health as a cross-cutting theme. The plan emphasizes the importance of interdisciplinary partnerships; expands reporting requirements to build the evidence base; and promotes the recruitment, retention, and advancement of women scientists.

NIH also has a [Strategic Plan for Research on the Health of Women](#); the latest version was released this year. The plan emphasizes the need for more interdisciplinary approaches, community involvement, and innovation in data science.

Collaborations are critical for advancing women's health research. Every 2 years, NIH releases the *NIH Report of the Advisory Committee on Research on Women's Health*, which outlines NIH-wide research programs and collaborations related to women's health across all ICs. Of note, a new section has been included in the latest report on cross-cutting innovative research topics.

As part of the activities outlined in Executive Order 14120, NIH committed to investing \$200 million in new interdisciplinary women's health research projects in FY25. The Executive Order integrates women's health across agencies and seeks to prioritize federal investments in women's health research.

Despite these efforts, many challenges remain that require dedication to research, policy, programs, and innovative solutions to help improve women's health. Today's workshop is a pivotal step with three goals: convening the scientific community, highlighting interdisciplinary research advances, and discussing future priorities. Dr. Schwetz thanked the attendees for their dedication, expertise, and passion.

Accepting the Challenge: Progress Toward Implementing the Executive Order on Women's Health Research

Janine Clayton, M.D., FARVO, NIH Associate Director for Research on Women's Health, Director of the Office of Research on Women's Health (ORWH)

Dr. Clayton discussed NIH's response to the President's call to transform women's health research, including efforts related to research and data standards, paths to funding, and innovation.

All NIH ICs advance women's health through research aligned with their areas of focus. This research accounts for interactions between biological, social, and environmental factors, which can have different effects at different life stages. Dr. Clayton and several IC Directors are co-chairing efforts to integrate this work across the agency and drive innovation, including through several collaborations:

- Discover Women's Health Research ([DiscoverWHR](#)) is a new effort developed through a partnership between ORWH and the National Library of Medicine (NLM). It provides a central location for researchers, practitioners, and members of the public to access information relevant to women's health, including open funding opportunities, clinical trials, grants supported in specific areas, and publications, as well as patient-friendly summaries of health topics.
- NIH established a [Research Condition and Disease Categorization \(RCDC\)](#) term to report investments in menopause research.
- In collaboration with the Centers for Disease Control and Prevention (CDC), NIH developed additional questions about menopause status that will be included in the 2025 CDC National Health Interview Survey, enabling better understanding of menopause effect.

NIH is also taking steps related to cross-cutting policies:

- Enhancing applicant instructions on data and standards in funding opportunity announcements
- Encouraging grant review panels to include women's health expertise, as appropriate
- Evaluating inclusion of women and accounting for SABV as part of scientific review
- Enhancing peer reviewer training
- Expanding the role of the NIH-wide SABV Working Group and creating IC-specific SABV plans

NIH understands the need to spur innovation through interaction with small businesses and entrepreneurs, as well as the need to reach all women and address health disparities. The agency developed a [Notice of Special Interest on Women's Health Research](#); all funding ICs have signed on and identified priority topics related to their mission areas. This step links women's health to multiple types of funding opportunities, enabling more investigators to obtain support for women's health research. NIH also has established a [central location](#) for women's health research funding opportunities.

Additional ORWH efforts include releasing the [NIH-Wide Strategic Plan for Research on the Health of Women](#) and the [Health of Women of U3 Populations Data Book](#), which highlights data on underserved, underrepresented, and underreported populations. ORWH also launched a [Roundtable Series](#) that has covered topics such as menopause, endometriosis, and maternal mental health, and its [2024 Annual Vivian W. Pinn Symposium](#) focused on autoimmune diseases. In addition, menopause and women's

health in midlife has been selected as the next topic for the [Pathways to Prevention Program](#); this will pave the way for the development of a menopause research agenda and action plan.

NIH is seizing the opportunity to advance women's health research across the lifespan. NIH is also working to narrow knowledge gaps through robust, innovative research; expanding research across the life course with an emphasis on midlife and menopause; and leveraging cross-cutting policies to accelerate progress. It is putting science, data, technology, and innovation to work to advance the health of women.

