

PERSPECTIVES ON ADVANCING NIH RESEARCH TO INFORM AND IMPROVE THE HEALTH OF WOMEN

National Institutes of Health
Office of the Director
Division of Program Coordination, Planning, and Strategic Initiatives
Office of Research on Women's Health

Full Report



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

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Executive Summary

Please note that this report refers to “women” to describe pregnant individuals, but ORWH and NIH recognize that people of various gender identities (including some transgender males, nonbinary individuals whose sex is female, and cisgender females) can give birth and receive maternity care.

Background

In their fiscal year (FY) 2021 reports, the [House](#) and [Senate](#) appropriations committees requested that the National Institutes of Health (NIH) convene a conference to evaluate research currently underway related to women's health, specifically regarding the following three topics:

1. rising rates of maternal morbidity and mortality (MMM)
2. rising rates of chronic debilitating conditions in women (CDCW)
3. stagnant cervical cancer survival rates

In response to Congress, the NIH Office of Research on Women's Health (ORWH) developed a strategy to collect input on the three priority areas from experts in women's health; members of the public; representatives from NIH Institutes, Centers, and Offices (ICOs); and members of the NIH Advisory Committee on Research on Women's Health (ACRWH). An ACRWH Women's Health Conference (WHC) Working Group was formed to review and discuss data on current NIH activities, plan the WHC, and prepare a report. On October 20, 2021, ORWH and the ACRWH co-hosted the WHC, titled [Advancing NIH Research on the Health of Women: A 2021 Conference](#), in conjunction with the ACRWH meeting held the following day. At the ACRWH meeting, the Committee reviewed summaries from the WHC, held a robust discussion, and voted on opportunities for future NIH research on women's health, MMM, CDCW, and cervical cancer survival.

Review of Current NIH Activities

As a first step in responding to the request from Congress, ORWH and the NIH Coordinating Committee on Research on Women's Health (CCRWH) formed a Planning Committee and established three “clusters” corresponding to the requested topics and a fourth cluster to harmonize the data. Co-led by a subject-matter expert from ORWH and an NIH scientist, each cluster was composed of subject-matter experts from NIH ICOs, other U.S. Department of Health and Human Services (HHS) agencies—including the Centers for Disease Control and Prevention, U.S. Food and Drug Administration, Centers for Medicare & Medicaid Services, and Health Resources and Services Administration—and the U.S. Department of Veterans Affairs. Each cluster completed focused assessments and reviews of the relevant NIH research portfolios; held discussions on its respective topic area; and presented analyses, findings, and recommendations to the ACRWH WHC Working Group. Wherever possible, as the official system of record for annual NIH funding on specific research topics, NIH's [Research, Condition, and Disease Categorization](#) system (RCDC) was used as a metric of funding.

Research on Women's Health

As measured by the Manual Categorization System–Women's Health (MCS-WH) reporting module, NIH spent 10.8 percent of its FY 2020 budget on [women's health research](#) (\$4,466 million). The identified grants processed by the MCS-WH reporting module include both female-specific conditions (e.g., gynecologic cancers, endometriosis) and diseases that affect both women and men but predominately affect women (e.g., fibromyalgia, rheumatoid

arthritis). The ICOs with the largest absolute funding directed toward women's health research included those with the largest overall budgets: the National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). When the budgets are evaluated by percentage, NICHD, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and National Institute on Minority Health and Health Disparities (NIMHD) allocated the largest fraction of their budgets to women's health (29%, 28%, and 25%, respectively).

As the congressionally mandated focal point for coordinating NIH research on the health of women (per Section 486 of the Public Health Service Act, [42 U.S.C. 287d](#)), ORWH collaborates with the constituent 27 NIH Institutes and Centers and the broader scientific community to ensure that sex and gender are integrated into an interdisciplinary scientific framework at NIH and throughout the biomedical research enterprise. In FY 2020, the ORWH budget was \$45 million—largely unchanged since 2003 (\$41 million).

Since the passage of the [NIH Revitalization Act of 1993](#), the representation of women in clinical research has improved, and today, roughly half of NIH-supported clinical trial participants are women.¹ However, substantial underrepresentation of women in clinical trials persists in multiple disease categories, including HIV/AIDS, chronic kidney disease, and cardiovascular diseases.² For diseases that affect primarily one sex, the funding patterns favor disorders that predominantly affect males when compared to burden of the disease within the population: The disparity between actual funding and the disease burden by sex was nearly twice as large for conditions that occur predominantly in males as for those more common in females.³

As part of its mission, ORWH provides inclusion data from across NIH in its currently biennial [Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2019–2020](#). Recent expansion of the NIH inclusion policy to incorporate inclusion across the lifespan in addition to sex and/or gender, race, and ethnicity as a result of [21st Century Cures Act](#) requirements will lead to the addition of age at enrollment to future reports. Inclusion data are also now being reported by [RCDC categories](#). In addition, NIH inclusion data are incorporated into the NIH Directors' Report formerly biennial, now triennial. Harmonization of data reported in the NIH Women's Health Research biennial report and the NIH Director's triennial report is essential to provide a comprehensive and clear picture of inclusion data that is in compliance with NIH inclusion policy; therefore, triennial women's health research reporting aligned with the triennial NIH Director's report would promote clarity and transparency.

Maternal Morbidity and Mortality

In response to the MMM public health crisis, NIH established a new RCDC category in 2017 for Maternal Health, which includes projects focused on pre-pregnancy through 1 year postpartum. In 2020, another RCDC category for Maternal Morbidity and Mortality was created to capture the subset of topics within the Maternal Health category specifically related to pregnancy complications and death associated with pregnancy. In FY 2020, the largest investment in MMM came from NICHD (\$76 million), followed by the National Heart, Lung, and Blood Institute (NHLBI, \$40 million); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, \$19 million); and National Institute of Mental Health (NIMH, \$18 million).

Current NIH activities specific to MMM include basic and translational science investigating the underlying physiology of pregnancy, as well as the pathophysiology of pregnancy-associated disorders through such programs as the [Human Placenta Project](#). Prospective clinical trials research investigating interventions to reduce maternal and infant morbidity, deaths, and complications is performed through NICHD's [Maternal-Fetal Medicine Units](#) Network. NHLBI supports projects on maternal cardiovascular health; NIDDK, on diabetes; National Institute of Environmental Health Sciences (NIEHS), on the environmental impact on maternal health; NIMH, on maternal psychiatric conditions; the National Institute on Drug Abuse (NIDA), on drug use; the National Institute on Alcohol Abuse and Alcoholism (NIAAA), on alcohol use disorders; and NIMHD, on structural inequities in maternal health.

Additionally, the NIH Maternal Mortality Task Force (MMTF), created early in FY 2020 to generate evidence-based solutions to the MMM crisis, is led by the NIH Office of the Director (OD), NICHD, and ORWH. The MMTF established the [Implementing a Maternal health and PRenancy Outcomes Vision for Everyone](#) (IMPROVE) initiative to support research to reduce preventable maternal deaths and improve health for women before, during, and after delivery. Reducing inequities related to such factors as race, age, and geographic region is prioritized. Furthermore, a [new collaboration](#) between ORWH and the National Institute of General Medical Sciences (NIGMS) is focused on studying women's health through the [Institutional Development Award](#) (IDeA) Program, which supported 13 awards on MMM in FY 2020. The IDeA Program is congressionally mandated and administered by NIGMS, with the goal of building research capacity in states and territories that historically have had low levels of NIH funding (23 states and Puerto Rico).

Rising Rates of Chronic Debilitating Conditions in Women

NIH supports a wide range of research on chronic diseases—covering screening and prevention, diagnostics, treatment and therapeutics, health disparities, and other aspects (e.g., mechanisms and pathogenesis). However, no single NIH RCDC for reporting medical research funding to the public encompasses chronic debilitating conditions. In 2010, HHS defined chronic illnesses as “conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living.”⁴ This definition was used to describe chronic debilitating conditions in women. A CDCW framework was created for the purposes of WHC planning and NIH portfolio analyses that categorized CDCW into the following categories: (1) female-specific, (2) more common in women and/or morbidity is greater for women, (3) occur in both sexes but potentially are understudied in women, and (4) high morbidity in women. Disability-adjusted life years, [defined by the World Health Organization](#) as “the loss of the equivalent of 1 year of full health,” were used as a metric by which to measure the burden of disease in women.

Using this definition and framework, a qualitative assessment of ICO priorities related to CDCW was performed. Each ICO represented within the CCRWH was invited to submit at least three of its highest-funded projects related to chronic debilitating conditions in women from FY 2018 to FY 2020. One hundred eighty-four priority projects were submitted by 11 ICOs. The associated RCDCs from these submitted projects demonstrated that all topics of chronic condition relevant to women, as defined in the WHC CDCW framework, are included in ongoing NIH-supported research. The largest proportion of projects were focused on conditions more common in women or for which morbidity was greater for women (49%), followed by conditions potentially understudied in women (25%), conditions with high morbidity in women (15%), and female-specific conditions (11%). This limited, descriptive summary provided a rough estimate of NIH-wide priorities related to research on CDCW.

Cervical Cancer

The RCDC for cervical cancer includes basic research, translation and clinical studies, and premalignant and invasive cervical diseases, as well as human papilloma virus (HPV) biology, prevention, screening, vaccination, treatment, and related health services. In FY 2020, NIH invested about \$113 million in cervical cancer research, with most projects funded by NCI (\$91 million). Cervical cancer research represents about 1.4 percent of the overall NCI budget based on RCDC. NIAID, NIMHD, and NICHD also fund research on cervical cancer, primarily focused on research on HPV biology, screening and prevention of pre-invasive cervical disease, and reducing disparities in screening and prevention in historically underrepresented communities.

Comparably, more NIH-supported projects are classified as research investigating etiology, prevention, early detection, and cancer control than as research focused directly on cervical cancer treatment. Almost all cases of cervical cancer are caused by infection of HPV. NIH supports a robust research program around the biology, prevention, and screening of HPV infection and cervical cancer. These efforts include projects directed toward development of novel preventive and therapeutic vaccines, [self-sampling](#) to overcome barriers to screening, and [one-dose HPV vaccination](#) efficacy. The clinical trials portfolio includes secondary prevention and health care delivery research. Ongoing clinical trials researching innovative care in cervical cancer treatment include studies

within NCI's clinical research networks: the [Experimental Therapeutics Clinical Trials Network \(ETCTN\)](#), [National Clinical Trials Network \(NCTN\)](#), and the [NCI Community Oncology Research Program \(NCORP\)](#).

Public Comments

On July 1, 2021, ORWH published a Request for Information (RFI) in the *Federal Register* ([86 FR 35099](#)) to inform the WHC. The RFI invited comments and testimonies from the extramural scientific community, professional societies, and the general public to assist with identifying research gaps, determining pitfalls in clinical practices, and obtaining real-life testimonial experiences (direct or indirect) related to any or all of the three congressionally specified public health issues.

Of the 247 comments received, 104 addressed MMM, 182 discussed CDCW, and 27 mentioned cervical cancer. Most comments were submitted by researchers or research groups (N = 56), followed by members of the public (N = 49), awareness and advocacy groups (N = 36), patients (N = 40), and health care providers (N = 34). The 10 most frequently identified keywords from the manual coding, ordered from most to least frequently mentioned, from the manual coding were as follows: (1) MMM, (2) racial disparities, (3) access to care, (4) provider training, (5) mental health, (6) Black or African American women, (7) screening, (8) quality of care, (9) time to diagnosis, and (10) social determinants of health. A summary of the comments is provided in [Appendix B](#).

Advancing NIH Research on the Health of Women: A 2021 Conference

Thirty-two [speakers discussed a wide range of topics](#) related to research on women's health and the three public health needs identified in the congressional request (MMM, CDCW, and cervical cancer survival). The full agenda can be found in [Appendix A](#). Conference proceedings are summarized in [Appendix C](#).

Research Gaps and Opportunities

Research to improve the health of women is embedded in the work and mission of all NIH ICOs. ORWH acts as the focal point for coordinating this research and ensures that sex and gender are integrated into an interdisciplinary scientific framework at NIH and throughout the broader scientific enterprise.

The following three crosscutting themes emerged from stakeholders participating in the WHC:

Implementation Research

Research to understand how best practices can be applied to women's health topics is urgently needed. The quality of care received by women varies tremendously by factors that include, but are not limited to, geographic location, insurance status, education attainment, and other social factors. Interventions—such as safety bundles, collections of best practices that offer a framework to incorporate established guidelines into health care practice using a standard approach to pregnancy and postpartum care—have demonstrated large-scale improvements in pregnancy outcomes yet remain unimplemented in many hospitals.^{5,6} Vaccines that prevent cervical cancer have been approved for use in the United States since 2006, yet just more than half of adolescents have completed the HPV vaccine series.⁷

Moreover, the paradigm of “one patient—one disease” no longer fits the medical necessities and needs of most patients with chronic diseases, and a more holistic, patient-centered view must be developed. Innovative trial design and outreach are needed to generate the data required to develop evidence-based care for women. Research to “scale up” successful interventions that have demonstrated improvements in the health of women, such as maternal safety bundles and cervical cancer screening, should be prioritized.

Research That Addresses Inequities in Care

Although race, ethnicity, and sex and/or gender reporting from applicable NIH-defined Phase 3 clinical trial results is now [required](#), identifying outcomes for populations with overlapping identities (e.g., Black women) remains challenging, limiting data on the health consequences of intersectionality. The burden of chronic debilitating conditions on women from underserved and underrepresented populations is not well described in current literature. The disproportionate disease burden of MMM and cervical cancer on women from historically underserved, understudied, and underrepresented populations is notable. Black, Alaska Native, and American Indian persons die from pregnancy-related causes at a rate almost three times as high as the rate for White women.⁸ Despite similar rates of cervical cancer screening and HPV vaccination, Black women remain 30 percent more likely to be diagnosed with cervical cancer and 75 percent more likely to die of disease than White women.⁹ Attention to these communities through community-engaged research is an urgent need.

Intentional Research on the Health of Women

The mission of ORWH includes strengthening and enhancing research related to diseases, disorders, and conditions that affect women; ensuring that research conducted and supported by NIH adequately addresses issues related to women's health; and ensuring that women are appropriately represented in biomedical and bio-behavioral research studies supported by the NIH. NIH has made significant advances in research focused on the health of women, spearheaded by ORWH and in collaborations with the various ICOs and stakeholders. Today women are enrolled into NIH-supported clinical research at similar rates to men. However, more work remains to be done, because inclusion is only one component of equity. The historic overreliance on male clinical research subjects has created gaps in our current evidence base regarding disorders and diseases that occur in women, including impacts on functioning and quality of life across the life course, which still must be addressed. Many female-specific conditions—including menopause, endometriosis, and fibroids—are chronic debilitating conditions that fall under the purview of multiple ICOs and currently have few standing funding opportunities. Filling the gaps in evidence pertinent to the health of women requires research that is centered on female-specific conditions as well as a better understanding of the prevention, diagnostic, and treatment needs that are unique to women. Despite the significant advances made to date, fundamental basic and translational research is needed on such topics as the initiation of labor, the root causes of preeclampsia, basic physiology of the uterus and of typical and atypical menstruation, the innate differences between male and female systems' pathogenesis of chronic conditions, and the discrepant carcinogenesis of various HPV types within the cervix.

Studies that provide detailed sex-disaggregated clinical outcomes data—tied to critical life-course windows, such as menarche and menopause—from a diverse population of women are needed to support this important work. To fill evidence gaps related to women's health, clinical trials networks with the following could be created: a specific emphasis on women (including pregnant persons), tools to design trials that answer questions specific to women, and capacity to enroll women of all ages and from diverse backgrounds into studies. Large-scale prospective cohort studies of women might likewise begin to fill some of our gaps in understanding the specific pathophysiology of CDCW.

The 2016 NIH [Sex as a Biologic Variable \(SABV\) policy](#) has led to advances in our understanding of relevant diseases that affect women. Despite the policy, gaps remain in basic and translational understanding of sex differences. Continued attention to and application and enforcement of the SABV policy will allow further understanding of how sex influences physiology and pathophysiology, paving the way for improved disease prevention and treatment strategies in the multitude of conditions that present differently and require different treatment in women and men.

Intentional funding opportunities can improve NIH-wide support of research on women's health. Intentional funding of studies of women by leveraging existing NIH resources—such as cohorts, biobanks, and bioinformatics—also can

advance the continued growth of the NIH women's health research portfolio. The review process can be improved through the creation of standing study sections within the NIH Center for Scientific Review on sex differences and women's health research and the inclusion of researchers with women's health expertise on additional study sections.

Conclusion

Improving the health of women benefits all members of our society.¹⁰ Increasing research on the health of women has been demonstrated to [produce significant returns on investment](#). The [2019–2023 Trans-NIH Strategic Plan for Women's Health Research](#) sets out an ambitious vision for a world in which the biomedical research enterprise thoroughly integrates sex and gender influences; every woman receives evidence-based disease prevention and treatment tailored to her own needs, circumstances, and goals; and all women in scientific careers reach their full potential.

Broad support for increased prioritization of research on women's health was expressed by members of the public, NIH stakeholders, ACRWH members, and the participants of the WHC.

Report Overview

Please note that this report refers to “women” to describe pregnant individuals, but ORWH and NIH recognize that people of various gender identities (including some transgender males, nonbinary individuals whose sex is female, and cisgender females) can give birth and receive maternity care.

The House and Senate have indicated that a greater focus on research related to obstetrics and gynecology is needed to address the following three high-priority areas: (1) rising rates of maternal morbidity and mortality (MMM), (2) rising rates of chronic debilitating conditions in women (CDCW), and (3) stagnant cervical cancer survival rates. Therefore, Congress directed the National Institutes of Health (NIH) to convene a consensus conference on women’s health to evaluate current research and provide an update as part of the fiscal year (FY) 2022 Congressional Justification that identifies priority areas for additional study to advance women’s health research, including reproductive sciences. Full information on the congressional Significant Item can be found on page 145 of the [House Committee on Appropriations report](#) and on page 123 of the [Senate Committee on Appropriations report](#). The update also is provided on page 150 of the [FY 2022 Congressional Justification](#).

In response to the congressional request for the Women’s Health Conference (WHC) and update, the NIH Office of Research on Women’s Health (ORWH) developed a strategy to obtain input on the three priority areas from experts in women’s health, members of the public, and representatives from NIH Institutes, Centers, and Offices (ICOs) ([Figure 1](#)). ORWH formed and guided the Coordinating Committee on Research on Women’s Health (CCRWH) WHC Planning Committee—a subgroup of CCRWH members and ICO representatives. ORWH also assembled, guided, and participated in the NIH Advisory Committee on Research on Women’s Health (ACRWH) WHC Working Group—a subgroup of ACRWH members and *ad hoc* subject-matter experts who planned, led, managed, and hosted the conference.

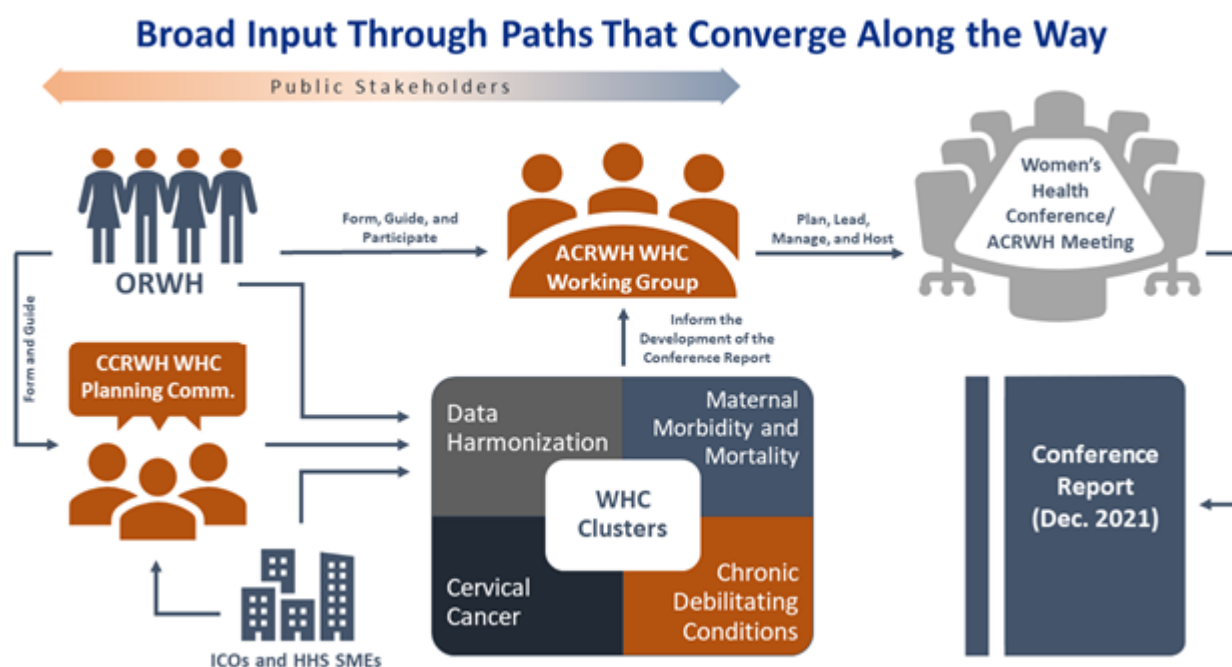


Figure 1. The strategy for the WHC and the conference report.

Definitions: ACRWH = Advisory Committee on Research on Women’s Health; CCRWH = Coordinating Committee on Research on Women’s Health; HHS = U.S. Department of Health and Human Services; ICOs = National Institutes of Health Institutes, Centers, and Offices; ORWH = Office of Research on Women’s Health; SMEs = subject-matter experts; WHC = Women’s Health Conference

Source: ORWH

The CCRWH WHC Planning Committee and ORWH established three “clusters” corresponding to the requested topics and a fourth cluster to harmonize the data. Co-led by a subject-matter expert from ORWH and an NIH scientist, each cluster was composed of subject-matter experts from NIH ICOs, other U.S. Department of Health and Human Services (HHS) agencies—including the Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS), and Health Resources and Services Administration (HRSA)—and the U.S. Department of Veterans Affairs. Each cluster completed focused assessments, reviews, and discussions on its respective topic area and presented findings, recommendations, and analyses to the ACRWH WHC Working Group. Whenever possible, as the official system of record for annual NIH funding on specific research topics, NIH’s [Research, Condition, and Disease Categorization \(RCDC\)](#) system was used as a metric of funding. The ACRWH WHC Working Group reviewed and discussed recommendations and data from the clusters and the CCRWH WHC Planning Committee while planning for the WHC and preparing this report.

On July 1, 2021, ORWH published a Request for Information (RFI) in the *Federal Register* ([86 FR 35099](#)) to inform the WHC. The RFI invited comments and testimonies from the extramural scientific community, professional societies, and the public to help identify research gaps, determine pitfalls in clinical practices, and obtain real-life testimonial experiences (direct or indirect) related to any or all of the three congressionally specified public health issues: MMM, CDCW, and cervical cancer survival rates. Members of the public could send questions to NIH and respond to the solicitation via email (whcc@od.nih.gov). The window for comments closed on September 15, 2021. Two hundred forty-seven comments were received from subject-matter experts and the public, and these helped shape the conference agenda. A summary of the comments is provided in [Appendix B](#).

The WHC, titled [Advancing NIH Research on the Health of Women: A 2021 Conference](#), was convened on October 20, 2021, intentionally coinciding with the ACRWH fall meeting on October 21, 2021. The goal of the conference was to assess the current state of NIH-supported women’s health research by identifying gaps and priorities in this area. The ultimate aims were to (1) recommend new NIH-wide women’s health research priorities for ORWH and the broader biomedical community and (2) develop recommendations for the future of NIH-funded women’s health research. The WHC agenda can be found in [Appendix A](#), and an overview of the conference proceeding can be found in [Appendix C](#). Meeting participants (1,084 attendees of the live session, 44 viewers of the live videocast, and 176 viewers of the [on-demand video recording](#) as of March 28, 2022) included women’s health researchers, NIH ICO representatives, and public stakeholders. Leading up to and after the meeting, ORWH worked closely with the ACRWH to prepare this conference report. At the ACRWH meeting following the WHC meeting, the WHC proceedings were summarized, and gaps in current research and opportunities for future research on the health of women and the three focus areas of the congressional request were reviewed and discussed. Subsequently, the ACRWH members voted on the specific gaps and opportunities that had been proposed and ranked by ACRWH working group members during meeting preparation.

Background: Public Health Needs in Three Focal Areas

Women's Health and Women's Health Research

- ORWH was established to ensure the inclusion of women in NIH-supported research.
- The health of women can be described best using a multidimensional framework for considering the effects of both internal (e.g., biological systems, processes, traits) and external (e.g., environmental, social) factors on the health of women across the life course.
- Research to advance the health of women depends on the consideration of [Sex as a Biological Variable \(SABV\)](#) in experimental design, data analysis, and reporting in biomedical and behavioral studies.
- The inclusion of women in clinical research is essential to generating science that can be generalized to all people who need an intervention.

In 1990, ORWH was established in response to concerns about the lack of inclusion of appropriate numbers of women in clinical research. The [formation of the Office](#) occurred within the broader context of increasing societal recognition that the health of women had been understudied and the growing interest in investigating sex differences in disease physiology. The acknowledgement that historically low representation of women in clinical trials had led to inadequate women's health care spurred the [NIH Revitalization Act of 1993](#). This law required NIH-funded researchers to enroll women and ethnic and/or racial minorities, including women of childbearing age, into clinical research trials.

NIH continually renews its longstanding commitment to research on the health of women, responds to public health and scientific priorities, and sets out a blueprint for the field in a strategic plan—the development of which is coordinated by ORWH in close collaboration with NIH ICOs. [Advancing Science for the Health of Women: 2019–2023 Trans-NIH Strategic Plan for Women's Health Research](#) serves as the current framework for advancing the NIH vision for this field: achieving a world in which the biomedical research enterprise fully integrates sex and gender influences, every woman receives evidence-based disease prevention and treatment tailored to her own needs, and women in scientific careers reach their full potential.¹¹

The strategic plan describes a multidimensional framework for considering the health of women across the life course ([Figure 2](#)), which is affected by many internal and external factors. The internal factors include genetic, molecular, cellular, and physiological processes within the human body. The external factors are contextual aspects of a woman's life and comprise environmental and social factors. Exposures to pollution, chemicals, stress, and [climate](#) are common examples of environmental factors. Social factors—such as gender, sexual orientation, and other social determinants of health—manifest on several levels, including the individual, family, community, and society. The complex intersection of these internal and external factors affects the health status, disease presentations, and treatment responses of women, as well as the effects of diseases and conditions on women's quality of life. Thus, consideration of a multidimensional framework is needed to improve the quality of women's lives, reduce their disease burden across the life course, and address health disparities for populations of women at greatest risk for certain diseases. This framework reflects the complex and intersecting factors that influence the health outcomes, disease presentations, and treatment responses of women, as well as how diseases and conditions affect their quality of life.¹² ORWH promotes the integration of this framework into experimental design, data analysis, and reporting to enhance the evidence base for women's health research and spur discoveries that improve outcomes, reduce disparities, and build a foundation for personalized medicine.^{13,14}

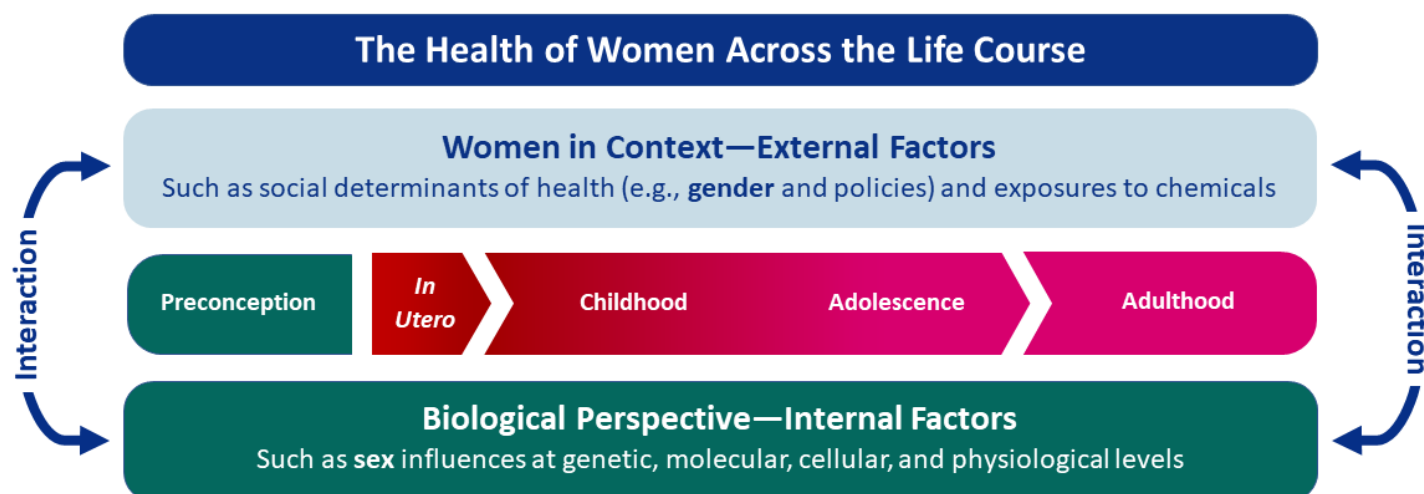


Figure 2. The ORWH multidimensional research framework representing the intersection of factors affecting the health of women.

Research to advance the health of women also depends on the consideration of SABV in experimental design, data analysis, and reporting in NIH-supported biomedical and biobehavioral research ([NOT-OD-15-102](#)).¹⁵ Incorporating SABV across the research continuum—from basic and preclinical studies to translational research to all phases of clinical trials—advances rigor, discovery, innovation, and health equity. Using SABV as a guiding principle throughout the research continuum can help address the critical needs in research on the health of women that are listed in this report by (1) identifying animal models and *ex vivo* human models (e.g., explants, organoids) that better reflect human diseases, (2) developing diagnostic tests and criteria that are sex- and gender-aware, and (3) understanding the increased risk of adverse events and reduced treatment effectiveness in women.¹⁶ To achieve the full integration of SABV (when there is not a good justification for single-sex research) across all fields of biomedical research and its incorporation into the training of researchers as standard practice, NIH has (1) provided additional guidance for researchers and grant reviewers to help implement its [SABV policy](#),^{17,18} (2) reported its multipronged efforts to further the implementation of the SABV policy,¹⁶ and (3) continued to work with partners to develop [online educational modules](#) that are free and open to researchers, clinicians, policymakers, and the public.

Having diverse cohorts within clinical trials is essential to generate science that can be generalized to all people who need an intervention. The *2019–2023 Trans-NIH Strategic Plan for Women’s Health Research* and NIH policy updates on the inclusion of women and minorities ([NOT-OD-18-014](#)) and people of all ages ([NOT-OD-18-116](#)) in clinical research encourage the intentional integration of these groups at every stage of the biomedical research continuum and in every discipline. The inclusion of pregnant and lactating participants in clinical trials is currently a focus at NIH, led by the *Eunice Kennedy Shriver National Institute of Child Health and Human Development* (NICHD) and the [Task Force on Research Specific to Pregnant Women and Lactating Women](#) (PRGLAC) and in alignment with the [21st Century Cures Act](#) (Public Law 114–255).