Interdisciplinary Innovations: The Future of Women's Health Research Across the Lifespan

Janine Clayton, M.D., FARVO, NIH Associate Director for Research on Women's Health, Director, ORWH

The [NIH-Wide Strategic Plan for Research on the Health of Women](#) includes five strategic goals that are intended to provide a roadmap to guide and inform NIH-supported research on various diseases and health conditions that affect women. Synergistic interdisciplinary connections are key to cross-cutting approaches to advance science and address the breadth of diseases and conditions that impact the health and well-being of women across the life course.

Representatives from several ICs discussed ongoing women's health research and future directions.

Cardiovascular Disease: State of the Science and Opportunities

Gina Wei, M.D., M.P.H., Senior Scientific Advisor on Women's Health, National Heart, Lung, and Blood Institute (NHLBI)

NHLBI is committed to improving women's health across the lifespan. Dr. Wei discussed advances and opportunities in maternal health and health at midlife.

Pregnancy can affect health long after delivery. The changing health profiles of pregnant women, including older age and higher rates of cardiovascular disease risk factors, affect women's future risk for heart disease and other major conditions.

NHLBI's nuMoM2b Heart Health Study is investigating the relationships between cardiovascular risk, maternal outcomes, and long-term health. It has followed 7,000 mothers since their first pregnancy. Over the past 10 years, the study has revealed important insights on pregnancy as a window to future health. Dr. Wei provided examples:

- Women who experience adverse pregnancy outcomes are more likely to develop hypertension within 2–7 years after delivery.
- Mothers who had sleep-disordered breathing during pregnancy have worse cardiometabolic profiles later in life.
- Entering pregnancy with obesity is a main driver of future heart disease.

The study's genomics and other omics bioassays will be generated and made available through NHLBI's precision medicine program, Trans-Omics for Precision Medicine (TOPMed), giving researchers opportunities to enhance prediction of adverse pregnancy outcomes and identify novel pathways for intervention.

The importance of pre-pregnancy health was also mentioned, using chronic hypertension as an example. Rates of pre-pregnancy hypertension have been rising. In 2022, the landmark NHLBI-funded Chronic Hypertension and Pregnancy (CHAP) trial demonstrated the benefit of treating even mild chronic hypertension during pregnancy, leading to a change in clinical practice guidelines: Women who received medications to treat their blood pressure to <140/90 mmHg, compared with a strategy of reserving treatment only for severe hypertension, had lower rates of adverse pregnancy outcomes without increased risk to babies. Future opportunities include implementation science to ensure that clinicians treat this condition appropriately and to stimulate discovery science using multi-omics data to develop new therapies.

An area of opportunity in women's health at midlife is in better understanding sex differences in cardiovascular disease. For example, women are typically older than men at the time of their first heart attack; also, cardiovascular disease rates are lower in women than in men at younger ages, but rates even out at ages 69–79.

Finally, researchers using data from UK Biobank and the Women's Health Initiative (WHI) found that earlier age at menopause is associated with shorter telomere length, a sign of aging. Women who had both premature menopause and shorter telomeres had the highest risk of developing coronary artery disease. Multi-omics data from WHI and other studies available through TOPMed will enable further insights on the mechanisms and consequences of early menopause.

A new NHLBI initiative will help capitalize on the opportunities that Dr. Wei described and enable advances in many other areas. The institute plans to use artificial intelligence (AI) and other advanced analytics to empower discoveries for prediction, diagnosis, and treatment of multiple disease areas across diverse populations and across the lifespan. As the first use case of the initiative, NHLBI is initially committing \$20 million to target women's health research, with midlife as the starting focus. The initiative will use rich, multidimensional data housed in TOPMed, which were contributed by more than 200,000 diverse research participants, more than half of whom are women.

Overall, NHLBI is working toward a future where women's health is enhanced across the lifespan; health disparities are eliminated; effective prediction, diagnosis, and treatment options are available; and precision medicine can preempt disease progress.

Gynecologic Health and Diseases

State of the Science and Opportunities

Diana Bianchi, M.D., Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Women's health is part of NICHD's mission, which includes understanding human development and improving reproductive health. The institute's 2020 strategic plan identified five research themes, all of which relate to women's health. Dr. Bianchi highlighted NICHD's work in one of many programs on women's health, which focuses on endometriosis.

Endometriosis, which affects 1 in 10 women worldwide, is associated with infertility, autoimmune disorders, cancer, and depression. Currently, endometriosis takes an average of 10 years to diagnose, and there are no noninvasive diagnostic techniques. NICHD is working to develop reliable, noninvasive tests that enable early, accurate diagnosis to facilitate treatment. The institute also is working on treatments; it has already used gene expression analysis to identify a potential new pain-relieving medication, fenoprofen.

In partnership with the National Institute of Biomedical Imaging and Bioengineering (NIBIB), NICHD is leveraging the Rapid Acceleration of Diagnostics Technology (RADx[®] Tech) "innovation funnel" program for the Advancing Cures and Therapies and ending ENDometriosis diagnostic delays (ACT ENDO) challenge. The RADx Tech approach was previously used to develop technologies for COVID-19 diagnosis. The project's goals are to accelerate the time to endometriosis diagnosis; eliminate the invasiveness of diagnostic techniques; and improve the accessibility, safety, convenience, and cost of diagnosis. Phase I submissions have been received, and final winners will be announced in 2026.

Research Innovation and Looking to the Future

Candace Tingen, Ph.D., Chief, Gynecologic Health and Disease Branch, NICHD

Dr. Tingen said that she believes women's health research is at an inflection point at which investments will lead to magnified returns. She highlighted advances in several areas.

In addition to improved diagnostic tools, improved therapeutics are needed for endometriosis. NICHD has invested in academic and small business grants for research seeking new drugs or repurposing existing drugs. A new therapeutic called ENDO-205 has shown promise; it shrinks lesions in 6 weeks with no hormones or side effects and will enter clinical trials in 2025.

Almost all women get uterine fibroids, but only some women will experience issues such as anemia, infertility, and miscarriage as a result. Black women are diagnosed with fibroids more often and tend to have larger and more numerous fibroids. Among women with uterine fibroids, Black women are twice as likely as their White counterparts to experience infertility, three times as likely to become anemic, and seven times as likely to need surgery. NICHD established two large research centers to explore and eliminate health disparities. To ensure that Black women's voices would be included at every step, the

institute required community involvement and partnered with two Black women-led organizations.

Gynecologic surgery is the most common surgery for women. NICHD is investing in research to make surgery safer, such as the development of a surgical simulator to allow clinicians in communities with low caseloads to practice, as well as biodegradable clips to improve healing.

The Pelvic Floor Disorders Network is changing the way people with pelvic floor disorders are treated; more than 25% of its studies are translated into updated clinical guidelines.

NICHD is also working to ensure that gynecologic pain is not normalized. Although it is common, it should be researched, understood, and treated. In 2024, the institute has quadrupled its gynecologic pain portfolio, and it is holding meetings and producing communications tools to ensure that research reaches women everywhere.

Immune System and Autoimmunity

State of the Science and Opportunities

Ellen Goldmuntz, M.D., Ph.D., Chief, Autoimmunity and Mucosal Immunology Branch, National Institute of Allergy and Infectious Diseases (NIAID)

One of the immune system's major roles is identifying and eliminating non-self microorganisms and substances. Autoimmunity is a breakdown in the system's ability to distinguish self from non-self. Episodes of transient autoimmunity occur in healthy people, and they can infrequently progress to clinical disease. Many NIH ICs contribute to the understanding of autoimmune diseases.

There are more than 100 autoimmune diseases, and they can affect single organs or multiple systems. They are common, affecting more than 24 million people in the United States—80% of whom are female. The incidence of some autoimmune diseases is increasing, but the reasons for the increase are unclear.

Dr. Goldmuntz described the evolution of an autoimmune disease, using type 1 diabetes as an example. In a healthy person, often one with a genetic risk, early T and B cell immune activation evolves into an antigen-specific immune response with development of autoantibodies directed against targets in the insulin-producing beta cells within the pancreatic islets. Over years, the individual develops increasing numbers of autoantibodies; at first, there are no symptoms, but there is progressive beta cell destruction. Ultimately, the full clinical condition develops.

Many treatments for autoimmune diseases have been approved in the last 15 years, reflecting NIH and industry's investment in basic and clinical research. However, the treatments do not cure disease, they have significant toxicity, and they do not treat everyone or all diseases. Future research opportunities include developing therapeutic approaches and personalized medicine to restore tolerance with a lower risk of toxicities; identifying risk factors, including environmental and genetic factors and infections; learning how to identify and intervene in early disease before tissue damage occurs; and identifying methods for prevention.