From its inception, ORWH has worked to increase the participation of women in biomedical research careers so that the brightest minds contribute to the biomedical research enterprise, regardless of background. Women undoubtedly have made progress in medicine; since 2003, half of medical school graduates have been women, and currently three-fifths (58%) of graduate students enrolled in biomedical doctoral programs are women.¹⁹ However, women remain disproportionately underrepresented in academic medicine leadership; they still represent only [22 percent of department chairs and 18 percent of deans](#).¹⁹ A robust biomedical workforce where women can thrive is critical for the health of women, because clinicians who are women are more likely to provide women’s health

care.²⁰ NIH has addressed this workforce gap by supporting research to identify best practices in the recruitment, retention, and advancement of women in academic medicine and continues the push for equity in advancement to leadership positions.^{19,21}

Maternal Morbidity and Mortality

- In the United States, the risk of death and complications from pregnancy and childbirth represents a public health crisis.
- A majority (over 60%) of U.S. maternal deaths are considered preventable.
- A disproportionate burden of MMM falls on non-White and rural populations.
- Pregnancy can be viewed as a stress test for lifelong health, because the physiological changes and complications experienced can increase risk of disease later in life.

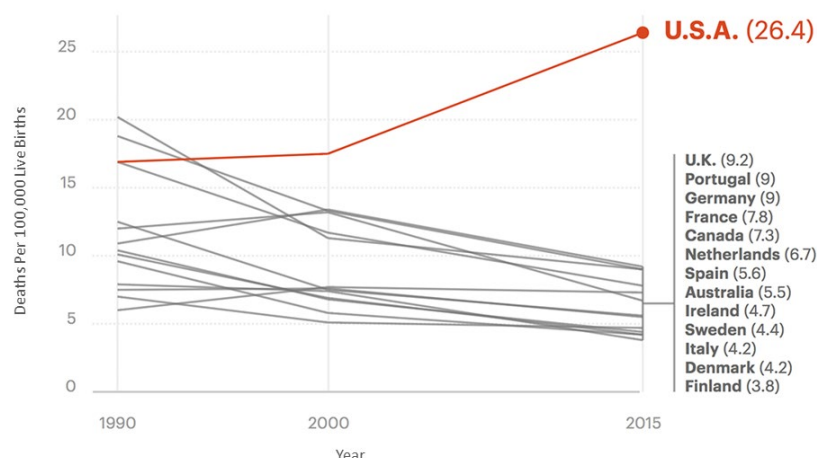


Figure 3. Maternal mortality is rising in the United States as it declines elsewhere.

Data were adapted from Patten SB, Javanbakht M, GBD 2015 Maternal Mortality Collaborators. *Global, Regional, and National Levels of Maternal Mortality, 1990–2015: A Systematic Analysis for the Global Burden of Disease Study 2015*. *Lancet*. 2017; **388**: 1775–812. doi: 10.1016/S0140-6736(16)31470-2. PMID: 28091383. Only data for 1990, 2000, and 2015 were made available in the journal.

Source: Martin N, Montagne R. *The Last Person You'd Expect to Die in Childbirth*. ProPublica and NPR. 2017. Available at: <https://www.propublica.org/article/die-in-childbirth-maternal-death-rate-health-care-system-1>.

Credit: Rob Weychert/ProPublica

During pregnancy and postpartum, many women experience complications affecting their physical, emotional, and social health; some develop serious, life-threatening conditions during this period. In the United States, the risk of death and complications from pregnancy and childbirth is a public health crisis. In 2020, 861 women died of maternal causes in the United States, for an overall maternal mortality rate (defined by the World Health Organization [WHO] as while pregnant or within 42 days of termination of pregnancy) of 23.8 deaths per 100,000 live births.²² Maternal mortality is greatly affected by women's access to health care and the rate of responsiveness of the health care system to their needs.²³ Access to care challenges due to the social determinants of health remain a major challenge in the United States. Rates of U.S. maternal mortality are considerably higher than those of peer countries (Figure 3).²⁴

Improvements in the accuracy of counting the rate of maternal deaths, including the addition of checkboxes to standard death records, have contributed to the increases in recorded MMM rates over the past 3 decades.^{25,26} Both WHO and CDC capture data and report on pregnancy-related causes of death and MMM via such systems as the [Pregnancy Mortality Surveillance System \(PMSS\)](#).

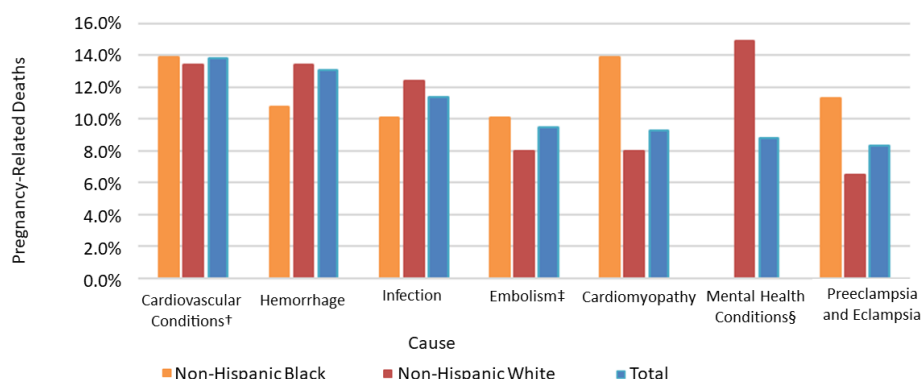
Table 1. Key Terms and Definitions Related to MMM

Term	Definition
maternal morbidity	Any health condition attributed to and/or aggravated by pregnancy and childbirth that has a negative impact on a women's well-being. (World Health Organization [WHO])
severe maternal morbidity (SMM)	Unexpected outcomes of labor and delivery that result in significant short- or long-term consequences to a woman's health. (Centers for Disease Control and Prevention [CDC])
maternal death	The death of a woman while pregnant or within 42 days of termination of pregnancy. This definition excludes deaths from accidental or incidental causes. (WHO and CDC)
pregnancy-related death	The death of a woman while pregnant or within 1 year of the end of a pregnancy—regardless of the outcome, duration, or site of the pregnancy—from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes. (CDC's Pregnancy Mortality Surveillance System [PMSS])
pregnancy-related mortality ratio (PRMR)	Estimate of the number of pregnancy-related deaths for every 100,000 live births. (CDC)

The distinction between pregnancy-related causes of death and pregnancy-associated deaths—that is, a maternal death that is attributable to a condition unaffected by the pregnancy, even if it occurred within 1 year of pregnancy—is important to note, because deaths of pregnant women from suicide, homicide, and drug overdose are currently considered pregnancy associated rather than pregnancy related and are not included in PMSS statistics.^{26,27} Maternal mortality is, therefore, most likely underreported, and occurs disproportionately in understudied and underrepresented populations.

Etiology of Maternal Morbidity and Mortality

An estimated 60–66 percent of U.S. maternal deaths are considered preventable.²⁸ Cardiovascular conditions (e.g., cardiomyopathy, cerebrovascular accidents) accounted for more than one-third of deaths, according to an analysis of data collected from 14 maternal mortality review committees (**Figure 4**).²⁸ These findings highlight the importance of managing preexisting risk factors and chronic conditions (e.g., obesity, hypertension, diabetes mellitus, mental health disorders) and complications that arise during pregnancy (e.g., hypertensive disorders of pregnancy, gestational diabetes) as a major strategy in the prevention of severe maternal morbidity (SMM) and maternal deaths.²⁹



[†]Cardiovascular conditions include deaths due to coronary artery disease, pulmonary hypertension, acquired and congenital valvular heart disease, vascular aneurysm, hypertensive cardiovascular disease, Marfan syndrome, conduction defects, vascular malformations, and other cardiovascular disease and excludes cardiomyopathy and preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia, which are categorized separately.

[‡]Embolism includes thrombotic pulmonary or other embolism (i.e., air, septic, or fat). It does not include amniotic fluid embolism.

[§]Mental health conditions include deaths due to suicide, overdose/poisoning, and unintentional injuries determined by the Maternal Mortality Review Committee to be related to a mental health condition.

Figure 4. Leading underlying causes of pregnancy-related deaths, overall and by race/ethnicity, using data from 14 maternal mortality review committees, 2008–2017.

Adapted from Davis NL, Smoots AN, Goodman DA. Pregnancy-Related Deaths: Data From 14 U.S. Maternal Mortality Review Committees, 2008–2017. Atlanta (GA): Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. 2019.

Advanced maternal age also is a major contributor to maternal mortality disparities; for several decades, age of first birth in the United States has been increasing. CDC data indicated that the 2019 maternal mortality rate for people who were 40 or older during their first pregnancy was six times higher than the rate for women younger than age 25 (75.5 deaths per 100,000 live births versus 12.6). An analysis of 2016–2017 CDC data, supplemented by text written on death certificates, demonstrated that the rate (factoring deaths during pregnancy and up to 42 days postpartum) for women ages 35–39 was twice as high as the rate for women younger than 35, the rate for women ages 40–44 was four times higher, and the rate for women ages 45–54 was 11 times higher.³⁰

Data on the timing of maternal deaths are available and potentially can guide research and clinical practice. Cardiovascular deaths, for example, primarily occur postpartum. An analysis of PMSS data from 13 states between the years 2011 and 2015 indicated that among pregnancy-related deaths for which data on the timing in relation to the birth or fetal death were provided (87.7% of the cases), 31 percent of deaths occur during pregnancy, 17 percent on the day of delivery, and more than half of pregnancy-associated deaths occur following delivery; following pregnancy, risk continues through 1 year postpartum.²⁸

Equity

Compounding the high burden of maternal mortality in the United States are large inequities disproportionately borne by non-White women. In 2020, non-Hispanic Black women experienced the highest maternal mortality rate, at 55.3 deaths per 100,000 live births—2.9 times higher than the rate for White women (19.1) and significantly higher than the rate for Hispanic women (18.2).²² Pregnancy-related deaths in the United States between 2007 and 2016 occurred at an overall rate of 16.7 per 100,000 live births, with rates for Hispanic (11.5), White (12.7), and Asian American/Pacific Islander (13.5) women below the overall level and those of American Indian/Alaska Native (29.7) and Black (40.8) women much higher.³¹ An in-depth analysis of death certificates from 2016 to 2017 found that the overall maternal mortality rate among Black women was higher than previously thought—3.5 times that of White women.³² Furthermore, maternal deaths occurring more than 42 days after pregnancy to 1 year postpartum were highest among Black women.³³

A growing body of research details the underlying structural factors driving many racial and ethnic inequities in MMM across the pregnancy continuum (Figure 5). Among hospitals serving majority Black patients (> 50% of deliveries), compared with those primarily serving White or Hispanic patients, overall performance on delivery-related indicators was lower, and higher rates of delivery complications have been described.³⁴ Integrating midwifery models and incorporating doulas into prenatal, delivery, and postpartum settings can provide person-centered, low-risk pregnancy care. Yet U.S. women have relatively limited access to midwifery care in many settings because of lack of insurance coverage, geographical variation

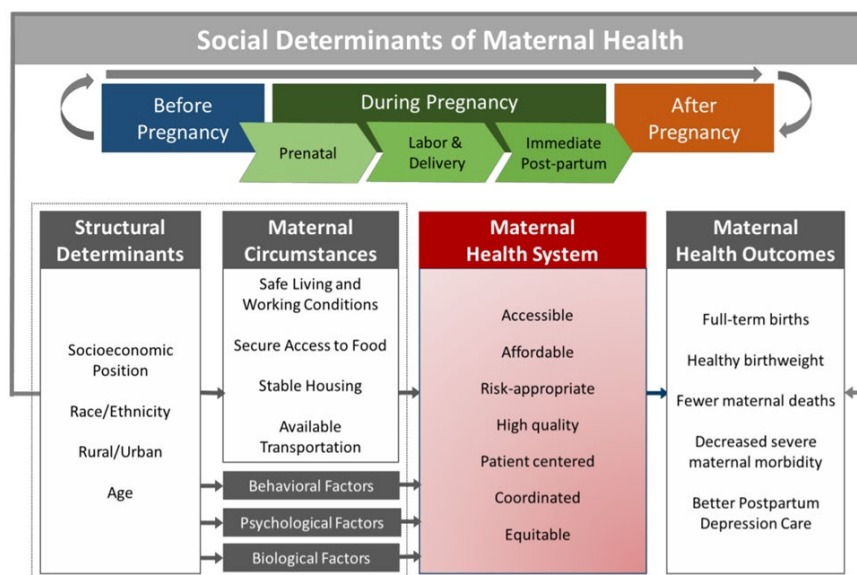


Figure 5. Social determinants of maternal health.

Source: Manyazewal T. Using the World Health Organization Health System Building Blocks Through Survey of Healthcare Professionals to Determine the Performance of Public Healthcare Facilities. Archives of Public Health. 2017 Dec; 75(1): 50. doi: 10.1186/s13690-017-0221-9. PMID: 29075485.

in certification requirements and admitting privileges, and lack of integration and coordination of midwifery care with obstetric care.³⁵ Furthermore, much of the obstetrics workforce (74% of obstetrician gynecologists and more than 90% of midwives) is White, leaving many women from underrepresented communities with racially or ethnically discordant providers.³⁵⁻³⁷

The quality of maternity care across the United States varies considerably, complicating our understanding of inequities.³⁸ Residence in remote areas and neighborhoods with low socioeconomic status has been linked to increased risk for negative maternal outcomes. In fact, a recent analysis showed that women living in rural areas have a 60 percent higher risk of pregnancy-related death than women in urban areas.³⁹ Higher risk of SMM and MMM among rural pregnant people and birthing people is linked to challenges in accessing specialty women's health services; longer average distances to treatment facilities, higher rates of uninsured or underinsured people, and higher frequency of chronic conditions have all been demonstrated.⁴⁰⁻⁴² More than half of rural counties lack a hospital providing maternity care or a delivering obstetrician (**Figure 6**), meaning that women in these areas often lack access to high-risk obstetric care.^{43,44}

Quality Improvements and Innovation

Since 2013, the Council on Patient Safety in Women's Health Care and the Alliance for Innovation on Maternal Health Program, through a cooperative agreement between the American College of Obstetricians and Gynecologists and the HRSA Maternal and Child Health Bureau, have developed 10 patient "safety bundles" for maternal health, including for racial and ethnic inequities in maternal health.⁴⁵ These bundles provide best practices for improving safety in maternity care to help clinicians and the obstetrical team and ensuring that facilities are prepared to consistently manage the care of high-risk pregnant women, including the most common preventable complications identified by CDC.^{46,47} The use of these bundles improves outcomes by ensuring reliable, evidence-based care delivery; promoting team collaboration; and helping organizations and health care teams systematically improve care processes.⁴⁶ Several states are addressing MMM by joining CDC's National Network of Perinatal Quality Collaboratives, which offers tools, resources, and advice from care teams who have implemented successful perinatal quality improvement projects.⁴⁶ California, for example, enacted a multipronged approach to reducing MMM in 2006 (**Figure 7**). By 2013, the state's maternal mortality rate had halved.⁵ The creation of a coordinated hospital-level collaborative and statewide initiatives in California also were associated with decreased rates of cesarean delivery between 2014 and 2019.⁴⁸

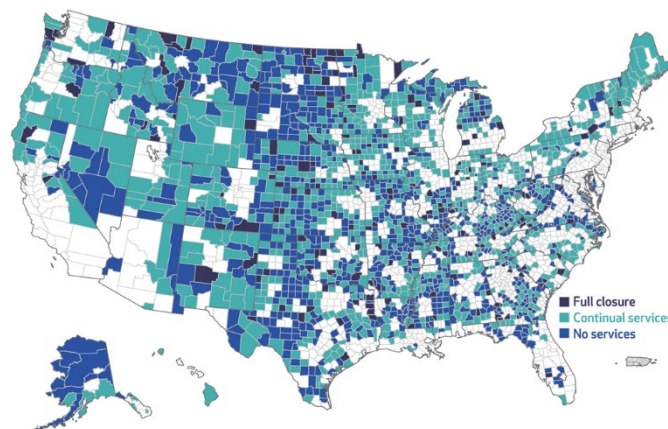


Figure 6. Hospital obstetric services in U.S. counties, 2004–2014.