Research Innovation and Looking to the Future

Daniel Rotrosen, M.D., Director, Division of Allergy, Immunology, and Transplantation, NIAID

NIAID sees innovations that could dramatically change the landscape for people with autoimmune diseases. Even for people with the same disease, the mechanisms underlying the disease may differ. Understanding these mechanisms will enable new target identification and precision medicine approaches that will eventually enhance therapeutic options and improve patient outcomes. Understanding patient heterogeneity will also enable smaller, faster clinical trials. Identifying people at risk for autoimmune diseases will enable early treatment and prevention approaches.

Dr. Rotrosen displayed an example of a widely used approach to understand genetic and immunologic heterogeneity. Using a variety of statistical approaches, patients with similar clinical features can be clustered into groups with different underlying mechanisms. NIH and industry-sponsored studies (e.g., the Accelerating Medicines Partnerships) are routinely generating such insights, often based on gene expression profiles and using this information to decode complex diseases, identify new therapeutic targets, and design clinical trials.

Novel approaches include chimeric antigen receptor T cells (CAR-T cells), which are genetically engineered to kill target cells, and bi-specific T cell engagers (BiTEs), which are biologics engineered to engage T cells. Both approaches arose from decades of congressional support for basic NIH-sponsored research.

One example of a BiTE is teclistamab. In a study of patients with lupus who did not respond to an immunosuppressive drug regimen, treatment with teclistamab led to normalization of both laboratory abnormalities and disease activity index scores within weeks. Another BiTE therapy used in rheumatoid arthritis led to reduction or elimination of joint symptoms and signs of inflammation. Results like these are driving optimism for the future of targeted therapies for autoimmune diseases.

Substance Use and Other Mental Health Disorders

State of the Science and Opportunities

Carlos Blanco, M.D., Ph.D., Director, Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse (NIDA)

Substance use disorders and other mental health disorders often co-occur. Either type of disorder may occur first, or they may occur at the same time. Both must be addressed. Finding therapies to do this requires collaboration among NIH ICs. Some disorders are more prevalent or progress more quickly in women; understanding why is important for prevention. In addition, some disorders have increased prevalence at specific times, such as during menarche and pregnancy.

NIDA aims to develop a menu of interventions. Prevention is key, because many people with mental health or substance use disorders will not seek treatment. Addressing risk factors for these disorders can also reduce risk of other disorders. Offering a variety of

treatment options is important because treatments must be palatable and effective for different patients.

Insurance often presents a barrier to treatment; legal concerns also prevent people from seeking treatment. When developing treatments, researchers must take into account a variety of stakeholders, including clinicians, health systems, and payers as well as patients.

Research Innovation and Looking to the Future

Rita Valentino, Ph.D., Director, Division of Neuroscience and Behavior, NIDA

There are striking sex differences in the characteristics and prevalence of many mental health disorders. Disorders associated with stress, such as depression, anxiety, and post-traumatic stress disorder, are more prevalent in women than in men, as are pain conditions. These disorders co-occur with substance use disorders, suggesting that common neurobiologic mechanisms underlie these disorders. Basic research is beginning to uncover common mechanisms, which will lead to new treatments.

Substance use disorder has several stages: recreational use; problematic, compulsive use; withdrawal; recovery; and relapse. Sex differences exist at each stage and in transitions between stages. Basic research in animal models is revealing how the brain changes at each stage and how the trajectory differs between sexes.

In humans, research that applies machine learning approaches across different imaging formats is revealing a neurobiological signature of craving. This is important because craving is highly associated with relapse. Studies suggest that different pathways in the brain are associated with relapse in men and women, underscoring the importance of sex-specific treatments.

Drugs or adverse events can reshape circuits in the brain during critical windows of brain development, with long-term consequences for mental health. NIDA is leading two large longitudinal studies of brain development from infancy to early adulthood, integrating brain imaging with measures of cognitive function as well as biologic, genetic, and socioeconomic factors. The goal is to determine how these factors interact to shape brain development and how this influences mental health and substance use trajectories in adulthood.