Analysis of data for 2003–2014 from the American Hospital Association Annual Survey, for 2004–2014 for county-level obstetric services status from the Centers for Medicare and Medicaid Services' Provider of Services files, and for 2013 for metropolitan and nonmetropolitan designation from the Office of Management and Budget.

Source: Hung P, Casey MM, Kozhimannil KB, Karaca-Mandic P, Moscovice IS. Rural–Urban Differences in Access to Hospital Obstetric and Neonatal Care: How Far Is the Closest One? *Journal of Perinatology*. 2018; **38**(6): 645-52. doi: 10.1038/s41372-018-0063-5

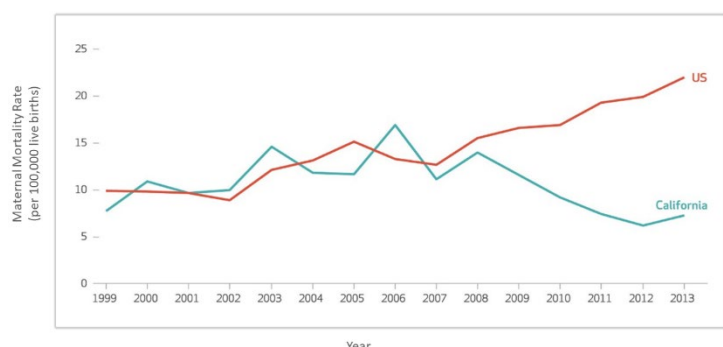


Figure 7. Maternal mortality rates per 100,000 live births in California and the United States, 1999–2013.

Data come from the following sources in the public domain. California data: California Department of Public Health, Center for Family Health, Maternal, Child and Adolescent Health Division, March 2015, and the California Birth and Death Statistical Master Files. U.S. data: 1999–2007 data come from the National Center for Health Statistics (NCHS), and 2008–2013 data come from CDC WONDER, Centers for Disease Control and Prevention.

Source: Main EK, Markow C, Gould J. Addressing Maternal Mortality and Morbidity in California Through Public–Private Partnerships. Health Affairs (Millwood). 2018; 37(9): 1484–93. doi: 10.1377/hlthaff.2018.0463. PMID: 30179538

Bundles with best practices for managing postpartum care also have been developed (“Postpartum Care Basics for Maternal Safety from Birth to the Comprehensive Postpartum Visit” and “Postpartum Care Basics for Maternal Safety: Transition from Maternity to Well-Woman Care”).⁴⁷

Extending eligibility for Medicaid is a policy intervention that has received considerable attention because Medicaid provides insurance coverage for a large percentage of U.S. pregnancies (42.1% of deliveries in 2019).⁴⁹ Currently, there are state-by-state differences in coverage for pregnant women beyond 60 days postpartum. State differences in income eligibility limits for public insurance (as a percentage of the Federal poverty level) mean that many publicly insured new parents lose coverage during the first year postpartum, when the risk for medical events is high.⁵⁰ States with expanded Medicaid coverage have lower maternal mortality rates and improved the health of women of childbearing age.⁵¹ Other work suggests that more structural interventions are needed to sufficiently improve perinatal health and birth outcomes nationwide.⁵²

Life Course Perspective

Health conditions occurring pre-pregnancy, during pregnancy, and postpartum contribute to lifelong physical, emotional, and social well-being.¹³ To improve transitions during the postpartum period and ensure that health conditions uncovered during pregnancy are addressed, the “Bridging the Chasm (BtC) Between Pregnancy and Women’s Health Over the Life Course” initiative was launched in 2018. BtC worked with stakeholders and identified six key areas for bridging the chasm between maternity care and primary care. The initiative’s recommendations included extending team-based care to the postpartum year and beyond, integrating doulas and community health workers, and expanding Medicaid coverage and new quality and pay-for-performance metrics to link maternity care with primary care.⁵³

Pregnancy can be viewed as a stress test for health, both during pregnancy and later in life, because the physiological changes and complications can increase the risk of death during and in the year after pregnancy and for disease later in life.⁵⁴ The life course perspective—considering how a woman’s overall health influences pregnancy and how complications and SMM affect her health after pregnancy and well beyond her childbearing years—is the framework to consider the interaction of risk and protective factors that shape health outcomes beyond pregnancy. This approach is critical to improving maternal health outcomes and, ultimately, women’s health.⁵⁵ For example, a diagnosis of early-onset hypertensive disorders of pregnancy is associated with more than twice the risk of developing incident cardiovascular disease (CVD) and more than a fourfold risk of developing incident hypertension.⁵⁶

Chronic Debilitating Conditions in Women

- With aging and women's longer life expectancy compared with men, chronic debilitating conditions and multimorbidity pose a significant burden on the health of women.
- The lack of a consistent, clear definition of chronic debilitating conditions makes it difficult to estimate the true prevalence and impact of chronic conditions within the U.S. population of women.
- The etiology of chronic conditions (e.g., osteoarthritis), symptoms of disease (e.g., heart attack), responses to treatment, and impacts on comorbidities experienced by women are often different than those experienced by men.
- Hormonal transitions (e.g., puberty, pregnancy, and menopause) are linked with the emergence of age- and sex-related differences in disease.

Chronic conditions include a wide array of diseases and disorders across the lifespan of women.⁵⁷ With aging and women's longer life expectancy compared with men, chronic debilitating conditions pose a significant burden on the health of women.

Definitions

In 2010, HHS defined chronic illnesses as “conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living.”⁵⁸ CMS developed a set of information products and analytics examining chronic conditions to provide researchers and policymakers with a better understanding of the burden of chronic conditions. For this purpose, [CMS currently defines 21 conditions as chronic](#).⁵⁹

- | | |
|---|---|
| • Alcohol Abuse | • Drug Abuse/Substance Abuse |
| • Alzheimer's Disease and Related Dementia | • Heart Failure |
| • Arthritis (Osteoarthritis and Rheumatoid) | • Hepatitis (Chronic Viral B & C) |
| • Asthma | • HIV/AIDS |
| • Atrial Fibrillation | • Hyperlipidemia (High cholesterol) |
| • Autism Spectrum Disorders | • Hypertension (High blood pressure) |
| • Cancer (Breast, Colorectal, Lung, and Prostate) | • Ischemic Heart Disease |
| • Chronic Kidney Disease | • Osteoporosis |
| • Chronic Obstructive Pulmonary Disease | • Schizophrenia and Other Psychotic Disorders |
| • Depression | • Stroke |
| • Diabetes | |

There is a strong association between the diagnosis of a chronic debilitating condition and the accumulation of chronic diseases with age. Rising rates of such conditions are one consequence of longer lifespans. Rates of multimorbidity, defined as the simultaneous occurrence of two or more diseases that may or may not share a causal link, also become more common with age. However, the lack of a consistent, well-defined definition of chronic diseases makes estimating the true prevalence of chronic conditions within the U.S. population difficult. Data from the 2018 National Health Interview Survey (NHIS) estimate more than half (51.8%) of adults had at least 1 of 10 commonly diagnosed chronic conditions (arthritis, cancer, chronic obstructive pulmonary disease [COPD],

coronary heart disease, asthma, diabetes, hepatitis, hypertension, stroke, and renal dysfunction), and 27.2 percent of U.S. adults had multiple chronic conditions.⁶⁰ A cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES) showed that 59.6 percent of U.S. civilians age 20 years or older had two or more chronic conditions, 38.5 percent had three or more, and 22.7 percent had more than four.⁶¹

Influence of Sex and Gender

Sex and gender differences in the prevalence and clinical presentation of chronic conditions have been documented. CMS data (fee-for-service beneficiaries, excluding Medicare Advantage enrollees), disaggregated by sex, note that six conditions occur more frequently in women (**Figure 8**): hypertension, arthritis, depression, dementia, osteoporosis, and asthma.⁵⁹ Women have multimorbidity more commonly than men because women have longer life expectancies than men.⁶² Lower socioeconomic status and lower education level are also risk factors for multimorbidity that further disadvantage women.⁶¹

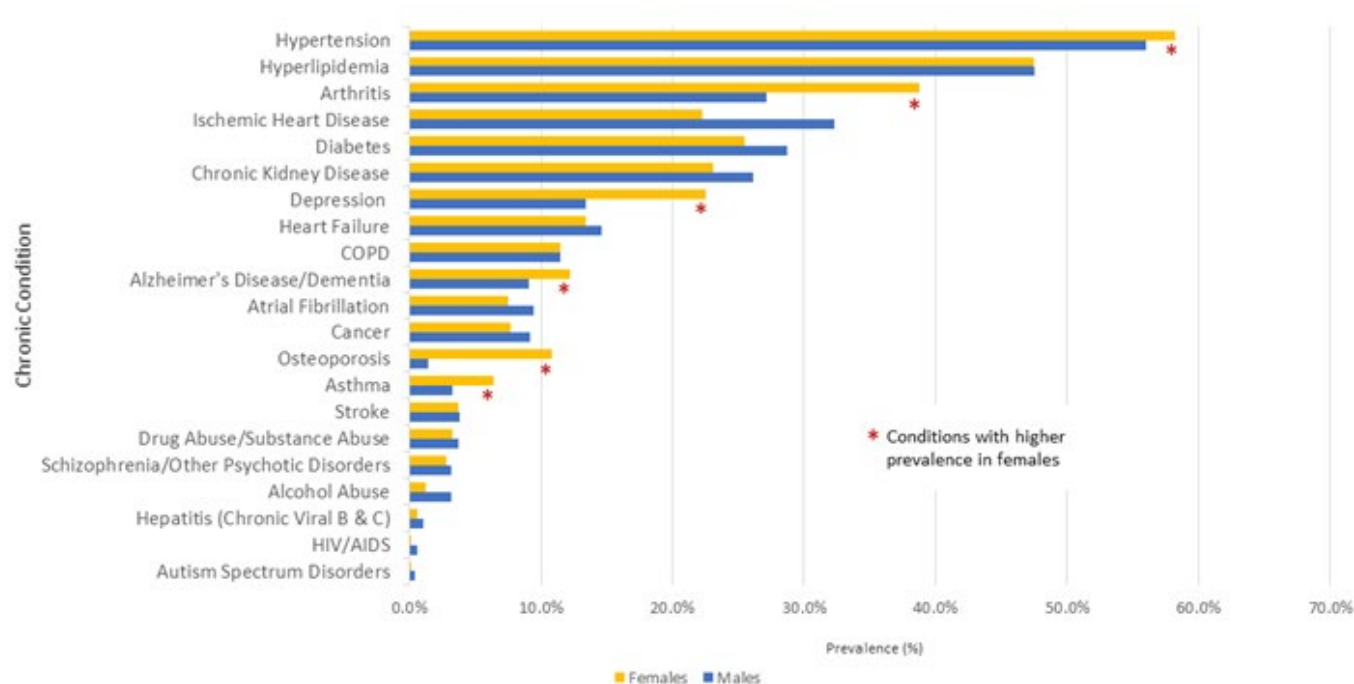


Figure 8. Prevalence of chronic conditions among fee-for-service Medicare beneficiaries by sex, 2018.

Definition: COPD = chronic obstructive pulmonary disease

Importantly, symptoms of disease experienced by women are often different from those experienced by men; because of our historical over-reliance on men in clinical research, the symptoms displayed by women often are referred to as “atypical.” For example, during a heart attack, women may experience back pain or pressure, rather than chest pain or pressure; dizziness; and extreme fatigue.⁶³ Similarly, women can experience nonspecific symptoms (e.g., confusion; general weakness, as opposed to weakness on one side of the body) during a stroke.⁶⁴ Lower response rates to first-line treatments in women also likely result from an evidence base created from clinical research where men made up the majority of participants. The “networks” of morbidity are different in women, with multimorbidity more likely to cross multiple organ systems than in men.⁶⁵ Additionally, the pattern of accumulation of morbidity—meaning what initial chronic conditions are diagnosed and how conditions are additive—differs by sex and gender.⁶⁶ In women with multimorbidity, the interactions among conditions are poorly understood and often inadequately treated.⁶¹

Another challenge in defining CDCW is the broad assumption that women's health is inexorably linked to reproductive health. Hormonal transitions are linked with the emergence of age- and sex-related differences in disease risk beyond conditions linked to reproduction. Sex differences in the innate and adaptive immune system after puberty can influence the risk for disease (e.g., asthma), autoimmunity, and response to vaccination and cancer therapies.⁶⁷ Chronic disease risk—including for coronary heart disease, cancers, musculoskeletal conditions, chronic pain, obesity, diabetes, and cognitive impairment—accumulate with age and generally increase after menopause, when reproductive hormone production declines.^{68,69} The rapid hormonal changes during the menopausal period influence several systems, including but not limited to vascular, neurocognitive, metabolic, genitourinary, sexual health, and bone metabolism. These changes correlate with an increase in systemic inflammatory biomarkers, which can indicate future poor performance-based outcomes (e.g., physical functioning).

CVD illustrates the need to incorporate the life course perspective (especially information on pregnancy and menopause) when considering women's health care. Hypertensive disorders during pregnancy can increase the risk of developing hypertension within 3 years after giving birth.⁷⁰ Menstrual abnormalities with or without a diagnosis of polycystic ovarian syndrome (PCOS) prior to menopause are associated with higher risk of CVD later in life.^{71,72} The likelihood of heart disease increases for all women after menopause, in part because the drop in estrogen is associated with vascular endothelial changes.⁷³ The Women's Health Initiative, which was the largest randomized, placebo-controlled trial evaluating menopausal hormone therapy (MHT) in postmenopausal women, demonstrated increased risk of CVD events with MHT. However, subsequent secondary analyses have demonstrated that these risks differ by hormonal preparation, age, and time since menopause. The ideal dosing and timing of hormonal therapy needed to mitigate CVD risk is unknown, as is the risk-to-benefit ratio of treating menopausal symptoms.⁷⁴

The social construct of gender and its effects on social roles, and interaction with individual providers and the health care system, influence the development and treatment of chronic diseases and multimorbidity in women. Gender differences have been documented for patient-provider interactions, showing that women's symptoms often are dismissed and diagnosis is delayed. Even when the diagnosis is made, women may face delays in referral for care or even not be offered care at the same rate as men. For example, late referral for osteoarthritis (based on patient or health care professional factors) for women results in worse function at the time of joint replacement surgery, affecting the level of function that women achieve after surgery.⁷⁵ Societal tolerance of a lack of research and treatment options for prevalent and high-burden, female-specific chronic diseases (e.g., endometriosis) might reflect low levels of awareness, stigma around menstrual disorders, and the expectation that the pain of women is somehow normal.⁷⁶

These issues are magnified for women from underrepresented racial and ethnic groups, those who are socioeconomically disadvantaged, and those without health insurance. Research shows that gender and other social determinants of health play a significant role in the risk for multimorbidity across the life course.⁶¹ Importantly, some female-specific chronic conditions occur more frequently in women in certain historically underrepresented racial and ethnic groups (e.g., uterine fibroids in Black women).⁷⁷ Racial and ethnic differences, as well as the effects of other social determinants of health in the prevalence of multimorbidity, remain controversial and less explored.⁶²

Development of a Framework for Chronic Debilitating Conditions in Women

Because of the many challenges associated with defining CDCW and the lack of female-specific chronic disease models, a framework was created for the WHC and NIH portfolio analyses ([Table 2](#)). This framework categorized CDCW into the following: (1) female specific, (2) more common in women and/or morbidity is greater for women, (3) potentially understudied in women, and (4) high morbidity for women.⁷⁸ Within this framework, disability-adjusted life years (DALYs), defined by WHO as "the loss of the equivalent of 1 year of full health," were used as a metric to measure the burden of disease. DALYs for a disease or health condition are the sum of the years of life lost due to premature mortality and the years lived with a disability due to prevalent cases of the disease or health condition in a population.⁷⁹