Finally, pregnancy is another important period of brain plasticity, during which drugs and adverse events can have long-term effects. Understanding the development of the maternal brain is important because mental health outcomes, substance use disorders, and overdose are major contributors to maternal mortality.

Midlife Health and the Menopausal Transition

State of the Science and Opportunities

Richard Hodes, M.D., Director, National Institute on Aging (NIA)

NIA's mission is to improve the health and quality of life of older adults. However, the institute recognizes that health outcomes are influenced by events throughout the life

course, including in early life. Also, because menopause is a universal aspect of aging in women, NIA leads menopause research at NIH but collaborates with multiple other ICs.

The influences of sex and sex differences on aging are relevant to basic biology, behavioral and social research, neuroscience, and geriatrics and clinical gerontology.

In basic science, studies are revealing that aging is not universal across all tissues or environments or across sex and gender. For example, an NIA program that tests interventions' impact on health in a rodent model has consistently found different effects in males and females. In addition, the Molecular Transducers of Physical Activity Consortium (MoTrPAC), a collaboration between ICs that studies how exercise affects the whole body, has found that the effects of exercise on organs differ between men and women. These findings are the basis for exciting future areas of research.

In behavioral and social science, NIA carries out many studies beginning in midlife and older age, such as the national survey of Midlife Development in the United States (MIDUS), but it also helps continue studies funded by other ICs, including NICHD, into older adulthood.

In neuroscience, research has found changes in the brain during menopause. It also has found that over the course of Alzheimer's disease progression, the multi-omic gene expression patterns differ in women and men.

In clinical research, the Study of Women's Health Across the Nation (SWAN) includes a diverse population of women and has found differences across racial and ethnic groups in the menopause transition.

All of this work illustrates how new approaches and techniques have enormous potential to advance discovery and reinforces the importance of studying women's health and SABV.

Research Innovation and Looking to the Future

Chhanda Dutta, Ph.D., Chief, Clinical Gerontology Branch, NIA

SWAN has found that women experience the menopause transition in different ways, which point to new areas of research. For example, women experience hot flashes in four categories: early onset, late onset, low or no hot flashes, and "super flashers." There are also multiple patterns of sleep disturbance and insomnia as well as blood pressure changes. Women with high sleep disturbance are at higher risk for cardiovascular events later in life. Studying women in different categories could help identify protective factors and risk factors.

One other finding relates to lipid profile changes during the menopause transition. A subgroup of women have an increase in high-density lipoprotein (HDL) cholesterol that is associated with atherosclerotic changes, indicating that high HDL cholesterol is not always cardioprotective.

Understanding why women's midlife experiences are so different requires innovation in science. NIA has supported several longitudinal studies, including SWAN, MIDUS, and Ms Brain, which focuses on how menopause and midlife affect the brain and heart health. All

of these studies include diverse populations of women and provide publicly available biospecimens. Analyzing the studies' samples and datasets can help researchers gain insights that are crucial for developing therapies.

Dr. Dutta echoed previous speakers' emphasis on the importance of the life course. The way women enter midlife is shaped by prior events. Integrating data from studies across NIH could provide insights into how the way women enter midlife affects later life outcomes.

Finally, Dr. Dutta highlighted a recent finding from NIA-supported research. Rapid bone loss occurs during menopause, leading to osteoporosis risk later in life. The research found a new hormone in the brain of female mice that stimulates bone growth and density. The finding may represent a new therapeutic advance for the treatment of osteoporosis.

Osteoporosis and Post-Menopausal Bone Health

State of the Science and Opportunities

Robert Carter, M.D., Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Dr. Carter emphasized the importance of bone health across the life course. Prioritizing research on bone health can improve women's health overall.

The most common cause of weak bones is osteoporosis. Almost 20% of women over age 50 have osteoporosis of the hip or spine; the rate is higher in women of color and increases dramatically during menopause. Osteoporosis causes bones to break more easily, leading to impaired quality of life and increased risk of death. However, NIH research has shown that women can take steps to improve their bone health and reduce the risk of fractures.

Research has shown that bone remodels throughout life and that physical activity and healthy diet at a young age improve bone health. Low bone mineral density predicts fracture risk, so doctors can identify those at greatest risk and intervene, although the screening rate is decreasing. NIH-funded research has led to bone-building and bone-preserving drugs, but improved treatments are still needed.

NIAMS' priorities are developing better drugs with fewer side effects and getting them to the women who need them; developing better scans; and identifying ways to determine which drugs are best suited to each individual. The White House Initiative on Women's Health Research provides a valuable opportunity to build on ongoing work to raise awareness and improve bone health for women today and in the future.

Research Innovation and Looking to the Future

Sundeep Khosla, M.D., Osteoporosis and Bone Biology Lab, Mayo Clinic

Dr. Khosla highlighted four areas in which more research and innovation are needed:

- **Identifying women with osteopenia who are most likely to have a fracture.** Current treatments are targeted at women with osteoporosis; however, because of their larger numbers, most fractures occur in women with osteopenia. Fracture rates rise as bone density decreases. Better imaging tools, better analysis of bone

density images, omics technologies, and AI approaches could help identify women with osteopenia who do not qualify for treatment under current guidelines but could be better targeted for fracture prevention.

- **Primary prevention of osteoporosis.** Most guidelines recommend the use of current drugs after a fracture or diagnosis of osteoporosis; options for prevention are lacking. One approach is to identify new pathways to target. An NIH-funded trial currently is under way to determine whether atenolol, a widely used β -blocker, can be repurposed to prevent osteoporosis. However, additional interventions are needed and should be based on a better understanding of the underlying bone biology.
- **A cure for osteoporosis.** Three approved drugs stimulate bone formation and increase bone mass, but their effects do not last. More research could help determine the mechanisms responsible for this waning effect and determine how to overcome it.
- **Treating osteoporosis in the context of multiple age-related morbidities.** Osteoporosis is often associated with comorbidities that also increase fracture risk, such as frailty. Better understanding the mechanisms that cause bone and muscle loss could help develop drugs to target both. At a broader level, understanding aging mechanisms across tissues, including bone, could identify targets to improve health span. Drugs such as metformin and a new class of drugs called senolytics may be useful for many diseases, including osteoporosis.

Sleep: State of the Science and Future Opportunities

Marishka Brown, Ph.D., Director, National Center on Sleep Disorders Research, NHLBI

The circadian system has a master genetic clock in the brain that responds to light as well as feeding schedules and physical activity. Sleep drive and circadian patterns work together to keep people awake during the day and to produce a consolidated period of sleep at night. In addition, clocks in tissues and organs throughout the body work together to maintain health.

Sleep is a cross-cutting, fundamental pillar of health for everyone, but there are differences in women. Also, sleep changes across the lifespan, as does sleep-associated risk. Dr. Brown highlighted a 2018 conference that covered a decade of federally funded research on sleep, circadian biology, and women's health. The conference, a collaboration between NHLBI, 11 other NIH ICs and Offices, and the Department of Health and Human Services (HHS) Office on Women's Health, identified three priorities for scientific research:

- Understanding the extent to which sex and gender impact sleep and sleep pathobiology across the lifespan
- Understanding the under-recognition and misdiagnosis of sleep disorders in women and girls
- Understanding the contribution of sleep deficiency to health disparities

Dr. Brown presented findings and future directions for sleep research. Large cohort studies at NHLBI collect sleep metrics, which helps researchers understand interactions between sleep and cardiovascular disease, as well as the cognitive impact of sleep.

Women face increased risk for cardiovascular disease during pregnancy, and there is an urgent need to identify modifiable risk factors and therapeutic strategies to prevent and mitigate this issue. A study found that among pregnant women with overweight or obesity, sleep-disordered breathing was associated with increased risk of preeclampsia and gestational diabetes. Although sleep problems in pregnancy are common, they are not inconsequential and should not be ignored. Current research is investigating impacts of sleep problems during pregnancy on the fetus. In addition, in collaboration with NICHD, NHLBI is conducting a Phase III clinical trial to determine whether treatment for sleep-disordered breathing affects hypertensive disorders of pregnancy.

Machine learning, AI, and other big data approaches are enabling unprecedented opportunities to understand the pathobiology of sleep and sleep disorders. The National Sleep Research Resource is a large sleep data repository funded by NHLBI, with additional funding to come from other ICs. One study published this year demonstrated a novel metric, airflow limitation, as an indicator of clinically significant sleep-disordered breathing in women. The standard measure of sleep apnea, the apnea-hypopnea index (AHI), is insufficient in women, especially pregnant women. The study found that associations with preeclampsia, hypertensive disorders of pregnancy, and lower infant birthweight were more apparent with flow limitation than with AHI.