Table 2. A Framework for CDCW

Condition Analysis Category	Condition (2019 United States Disability Adjusted Life Years [DALYs] for conditions where available)								
Female Specific	Cancers of the Female Reproductive Tract* (900,843)	Dysmenorrhea/ Abnormal Menses (289,608)	Fibroids* (64,009)	Endometriosis* and Adenomyosis (53,777)	Infertility*/ Early Pregnancy Loss (26,355)	Polycystic Ovary Syndrome (42,738)	Pelvic Floor Disorders, Organ Prolapse (21,613)	Menopausal Symptoms, Pelvic Inflammatory Disease,* Vulvodynia*/Chronic Gynecologic Pain Disorders—Pelvic and Vulvar, Vaginosis	
More Common in Women and/or Morbidity Is Greater for Women	Depressive Disorders (1,704,524)	Migraine/ Headache (1,573,325)	Breast Cancer* (1,387,670)	Asthma (820,435)	Autoimmune Diseases (Including Rheumatoid Arthritis,* Systemic Lupus Erythematosus,*Sjögren’s,* Scleroderma*)	Rheumatoid Arthritis* (187,902)	Multiple Sclerosis (143,123)	Sexually Transmitted Infections (STIs) (37,316)	Temporo-Mandibular Muscle/Joint Disorder (TMJD),* Chronic Fatigue Syndrome,* Fibromyalgia,* Candidiasis, Irritable Bowel Syndrome, Interstitial Cystitis,* HPV Infection,* Osteoporosis,* Eating Disorders
Potentially Understudied in Women	Unintentional Injuries (Includes Violence Against Women)* (2,050,026)	Alzheimer’s Disease/ Dementia (1,296,376)	Osteoarthritis (1,257,042)	Endocrine, Metabolic, Blood, and Immune Disorders	Recurrent Urinary Tract Infection/ Interstitial Nephritis	HIV (118,596)	Exogenous Hormone Use, Neuropathy, Post-Traumatic Stress Disorder, Overactive Bladder/Incontinence, Chronic Pain (Including Chronic Pelvic Pain)		
High Morbidity for Women	Heart Disease (3,396,660)	Lower Back Pain (3,168,583)	Chronic Obstructive Pulmonary Disease (2,568,947)	Drug Use Disorders (2,323,237)	Stroke (2,098,900)	Diabetes (2,010,853)	Obesity/Metabolic Disease, Influenza and Pneumonia		
*Per Manual Categorization System-Women’s Health reporting guidance, the starred Research, Condition, and Disease Categorizations (RCDC) are considered particularly relevant to women’s health. Sources: DALYs obtained from http://ghdx.healthdata.org/gbd-results-tool ; RCDC spending obtained from https://report.nih.gov/funding/categorical-spending# .									

The diagnosis and treatment of female-specific chronic diseases can be complex because of the previously mentioned impacts of gender on health. These factors, in addition to a history of inadequate clinical research, contribute to the underdiagnosis and insufficient evidence base for diagnosis and treatment of female-specific conditions, which might negatively affect outcomes.⁸⁰ Receiving a definitive diagnosis of endometriosis typically requires 4–11 years from symptom onset.⁸¹ PCOS increases the risk for other chronic health problems (e.g., depression, anxiety, and eating disorders); can have multiple phenotypes; and may be linked with obesity, infertility, endometrial cancer, and other malignancies.^{82,83} Studies of medical treatment for fibroids, the most common gynecological disorder, have been of low or moderate quality.⁸⁴

Many chronic conditions are not female specific but occur at substantially higher rates in women than in men. These include, but are not limited to, depression; headache, including migraine; breast cancer; asthma; and autoimmune diseases, including rheumatoid arthritis. Women constitute nearly 80 percent of the population affected by autoimmune disease and bear a disproportionately high morbidity associated with this spectrum of conditions. The influence of female hormones on the immune system is thought to be a major component of this gender gap.⁸⁵ Other disorders, such as depression, are thought to be disproportionately high among women for a combination of innate factors (e.g., fluctuations in hormones), as well as social factors (e.g., high rates of exposure to intimate partner violence).^{86,87}

Other chronic debilitating conditions are not female specific and do not have sex-specific etiologies but remain studied more commonly in men than in women. These include such disorders as HIV, which does not have a sex-specific etiology, and Alzheimer's disease and dementia, about which sex-specific risk factors have been identified. These conditions increasingly affect women yet remain socioculturally associated with men.^{88,89}

Many chronic conditions with higher incidence in men cause significant morbidity in women but go unrecognized as significant women's health issues. Among American women and health care providers, only 45 percent of women knew that CVD is the leading cause of death among women.⁹⁰ Sex differences in cardiovascular structure and function increase the risk of worse CVD outcomes for women. This disparity may relate to the onset of CVD at an older age (by about 10 years) and the greater likelihood of co-occurring chronic diseases among women.⁹¹ COPD historically affected many more men than women, but its prevalence among women has equaled that of men since 2008, due in part to increased tobacco use among women worldwide. Despite this evidence, women remain underdiagnosed compared with men and receive fewer spirometry tests and medical consultations.⁹² Among patients with diabetes, there is a higher prevalence of obesity and poorer blood pressure control in women, both of which can cause cardiovascular complications. Diabetes also is a stronger risk factor for stroke in women than in men.^{93,94}

Stagnant Cervical Cancer Survival Rates

- In the United States, the incidence of cervical cancer declined significantly in the decades following the introduction of widespread cancer screening programs in the 1950s.
- Despite the effectiveness of screening in preventing cervical cancer and the availability of a vaccine that prevents this disease, survival rates have changed minimally over the past 2 decades.
- Large geographic, racial, and ethnic inequities in mortality from cervical cancer are seen across the United States.

Cervical cancer is a global public health problem, and the burden of this condition is inversely related to social and economic development.⁹⁵ Worldwide, it is the second-most common cancer among women, with an estimated

604,127 new cases in 2020.⁹⁶ In 2020, an estimated 342,000 women died from cervical cancer worldwide, and mortality rates were considerably higher in lower-resource countries.⁹⁶

In the United States, the incidence of cervical cancer declined significantly in the decades following the introduction of widespread cancer screening programs in the 1950s. However, the Surveillance, Epidemiology, and End Results (SEER) Program estimates that by the end of 2021 in the United States, there will have been 14,480 new cases of cervical cancer, with an incidence rate of 7.5 per 100,000 women.⁹⁷ There are large geographic variations in cervical cancer incidence—for example, rates in Arkansas and Kentucky are two to three times higher than in Vermont and New Hampshire.⁹⁸ In the United States, the 5-year relative survival rate for women diagnosed with cervical cancer between 2011 and 2017 was 66.3 percent.⁹⁷ The age-adjusted death rate from cervical cancer fell by 0.7 percent annually between 2009 and 2018, with a projected 2021 rate of 2.2 per 100,000 women. This survival improvement is less than recent survival benefits observed in other cancers affecting women (e.g., breast, ovarian, lung).^{99,100}

Human papilloma virus (HPV) is the established cause of nearly all cervical cancers. The natural history of HPV-related carcinogenesis is well understood and widely accepted. HPV infection is acquired by most individuals of both sexes at some point during their life. Of more than 100 subtypes, several are carcinogenic, and types 16 and 18 cause roughly 70 percent of cervical cancer. Although most viral changes to the cervix will regress within 6 to 18 months of HPV infection and those lesions that do not resolve can progress to cancer, the progression takes 12–15 years and occurs in steps from low-grade abnormalities to high-grade premalignancies to an early invasive cancer. In addition to its role in cervical cancer, HPV causes most cancers of the anal canal, vagina, penis, and vulva, and approximately one-quarter of cancers of the head and neck.¹⁰¹ Multiple opportunities for cancer prevention and screening (Figure 9) can be exploited across this timeline.¹⁰²

Screening and Prevention

The predictable and lengthy latent period between HPV infection and progression to cervical cancer has allowed for successful cancer prevention through screening interventions.¹⁰² Both liquid-based cytology and high-risk HPV testing have improved the test characteristics of screening, allowing the most recent screening guidelines from the U.S. Preventive Services Task Force to extend intervals between screening from yearly to every 3–5 years, depending on a patient's risk.¹⁰³ Despite the effectiveness of screening in preventing cervical cancer, several groups remain at risk of underscreening, including those who have less education, are living below the Federal poverty level, are under- or uninsured, or do not have usual sources of care.¹⁰⁴ Although routine cervical cancer screening is recommended and covered under the Affordable Care Act, a recent survey of 702 low-income women who were uninsured or publicly insured found that they perceived multiple barriers to engaging in this crucial preventive

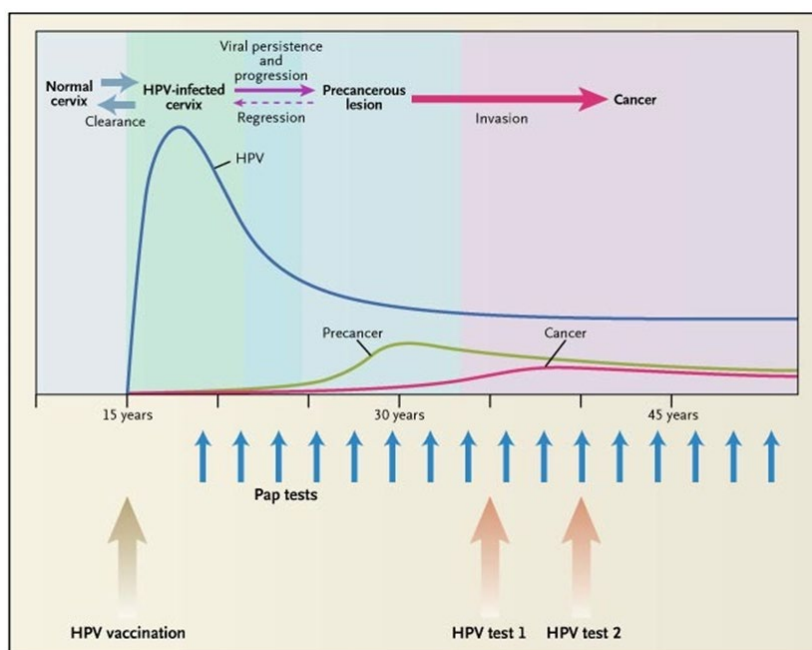


Figure 9. The natural history of HPV infection and cervical cancer and opportunities for screening and prevention.

Definition: HPV = human papilloma virus

Source: Schiffman M, Castle PE. *The Promise of Global Cervical Cancer Prevention*. New England Journal of Medicine. 2005; **353**(20): 2101-4. doi: 10.1056/NEJMp058171. PMID: 16291978.

service, with 72 percent citing financial barriers, such as the costs of screening and follow-up visits.¹⁰⁵ More than half of women diagnosed with cervical cancer in the United States have never been screened.¹⁰⁶

Following abnormal cervical cancer screening, many women require more frequent surveillance (yearly screening), and some require colposcopy-directed biopsies. Ensuring adequate follow-up after abnormal cervical cancer screening is a challenge for many patients for multiple reasons, such as financial barriers or lack of access to specialty care.¹⁰⁷ Nearly 24 percent of patients with an abnormality identified during screening do not receive adequate follow-up.¹⁰⁸

HPV vaccines have been available in the United States as a cervical cancer prevention tool since 2006. The Advisory Committee on Immunization Practices currently recommends a two-dose vaccination regimen for boys and girls at age 11 or 12, with catch-up vaccination recommended up to age 26 and consideration of vaccination up to age 45.¹⁰⁹ However, uptake of the HPV vaccine in the United States continues to be generally lower than that of other childhood vaccines (**Figure 10**), with only 40 percent of eligible people (70% of adolescents) vaccinated in 2018.^{110,111} Large geographic variations in vaccination exist (**Figure 11**), with individuals who live in the South and some Western states at highest risk for not being vaccinated against HPV.¹¹² U.S. HPV vaccination rates lag behind those of other high-income countries, such as Canada and Australia.¹¹³ The first report of population-level efficacy of vaccination in preventing invasive cervical cancer was published in 2020, presenting Swedish data.¹¹⁴

Diagnosis and Treatment

Stage at diagnosis is the most important prognostic factor of cervical cancer survival and, due to the high burden of disease in low-resource settings, remains primarily clinically defined.¹¹⁵ In 2018, the International Federation of Gynecology and Obstetrics (FIGO) provided cervical cancer definitions and a staging system that are accepted uniformly and endorsed by the American Joint Committee on Cancer.¹¹⁶ In high-resource settings, such as the United States, all imaging modalities—including computed tomography, magnetic resonance, and positron emission tomography—are utilized in diagnosis and staging.¹¹⁷

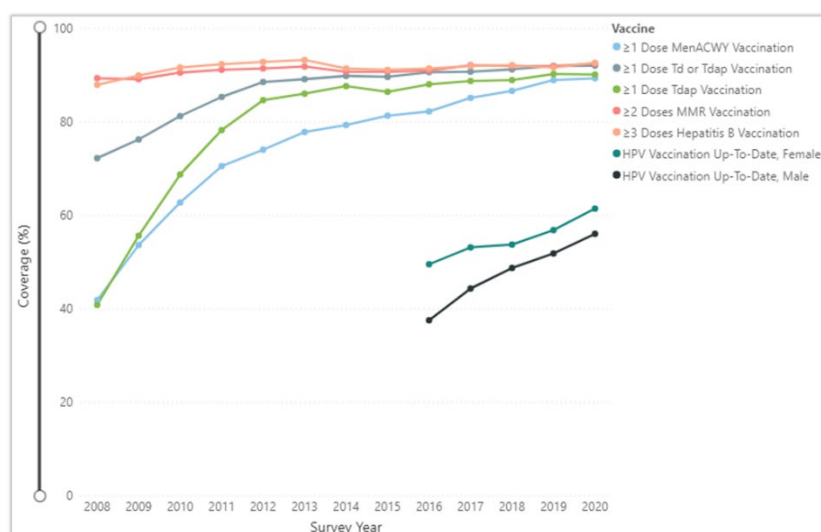


Figure 10. Vaccination coverage by year among adolescents ages 13–17 years, United States, National Immunization.

Definitions: HPV = human papilloma virus; MenACWY = meningococcal conjugate; MMR = measles-mumps-rubella; Td/Tdap = tetanus and diphtheria/tetanus, diphtheria, and pertussis

Source: <https://www.cdc.gov/vaccines/imz-managers/coverage/teenavaxview/data-reports/index.html>

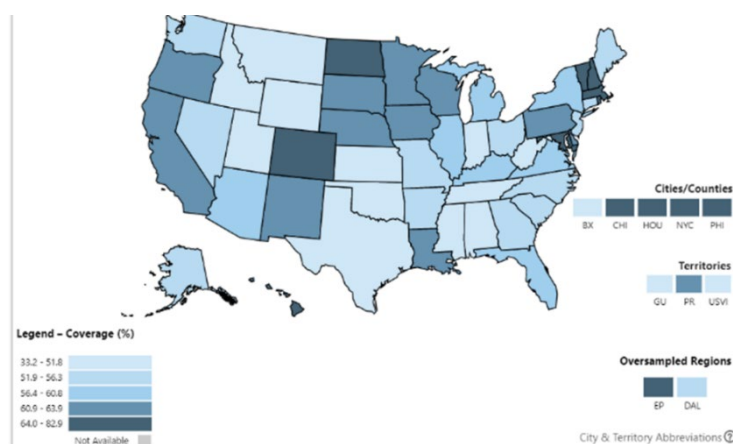


Figure 11. ≥2 doses HPV vaccination coverage among adolescents ages 13–17 years, 2019, National Immunization Survey-Teen.

Source: <https://www.cdc.gov/vaccines/imz-managers/coverage/teenavaxview/data-reports/index.html>

Nearly half (44%) of patients are diagnosed with early-stage cervical cancer that can be treated with surgery, with or without postoperative radiation or combined chemoradiotherapy.^{97,117} For those women diagnosed with locally advanced disease (regional disease beyond the cervix), pelvic external beam radiation therapy with intracavitary brachytherapy and concurrent chemotherapy is the standard-of-care treatment. Despite the strong association between receipt of brachytherapy and decreased recurrence rates, recent improved survival surveillance data demonstrate that nearly half of women with cervical cancer in the United States do not receive intracavitary radiation.¹¹⁸

Chemotherapy is the standard therapy in patients with metastatic and recurrent disease. Published in 2017, the results of a National Cancer Institute (NCI)–supported clinical trial, GOG 240, demonstrated a 3-month improved survival rate for patients who received bevacizumab in addition to chemotherapy, making the three-drug regimen (carboplatin, paclitaxel, and bevacizumab) the new standard of care.¹¹⁹ Additional novel agents—including cemiplimab, tisotumab vedotin, and pembrolizumab—recently have been approved for use in metastatic and recurrent cervical cancer following industry-sponsored clinical trials.

Equity

Declines in incidence and mortality have been more pronounced (**Figure 12**) for women from historically underrepresented racial and ethnic communities than for non-Hispanic White women.¹²⁰ Despite similar rates of cervical cancer screening and HPV vaccination, Black women remain 30 percent more likely to be diagnosed with cervical cancer and 75 percent more likely to die of disease than White women.⁹ The mortality difference most likely is driven by stage at diagnosis, because Black women are more likely to have advanced or metastatic disease. There also are noted disparities in the receipt of care provided to Black women following an abnormal screen result and after a cancer diagnosis. Even when adjusted for stage at diagnosis, Black women are less likely to receive surgery than White women, and they receive external beam radiation therapy without brachytherapy more frequently than White women.¹²¹ These findings point to the need for targeted interventions to improve the timeliness of treatment and follow-up care in the overall population, and especially among Black women.⁹⁹

Population characteristics that place women at greater risk for incidence and mortality from cervical cancer, such as poverty, older age, and a lack of or inadequate health insurance coverage, are disproportionately concentrated in the less populated, rural areas of the United States. Women who live in rural census tracts are disproportionately burdened with cervical cancer, as compared to those living in nonrural census tracts.¹²² Health care facilities providing preventative, screening, diagnostic, and therapeutic interventions for patients at risk for or diagnosed with cervical cancer are limited for patients living in rural communities.¹²³ Half of rural residents travel 60 miles or more to reach the nearest gynecologic oncologist.¹²⁴

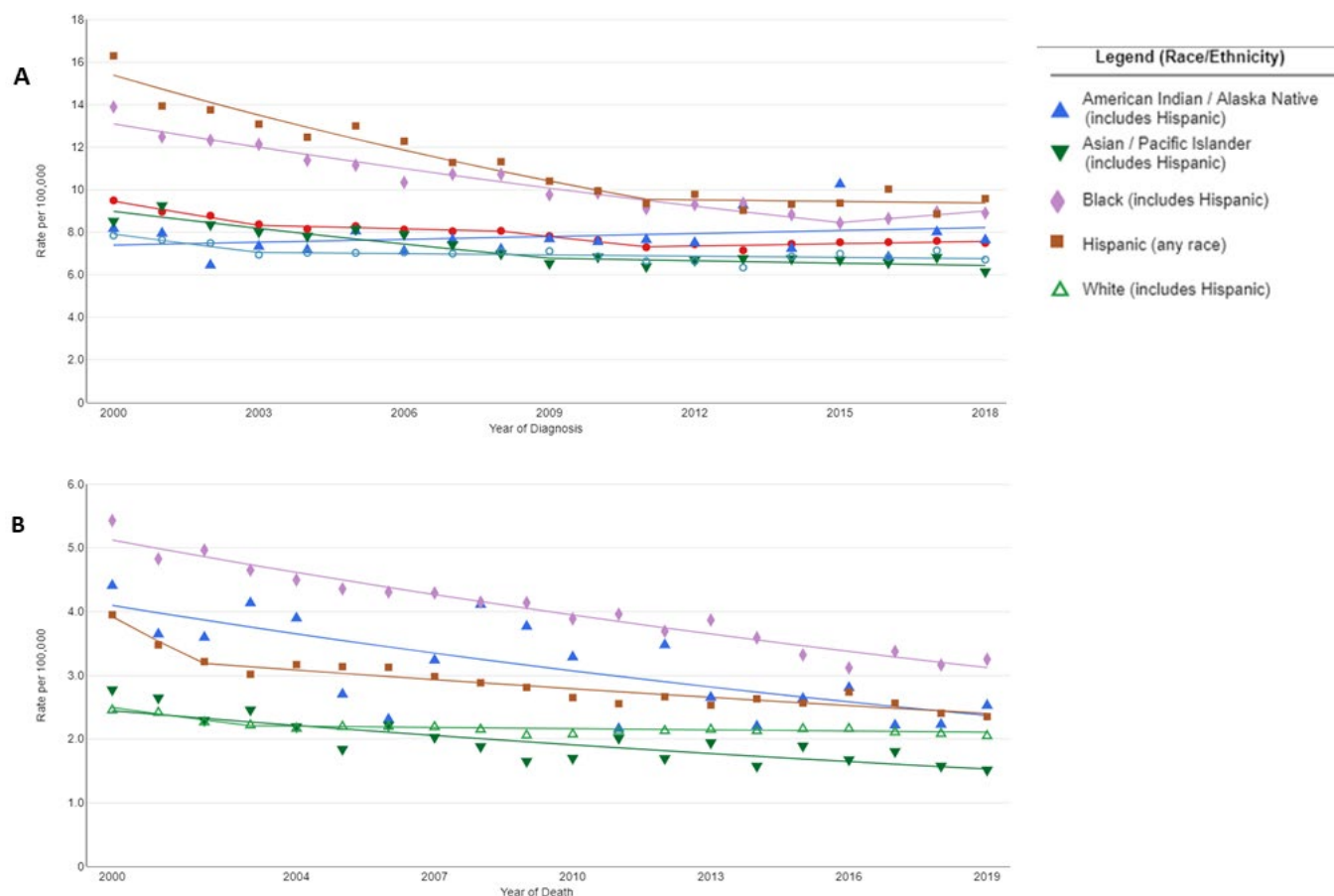


Figure 12. Cervix uteri, recent trends in SEER age-adjusted incidence (A) and mortality (B) rates by race and ethnicity.

Definition: SEER = Surveillance, Epidemiology, and End Results

*Source: SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 2021 September 27]. Available from <https://seer.cancer.gov/explorer>.*

Current NIH Activities

NIH uses [RCDC](#) reports as its official system of record for how much funding is invested annually to support research on specific topics. The purpose of this system is to provide consistent and transparent information to the public about NIH-funded research. Reporting is retrospective, not prospective, and each year, the ICOs validate the projects that fall into these categories. Categories are overlapping, so projects can—and often do—fall into multiple categories. In preparation for the WHC and this report, RCDC analysis was used wherever possible to measure current NIH activities in women’s health research, MMM, chronic debilitating conditions, and cervical cancer. Limitations of the RCDC system include the fact that projects are reviewed retrospectively—reflecting prior investments instead of future allocations—and projects can be included in more than one RCDC category, which could affect interpretation. Grant and funding record analyses presented in this report were conducted using RCDC data. Data tables from each ICO’s appropriations history from the NIH Office of Budget also were included in the analyses. The analyses excluded NIH Buildings and Facilities costs.

Women’s Health/Women’s Health Research

- ORWH coordinates NIH-supported scientific inquiry on sex differences in health and promotes research on the health of women.
- In FY 2020, NIH spent 10.8 percent of its funding for grants, contracts, and other funding mechanisms on women’s health research (\$4,446 million).
- Although about half of NIH-supported clinical trial participants are women, women continue to be underrepresented in studies on some disease categories.
- Disparities in funding have been described for conditions that affect women.

As the congressionally mandated focal point for coordinating research on the health of women at NIH (per Section 486 of the NIH Revitalization Act of 1993), ORWH collaborates with the constituent NIH Institutes and Centers (ICs) and the broader scientific community to advance research on the health of women by ensuring that sex and gender are integrated into an interdisciplinary scientific framework at NIH and throughout the biomedical research enterprise. [ORWH signature programs](#) and collaborative activities enhance research related to diseases and conditions that affect women; ensure that research conducted and supported by NIH addresses women’s health issues; and promote opportunities and support for the recruitment, retention, reentry, and advancement of women in biomedical careers. The [Report of the Advisory Committee on Research on Women’s Health: Fiscal Years 2019–2020](#) biennial report details the NIH-wide programs and accomplishments carried out in fulfillment of ORWH’s core mission.

In May 2021, ORWH hosted the [5th Annual NIH Vivian W. Pinn Symposium](#) (named in honor of Dr. Vivian Pinn, the first full-time director of ORWH), which focused on the integration of sex and gender considerations across the biomedical research enterprise, laying a foundation for strengthening the science of women’s health research and informing the conference. This platform engaged panelists and participants across biomedical sectors that have a stake in research focused on the health of women, with the ultimate goal of driving progress toward a healthier future.

In 2019, NIH updated its RCDC report for women’s health. The updated version became the automated Manual Categorization System–Women’s Health (MCS-WH) reporting module. MCS-WH includes an automated RCDC text mining process of women’s health–related projects and was utilized to estimate current NIH spending in research

focused on women's health. The identified grants processed by the MCS-WH reporting module include both female-specific conditions (e.g., gynecologic cancers, endometriosis) and diseases that affect both women and men but predominately affect women (e.g., fibromyalgia, rheumatoid arthritis). As measured by MCS-WH, NIH spent 10.8 percent of its funding for grants, contracts, and other funding mechanisms on women's health research in FY 2020 (\$4,466 million). Regarding the percentages of ICs' budgets that were dedicated to women's health research, these figures align with the ICs' missions (Figure 13). There are large variations in the budgets of each IC. As such, the ICs with the largest budgets tended to fund larger dollar amounts for women's health research. The Institutes that spent the largest amounts of funding on women's health research include NCI; the National Institute of Allergy and Infectious Diseases (NIAID); NHLBI; and the National Heart, Lung, and Blood Institute (NHLBI). When evaluated by percentage, however, NICHD, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute on Minority Health and Health Disparities (NIMHD) spent the largest fraction of their budgets on women's health (29%, 28%, and 25%, respectively).

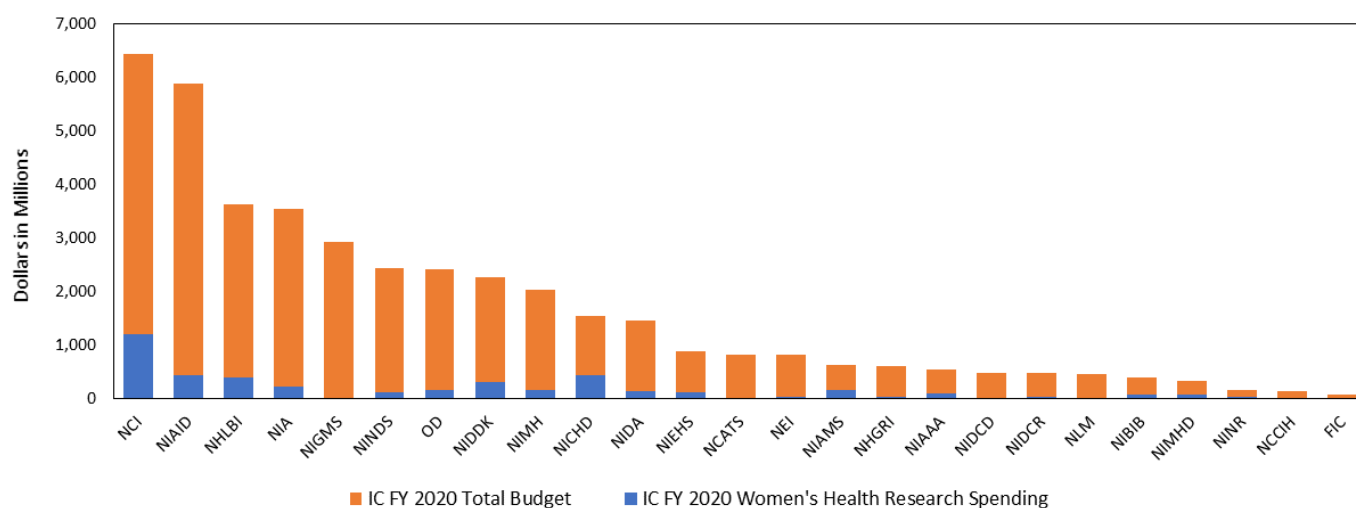


Figure 13. Total budget and women's health research spending by NIH Institute and Center, fiscal year 2020 (NIH women's health research total = \$4,466 million).

Definitions: FIC = Fogarty International Center; IC = NIH Institute or Center; NCATS = National Center for Advancing Translational Sciences; NCCIH = National Center for Complementary and Integrative Health; NCI = National Cancer Institute; NEI = National Eye Institute; NHGRI = National Human Genome Research Institute; NHLBI = National Heart, Lung, and Blood Institute; NIA = National Institute on Aging; NIAAA = National Institute on Alcohol Abuse and Alcoholism; 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; NIDA = National Institute on Drug Abuse; NIDCD = National Institute of Deafness and Other Communication Disorders; NIDCR = National Institute of Dental and Craniofacial Research; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS = National Institute of Environmental Health Sciences; NIGMS = National Institute of General Medical Sciences; NIMH = National Institute of Mental Health; NIMHD = National Institute on Minority Health and Health Disparities; NINDS = National Institute of Neurological Disorders and Stroke; NLM = National Library of Medicine; NINR = National Institute of Nursing Research; OD = National Institutes of Health Office of the Director

Sources:

1. Women's health spending data derived from NIH Research, Condition, and Disease Categorization data system frozen file.
2. IC total budget excludes buildings and facilities costs; data derived from NIH Office of Budget "Appropriations History by Institute/Center" file, https://officeofbudget.od.nih.gov/approp_hist.html

NIH funds a wide range of research on women's health—including research projects (52.4% R mechanism), cooperative agreements (21.5% U mechanism), intramural research (8.9% Z mechanism), and research program projects and centers (7.0% P mechanism). ICs also support research on women's health by co-funding ORWH signature programs, with the leading Institutes being NICHD (32%), the National Institute on Aging (NIA; 16%),

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; 10%), and National Institute on Drug Abuse (NIDA; 7%). ICOs co-fund many ORWH programs—including the [Building Interdisciplinary Research Careers in Women's Health \(BIRCWH\)](#) program, the [Specialized Centers of Research Excellence on Sex Differences \(SCORE\)](#) program, the sex and gender [R01](#) and [administrative supplements programs](#), and the [U3 Administrative Supplement Program](#).

NIH-wide grant applications are reviewed by study sections in the NIH Center for Scientific Review. These study sections are either standing study sections whose members have been appointed for multiyear terms of service or *ad hoc* Special Emphasis Panels (SEPs). Investigators can submit unsolicited applications (investigator-initiated research) on any topic of their choosing or solicited applications in response to a specific NIH solicitation. From FY 2018 to FY 2021, most successful NIH grants were unsolicited (80%), and 56 percent were reviewed by SEPs. However, research projects categorized as women's health had a markedly different distribution. Only 52 percent were unsolicited, and 76 percent were reviewed by SEPs as opposed to standing study sections (internal ORWH analysis). RCDC categories for female-specific conditions (endometriosis, fibroids, and vulvodynia) demonstrated that approximately half (50%, 63%, and 50%, respectively) of all funded gynecology-related grants were solicited, and the majority (60%, 67%, and 50%, respectively) were reviewed by SEPs as opposed to standing study sections.

ORWH serves as the fulcrum for NIH-supported scientific inquiry on sex differences in health research. One of ORWH's signature programs, [SCORE](#), serves as a national resource for translational research at multiple levels of analysis to identify the role of biological sex differences in the health of women. SCORE awards have been made in collaboration with IC partners supporting a diversity of topics in women's health and sex difference research, including chronic pain, addiction, female urinary tract and reproductive organs, infectious diseases and immunity, metabolic disorders, age-related cognitive decline, and mental health. These Centers of Research Excellence are vital hubs, providing leadership in the development and promotion of standards and policies for the consideration of SABV policy and training in experimental design and analyses that consider sex or gender.