Sleep deficiency is a fundamental experience of menopause; up to 60% of women experience new sleep challenges between perimenopause and the post-menopause transition. Especially among older women, sleep apnea is associated with increased risk for cognitive impairment. Poor sleep quality and sleep loss are associated with Alzheimer's disease and Alzheimer's-related dementia. A study from the NIDA Director's lab found that one night of sleep deprivation increased amyloid beta, a hallmark of Alzheimer's disease. These findings indicated that intervening to improve sleep could help prevent or delay onset of cognitive decline; studies are under way at NIA to investigate this possibility.

Black and Hispanic women experience more sleep problems than White women. Research has found that location, rather than race, is key for understanding these disparities. Sleep is a determinant of health, and it intersects with other determinants of health. For example, living in a food desert and sleep problems can both lead to poorer nutrition. People with sleep deprivation tend to make less healthy food choices.

The timing of meals is also important for health. Misaligned circadian rhythms lead to an increase in hunger hormone and a decrease in satiety hormone, leading to overeating. This dysregulation does not occur in men in the same way. This finding presents an opportunity for intervention: Research has found that changing mealtimes to ensure that people eat during the day prevents adverse effects of eating at night. Leveraging knowledge about circadian rhythm biology can lead to interventions that help prevent or preempt disease.

Turning the Possible into Reality: Next Steps and Future Directions

Moderator: Vivian Ota Wang, Ph.D., FACMG, CGC, Deputy Director, ORWH

Panel: Dr. Bertagnolli, Director, NIH; Dr. Bianchi, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development; Dr. Carter, Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases; Dr. Hodes, Director, National Institute on Aging; Walter J. Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke (NINDS); Helene M. Langevin, M.D., Director, National Center for Complementary and Integrative Health (NCCIH); Stephen Sherry, Ph.D., Acting Director, National Library of Medicine; Bruce J. Tromberg, Ph.D., Director, National Institute of Biomedical Imaging and Bioengineering

Dr. Ota Wang emphasized that the workshop has provided a glimpse of the depth of NIH's work. The next step is to address research needs to advance women's health across the lifespan.

The panelists introduced themselves; all are NIH leaders who are making a difference for women's health.

Dr. Ota Wang said that science must take into account the complexity of women's lived experiences as well as considering a whole-body perspective. She asked the panelists how NIH can move interdisciplinary science forward, including through more collaborations between ICs.

Dr. Bertagnolli said that the workshop has highlighted remarkable examples of collaboration. Health is partly based on genetics, but it is also influenced by everything else in a person's life. That is why it takes 27 ICs to solve any problem; they are all interrelated. NIH uses a multifocal approach to every problem.

Dr. Tromberg said that NIBIB approaches problems with an engineering perspective, aiming to create models that describe all components of a system. It collaborates with all other ICs to bring integrative systems thinking into new technologies to facilitate discovery.

Dr. Langevin said that NCCIH also takes a multisystem and multiscale approach to consider the whole person. New tools have enabled this approach within the past 10–15 years. The time is right to take on an ambitious agenda.

Dr. Bianchi said that NICHD and NIA were formerly parts of the same institute. Both institutes take a lifespan approach, which is critical for women's health because of inflection points such as pregnancy and menopause. All ICs bring different perspectives to collaborations.

Dr. Hodes said that researchers are now able to do things that seemed far-fetched not long ago. Developing a system to study whole-person health once seemed impossible. Now, with longitudinal studies, multi-omics, and personalized health, research can identify factors in health and disease in individuals across the lifespan. One example is a recent BRAIN Initiative study with remarkable insights into the pathways that precede and accompany symptomatic Alzheimer's disease; the study opens new avenues of inquiry

and targets for intervention that will vary between men and women and across individuals. There has never been a more exciting time in science.

Dr. Koroshetz said that transformations in science occur more with the development of new tools than with new ideas. New tools are opening new avenues of research. Genomic medicine is an exciting new tool that is much more precise than other drugs; it will enable treatments that specifically target problems without causing adverse effects elsewhere in the body. One example of an application in women's health is gene editing for Rett syndrome, a condition that predominantly affects girls.