Since the passage of the NIH Revitalization Act of 1993, representation of women in clinical research has improved. Now, roughly half of NIH-supported clinical trials participants are women.¹ Work remains, however, to ensure that women are equitably enrolled into clinical trials. When compared with population prevalence, substantial underrepresentation of female enrollment into clinical trials persists in multiple disease categories, including HIV/AIDS, chronic kidney diseases, and cardiovascular diseases.² Disparities in funding also have been described for diseases that affect women. For many diseases that affect primarily one sex, the funding pattern favors those that primarily affect males with respect to burden of the disease within the population (**Figure 14 A**). Based on DALYs, there are no differences in disease burden between males and females (**Figure 14 B**). However, female-dominant diseases are statistically more likely to be underfunded than male-dominant diseases (**Figure 14 B**, $p < 0.05$). The disparity between actual funding and the disease burden by sex is nearly twice as large for diseases that favor females versus those that favor males.³ Additionally, adherence to NIH guidelines in the analysis and reporting of research results by sex remains a challenge. A recent evaluation estimated that fewer than a third of published studies reported at least one outcome by sex or explicitly included sex as a covariate in statistical analysis. Explanations for the exclusion of sex in analyses were rare.¹

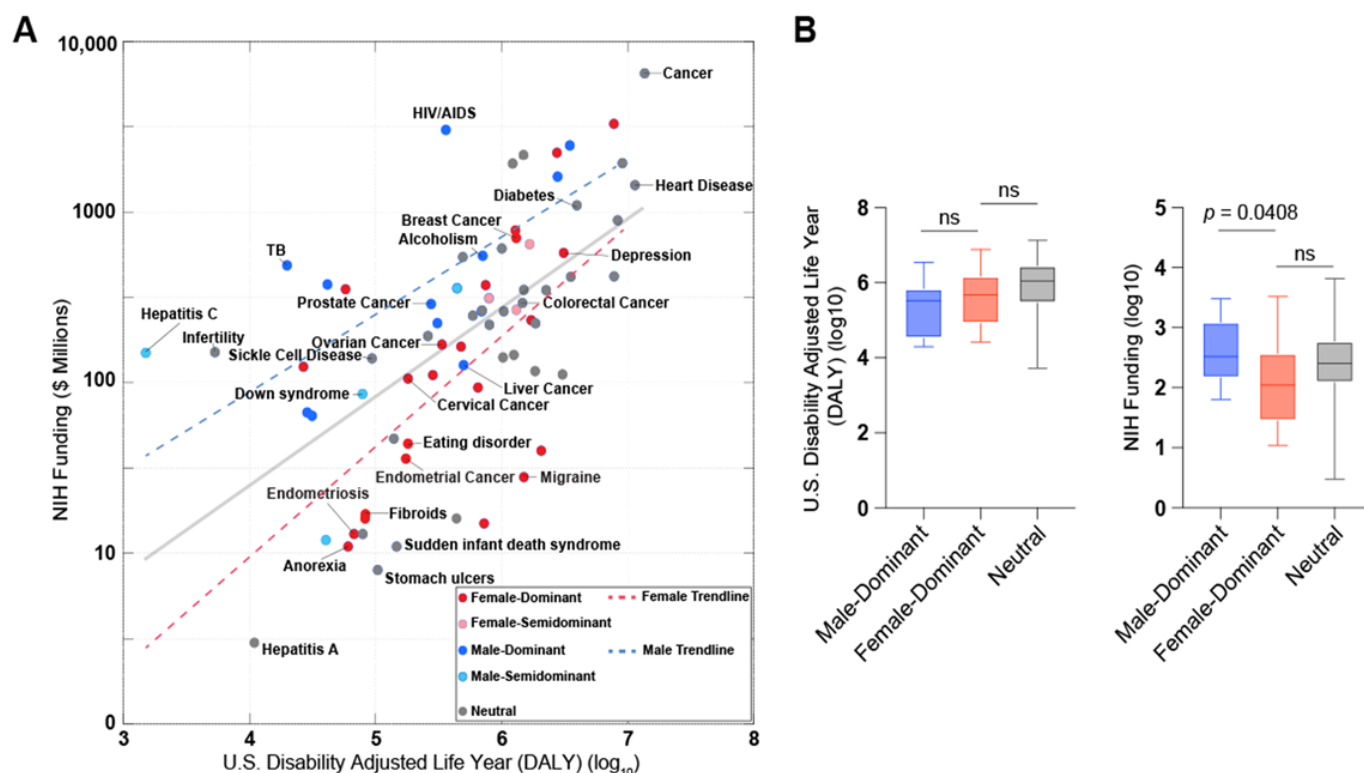


Figure 14. Sex disparities in NIH funding for diseases.

(A) NIH funding (2019) versus U.S. burden of disease. The lines represent linear regression trendlines. (B) Boxplots showing the distribution U.S. burden of disease and NIH funding among male-dominant, female-dominant, and neutral diseases. Statistic in B is a Mann-Whitney U test. Definition: DALY = disability adjusted life year

Source: Graphs were created using data from Mirin, Arthur A. "Gender disparity in the funding of diseases by the U.S. National Institutes of Health." *Journal of Women's Health* 2021; **30**(7): 956-63.³

Maternal Health and Maternal Morbidity and Mortality

- In response to the public health crisis of MMM, NIH invested \$405,994,474 in maternal health research and \$223,522,448 in MMM research in FY 2020.
- NIH supports multiple projects investigating the underlying physiology of pregnancy and pathophysiology of pregnancy-associated disorders.
- NICHD's Maternal-Fetal Medicine Units Network is a research network that primarily conducts randomized trials to reduce maternal and infant morbidity, deaths, and complications.
- Several NIH-wide programs, including [Implementing a Maternal health and PRenancy Outcomes Vision for Everyone \(IMPROVE\)](#) and the Institutional Development Award (IDeA) states, have directed attention toward research to reduce MMM.

NIH encourages scientists to study pregnancy as part of the life course. Due to disturbing trends in pregnancy-related morbidity and mortality, NIH has made several changes to metrics that capture research efforts related to maternal health. In 2017, NIH established a Maternal Health RCDC that encompasses projects focused on pre-pregnancy through 1 year postpartum that include a direct maternal health-related intervention, impact, or

outcome. In 2020, another RCDC, Maternal Morbidity and Mortality, was established to capture the subset of topics within the Maternal Health RCDC specifically related to pregnancy complications and death associated with pregnancy. In FY 2020, NIH invested \$406,679,474 in maternal health research and \$223,522,448 in MMM research ([Figure 15](#)). The largest FY 2020 investment in MMM came from NICHD (\$76 million), followed by NHLBI (\$40 million), NIDDK (\$19 million), and the National Institute of Mental Health (NIMH; \$18 million). Research project grants represent the majority (60%) of the MMM funding, followed by cooperative agreements (16%) and intramural research (10%).

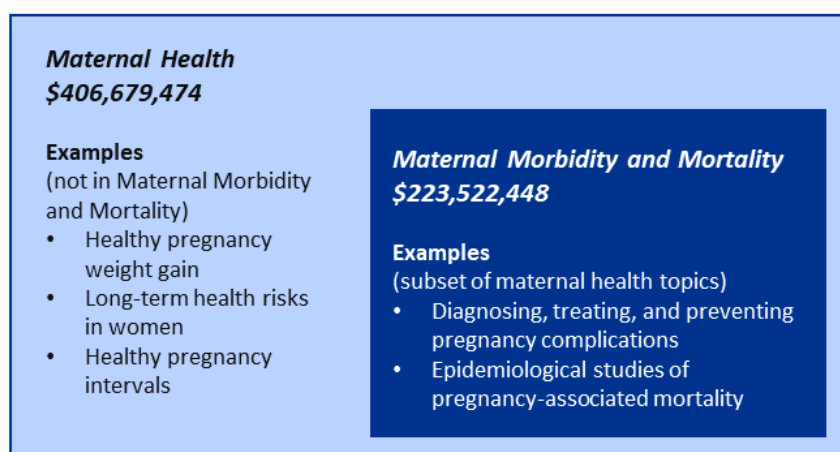


Figure 15. NIH investment in maternal health and maternal morbidity and mortality research, fiscal year 2020.

In 2019, ORWH's 4th Annual NIH Vivian W. Pinn Symposium was titled "Improving Maternal Health: Behind the Numbers." The symposium's presentations focused on the lasting medical complications that can result from pregnancy, and the speakers reviewed current statistics and health services research and provided an overview of relevant Federal programs. New approaches to improving women's health before, during, and after pregnancy were proposed. This symposium was summarized in a [special issue on MMM](#) published in the *Journal of Women's Health*.

NIH supports multiple projects investigating the underlying physiology of pregnancy, as well as the pathophysiology of pregnancy-associated disorders (e.g., preeclampsia, abruption). NICHD's [Human Placenta Project](#), one of the largest of these projects, is a collaborative research effort to understand the role of the placenta in health and disease, with an ultimate objective of developing new tools to identify placental dysfunction in real time and learn how it changes throughout pregnancy.¹²⁵ Ongoing studies focus on the potential role of cell-free total and fetal DNA in maternal plasma as a means for first-trimester identification of later pregnancy complications, such as preeclampsia. Prior research found that placental DNA methylation of genes implicated in cardiometabolic diseases was associated with increased maternal blood pressure during pregnancy.¹²⁶

Clinical Research

NICHD's [MFMU Network](#), established in 1986, is made up of 12 centers (36 hospitals) that participate collaboratively using common protocols, primarily to conduct randomized trials to reduce maternal and infant morbidity, complications, and deaths. This network has completed several practice-changing clinical trials on such topics as low-dose aspirin to prevent preeclampsia; antenatal, late-preterm steroid delivery to prevent adverse neonatal outcomes; and the optimal timing of elective induction of labor.^{127,128} Current ongoing trials include the [Pravastatin for Prevention of Preeclampsia \(PREP\) trial](#), which seeks to determine whether daily pravastatin will reduce the risk of preeclampsia in high-risk women; [Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean](#), which assesses whether the preemptive use of tranexamic acid can lower the risk of postpartum hemorrhage in women who undergo a cesarean delivery; and the [Gestational Research Assessments for COVID-19](#) study, which examines whether pandemic-related health care delivery changes affected the rate of pregnancy complications/cesarean delivery.

Additionally, MFMU trials have provided rich data for secondary analysis. A recent publication, for example, demonstrated that adverse neonatal and maternal outcomes were four times more likely with medically indicated

preterm births than with spontaneous preterm births.¹²⁹ Another recent secondary analysis showed that the duration of operative vaginal delivery, rather than the attempted number of pop-offs (vacuum) or pulls (forceps), was associated with adverse neonatal outcomes.¹³⁰ Recent MFMU publications have used secondary analyses to evaluate racial and ethnic disparities. These include a study demonstrating that adverse perinatal outcomes that were highest for Black patients were no longer observed after adjusting for sociodemographic factors, as well as a study suggesting that improved obstetrical quality of care could be associated with such factors as organizational unit culture and lower levels of provider fatigue.¹³¹

The NICHD, NIEHS, and NIMHD–supported [Maternal and Infant Environmental Health Riskscape \(MIEHR\) Research Center](#) aims to determine the contributions of exposures (including the biological, physical, social, and built environments) at the individual and neighborhood levels on maternal and infant health and disparities in outcomes. Focal areas include preterm birth and hypertensive disorders of pregnancy. The MIEHR Center’s perinatal database and biospecimen repository serve as invaluable resources for interdisciplinary research projects on maternal and infant health. Additional goals include promoting career development of the next generation of environmental health researchers from populations that are underserved and experience health disparities and engaging communities as partners in research.¹³²

Several NIH-supported ongoing projects explore the effects of pregnancy-associated conditions on subsequent health in women. The ongoing [Prenatal Blood Pressure Patterns to Predict Pregnancy-Related Hypertension and Later Life Cardiovascular Risk study](#), funded by NHLBI, is working to identify blood pressure patterns during pregnancy that indicate serious pregnancy-related blood pressure disorders and predict maternal CVD outcomes later in life. NHLBI, with co-funding from NICHD, also supports the [Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be \(nuMoM2b\)](#), which examines the relationship between adverse pregnancy outcomes and later cardiovascular health in a diverse cohort of 4,508 women. An NIDDK clinical research consortium, [Glycemic Observation and Metabolic Outcomes in Mothers and Offspring \(GO MOMs\)](#), will explore glucose changes throughout pregnancy, and findings could inform the development of new gestational diabetes screening, diagnosis, and treatment approaches. The [Mississippi Center of Excellence in Perinatal Research \(MS CEPR\)](#), supported by the National Institute of General Medical Sciences (NIGMS), is conducting research on adverse events related to pregnancy and subsequent outcomes in mothers and offspring. MS CEPR investigators have designed an approach to monitoring postpartum blood pressure using telemetry to track and reduce complications of hypertensive pregnancies. Researchers supported by NIA have identified vascular system changes that could explain the higher risk of postmenopausal cognitive decline in patients who develop preeclampsia during pregnancy.¹⁸

NIH-Wide Maternal Morbidity and Mortality Activities

In addition to supporting basic research and clinical network programs, NIH also has established initiatives to generate tailored, evidence-based solutions as a response to the MMM public health crisis. The Maternal Mortality Task Force (MMTF) was created early in FY 2020 and is led by the NIH Office of the Director, NICHD, and ORWH. The MMTF established the IMPROVE initiative to support research to reduce preventable maternal deaths and improve health for women before, during, and after delivery, including deaths related to race, age, and geographic region. IMPROVE focuses on promoting the study of the leading causes of maternal morbidity in the United States—CVD, infection, and immunity—as well as other health conditions and social factors that can play a role, such as mental health disorders, diabetes, obesity, and substance use disorders. The initiative also supports investigations into the causes and identification of significant pregnancy-related health complications, with the ultimate goal of developing and studying targeted interventions that decrease the occurrence of such complications. Collectively, the work will help create tailored, evidence-based solutions for women across the country.

The IMPROVE initiative uses an integrated approach to leveraging and expanding social, biobehavioral, and fundamental science strategies and incorporates community partnerships in areas with high rates of maternal

deaths and complications.¹³³ In FY 2020, 37 IMPROVE awards were granted, totaling \$7.2 million. This supplement program focused on three main goals: (1) Incorporate community partnerships and participation in domestic pregnancy-related and pregnancy-associated morbidity and maternal mortality research to resolve health disparities and achieve equity in maternal health; (2) Expand research on the leading causes of pregnancy-related and pregnancy-associated morbidity and maternal mortality in the United States to strengthen evidence-based care and prevention strategies and improve outcomes; and (3) Develop an integrated understanding of pregnancy-related and pregnancy-associated morbidity and mortality causes, including underlying comorbidities and mechanisms, to identify preventable risk factors and develop effective early interventions.

To address access and infrastructure gaps that contribute to rural health disparities and higher MMM, NIH-funded scientists have expanded their research on women's health through the [IDeA](#) program. The IDeA program is congressionally mandated and administered by NIGMS, with the goal of building research capacity in states and territories with historically low levels of NIH funding (23 states and Puerto Rico). In support of NIH-wide efforts to address key issues of women's health and the high rates of MMM, this initiative has awarded more than \$9 million since FY 2020 to support 34 grants in 19 IDeA states and Puerto Rico. Of these, 13 awards support research on MMM. Although most IDeA states have received awards for women's health and MMM research projects through the Administrative Supplements for Research on Women's Health in IDeA States—co-led by NIGMS and ORWH—a geographic gap remains because several IDeA states do not yet have NIH-supported MMM grants.

Chronic Debilitating Conditions in Women

- NIH supports a wide range of research on chronic debilitating conditions across all ICOs.
- Research investment on this topic is not captured by the official RCDC system that tracks NIH research funding, making estimates of research activity imprecise.
- Few projects addressing chronic debilitating conditions or multimorbidity specifically are focused on women's health.
- NIH and ORWH support research on the role of biological sex differences in chronic debilitating conditions.