Dr. Bertagnolli added that at any given time, NIH has 2,000 to 3,000 collaborations with other government agencies. NIH works with all HHS agencies as well as the Departments of Defense, Energy, and Commerce. Those relationships are critical and fit the spirit of the Executive Order.

Dr. Sherry said that all of the ideas shared speak to the power of information. NLM's role is to organize and effect democratic, rapid access to information. NLM does not hold all of the data but is working on new strategies for rapid, equitable access, including changing standards to eliminate prejudice and inaccuracies and training a workforce across the country.

Dr. Carter said that NIAMS' strength is uncovering fundamental knowledge and determining how it could be applied, but others' strength is implementation. For bone health, working with other agencies to promote awareness and screening could have immediate benefit.

Dr. Hodes said that with gains in scientific capability comes an enhanced obligation to consider communication and maintenance of public trust. Researchers must make their results relevant and available to the broadest population in an ethical way.

Dr. Carter added that it is time to understand the differences that sex makes in biological pathways; researchers now have the tools to take on this challenge.

Dr. Bertagnolli said that NIH leaders take incredible joy in their work, thinking every day about how to improve the world. She hoped the discussion had demonstrated how open they are to work and share resources with anyone to solve problems for women.

Closing

Janine Clayton, M.D., FARVO, NIH Associate Director for Research on Women's Health, Director, ORWH

Dr. Clayton thanked the ICs, colleagues in HHS, and the Gender Policy Council for supporting and guiding the implementation of the Executive Order. NIH has been building on the momentum of the Executive Order through innovative, interdisciplinary research to turn discovery into health for all women, and Dr. Clayton looked forward to continuing these partnerships.

Appendix A: Speakers

Progress and Priorities for Women's Health Research

Jennifer Klein, Director, White House Gender Policy Council

Carolyn Mazure, Ph.D., Chair, White House Initiative on Women's Health Research

Monica Bertagnolli, M.D., Director, National Institutes of Health (NIH)

Tara Schwetz, Ph.D., NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives

Janine Clayton, M.D., FARVO, NIH Associate Director for Research on Women's Health, Director of the Office of Research on Women's Health (ORWH)

State of the Science and Future Directions

Gina Wei, M.D., M.P.H., Senior Scientific Advisor on Women's Health, National Heart, Lung, and Blood Institute (NHLBI)

Diana Bianchi, M.D., Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Candace Tingen, Ph.D., Chief, Gynecologic Health and Disease Branch, NICHD

Ellen Goldmuntz, M.D., Ph.D., Chief, Autoimmunity and Mucosal Immunology Branch, National Institute of Allergy and Infectious Diseases (NIAID)

Daniel Rotrosen, M.D., Director, Division of Allergy, Immunology, and Transplantation, NIAID

Carlos Blanco, M.D., Ph.D., Director, Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse (NIDA)

Rita Valentino, Ph.D., Director, Division of Neuroscience and Behavior, NIDA

Richard Hodes, M.D., Director, National Institute on Aging (NIA)

Chhanda Dutta, Ph.D., Chief, Clinical Gerontology Branch, NIA

Robert Carter, M.D., Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Sundeep Khosla, M.D., Osteoporosis and Bone Biology Lab, Mayo Clinic

Marishka Brown, Ph.D., Director, National Center on Sleep Disorders Research, NHLBI

Panel Discussion

Moderator: Vivian Ota Wang, Ph.D., FACMG, CGC, Deputy Director, ORWH, NIH

Monica Bertagnolli, M.D., Director, NIH

Diana Bianchi, M.D., Director, NICHD

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Walter J. Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke

Helene M. Langevin, M.D., Director, National Center for Complementary and Integrative Health

Stephen Sherry, Ph.D., Acting Director, National Library of Medicine

Bruce J. Tromberg, Ph.D., Director, National Institute of Biomedical Imaging and Bioengineering

Appendix B: Acronyms

Agencies cited

Acronym	Agency
HHS	U.S. Department of Health and Human Services
NIH	National Institutes of Health

NIH Institutes, Centers, and Offices (ICOs) cited

Acronym	ICO
NCI	National Cancer Institute
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
NLM	National Library of Medicine
ORWH	Office of Research on Women's Health