NIH supports a wide range of research on chronic diseases—covering screening and prevention, diagnostics, treatment and therapeutics, health disparities, and other activities (e.g., mechanisms and pathogenesis). However, no single NIH RCDC category of medical research for reporting funding to the public at the end of each fiscal year captures chronic debilitating conditions. Moreover, ICOs define chronic debilitating conditions differently, and morbidities related to specific conditions receive ICO-specific research focus.

Chronic Debilitating Conditions Framework

Using currently available RCDCs and the framework developed for the WHC defining CDCW as (1) female specific, (2) more common in women and/or morbidity is greater for women, (3) potentially understudied in women, and (4) high morbidity for women, trends in NIH spending were captured in each category ([Figures 16–19](#)).

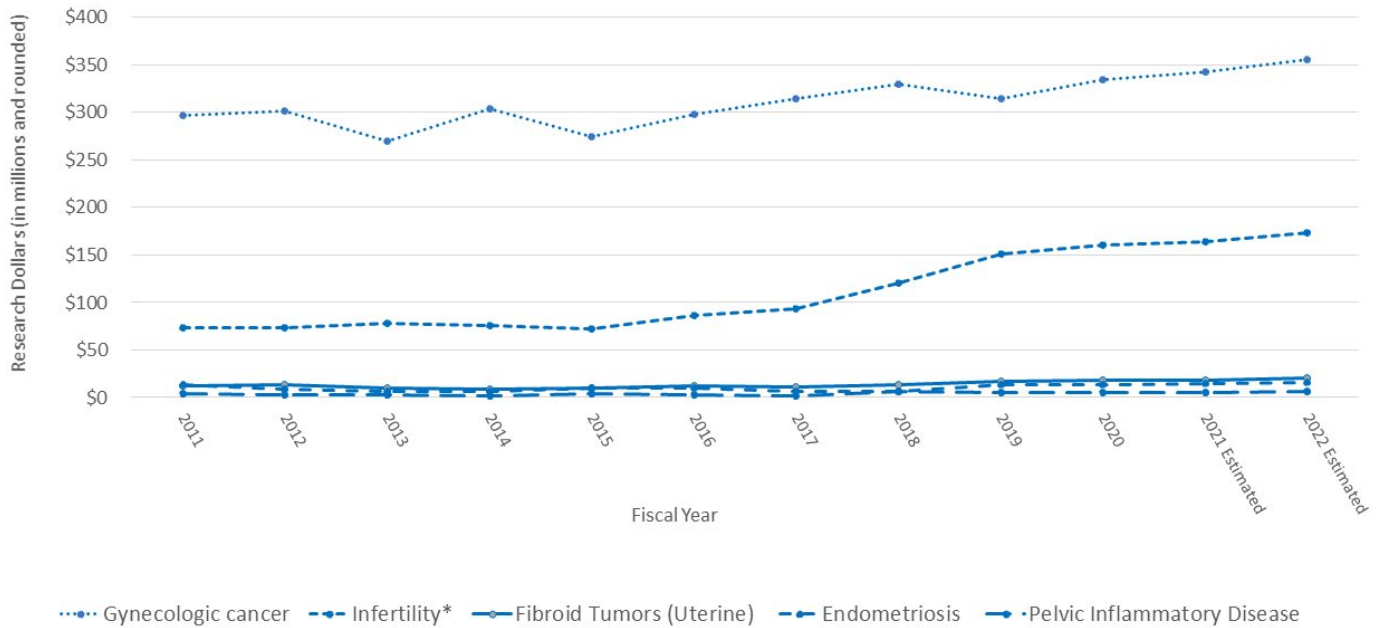


Figure 16. NIH spending by Research, Condition, and Disease Categorization on female-specific conditions.

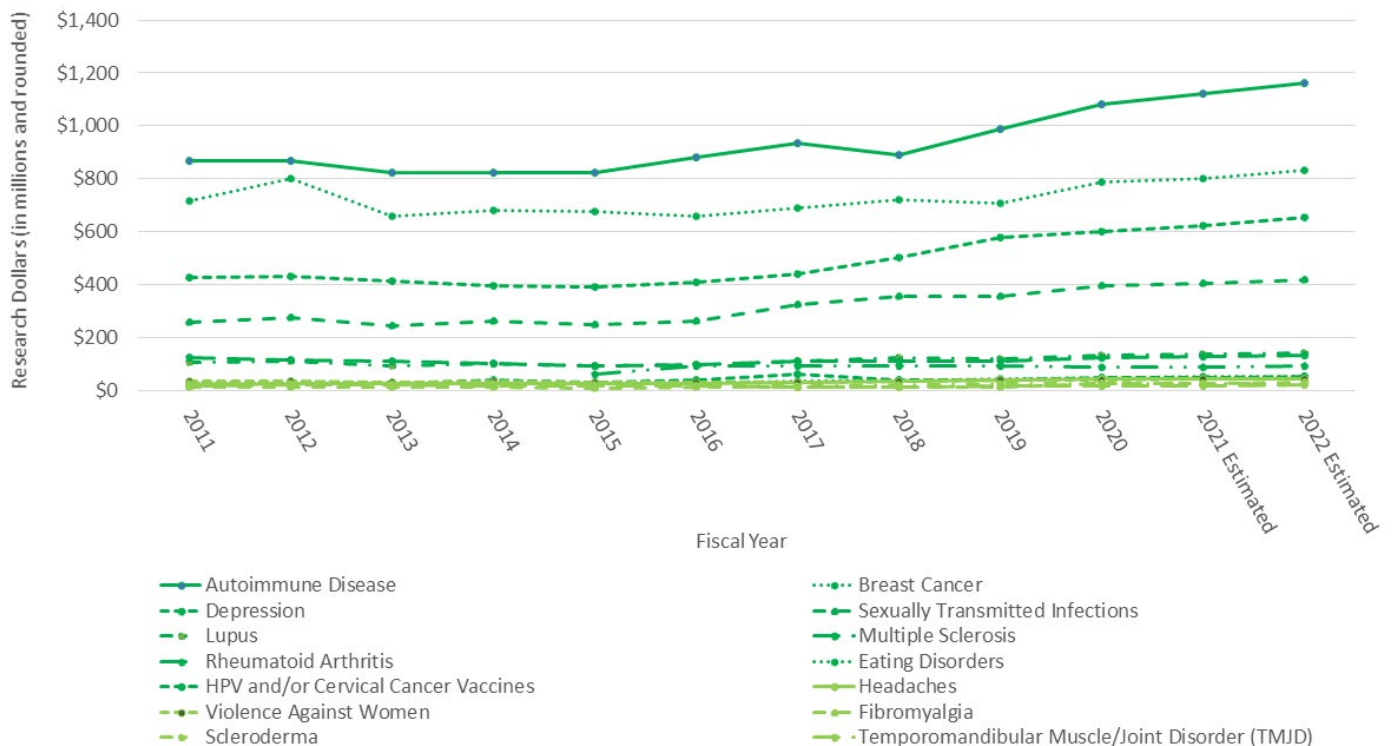


Figure 17. NIH spending by Research, Condition, and Disease Categorization on conditions that are more common in women and/or where morbidity is greater for women.

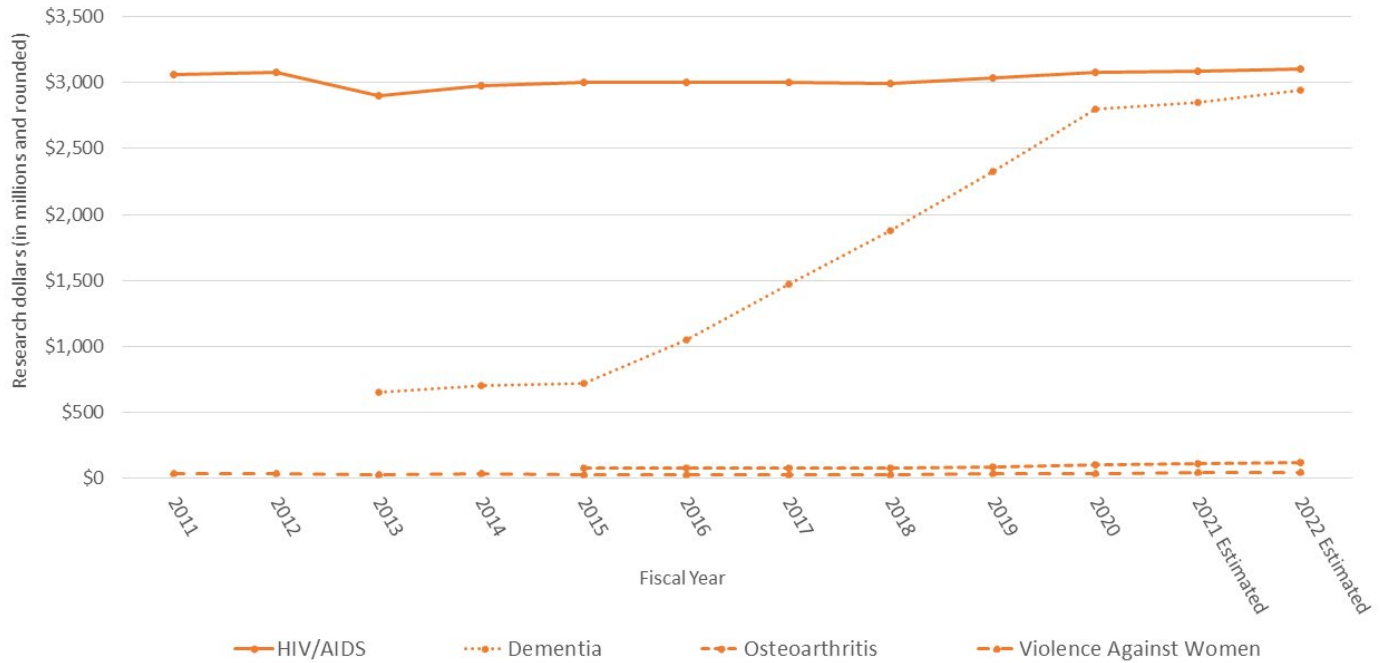


Figure 18. NIH spending by Research, Condition, and Disease Categorization on conditions potentially understudied in women.

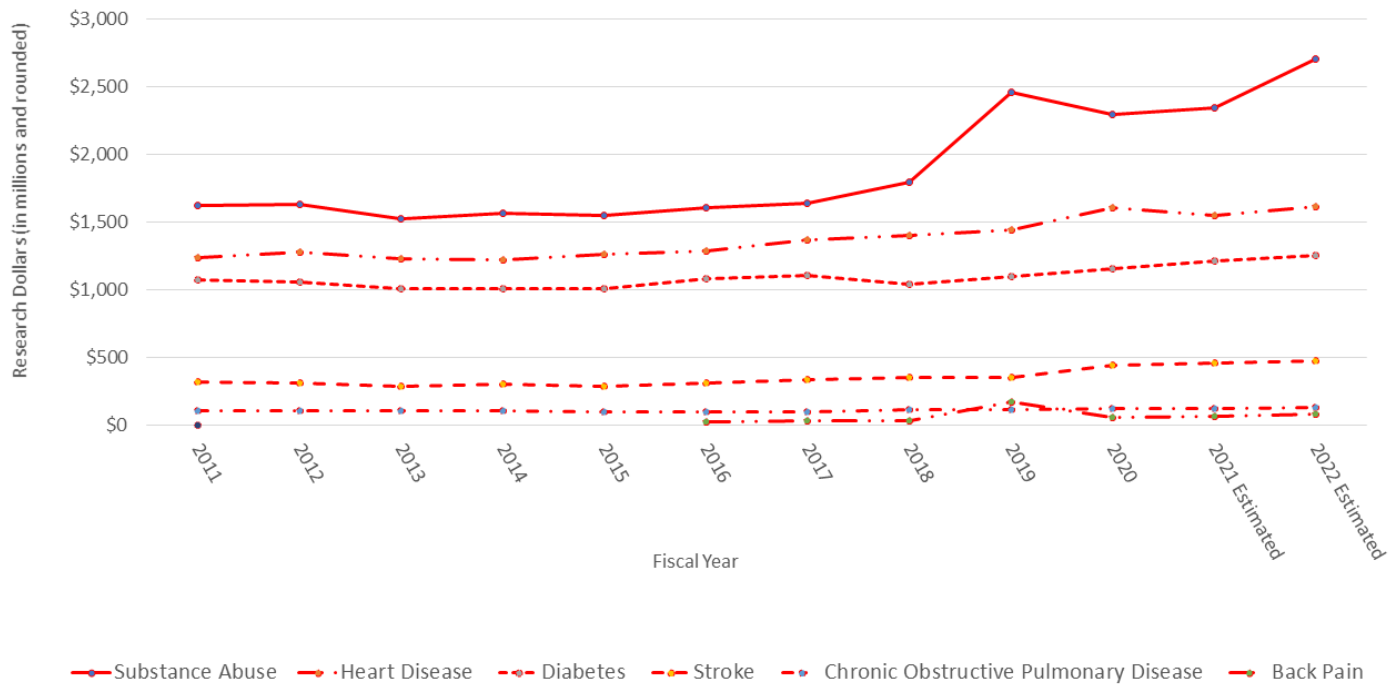


Figure 19. NIH spending by Research, Condition, and Disease Categorization on conditions with high morbidity in women.

In FY 2020, the largest investments in research on female-specific chronic debilitating conditions were on gynecological cancers and infertility. For conditions more common among women, the largest investments in research were on autoimmune diseases, breast cancer, and depression. The unofficial NIH spending on conditions that occur in both sexes but are potentially neglected in women was largest for research on HIV/AIDS and dementia. For conditions associated with high morbidity in women in FY 2020, the largest investment was in research on substance use disorder (due to the [Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®](#)), heart disease, diabetes, and stroke.

This portfolio analysis of CDCW subsequently was incorporated into the multidimensional framework described in [Table 3](#) to understand the association between NIH-wide research priorities as they relate to the burden of disease among women. The DALYs metric used in this framework allowed the WHC Planning Committee to assess the alignment of the NIH portfolio with the health needs of women with chronic debilitating conditions. The ratio of FY 2020 spending per DALY within the WHC framework for chronic conditions with available RCDCs was calculated; for instance, migraine/headache is funded at \$27 per DALY, whereas sexually transmitted infections are funded at \$10,558 per DALY. This ratio illustrates conditions with highest amounts of research spending are not aligned with conditions bearing the highest DALY burdens in women (the DALYs are highest on the left side of [Table 3](#)). Thus, current NIH investments do not align with conditions that lead to higher disability among women. This analysis is limited by the availability of NIH RCDC codes and the accuracy of categorization of individual projects using these codes.

Table 3. FY 2020 NIH Spending per DALY in Women for Chronic Debilitating Conditions by RCDC

Condition Analysis Category	Condition (2019 Disability Adjusted Life Years [DALYs], United States) Ratio of Fiscal Year 2020 U.S. Spending per 2019 DALY (for Conditions with an Available Research, Condition, and Disease Categorization [RCDC])								
Female Specific	Cancers of the Female Reproductive Tract* (900,843) \$372	Dysmenor rhea/ Abnormal Menses (289,608)	Fibroids* (64,009) \$281	Endometriosis* and Adenomyosis (53,777) \$260	Infertility*/ Early Pregnancy Loss (26,355) \$6,108	Polycystic Ovary Syndrome (42,738)	Pelvic Floor Disorders, Organ Prolapse (21,613)	Menopausal Symptoms, Pelvic Inflammatory Disease,* Vulvodynia*/Chronic Gynecologic Pain Disorders Pelvic and Vulvar, Vaginosis	
More Common in Women and/or Morbidity Is Greater for Women	Depressive Disorders (1,704,524) \$353	Migraine/ Headache (1,573,325) \$27	Breast Cancer* (1,387,670) \$568	Asthma (820,435) \$411	Autoimmune Diseases (Including Rheumatoid Arthritis*, Systemic Lupus Erythematosus*, Sjögren’s Syndrome*, Scleroderma*)	Rheumatoid Arthritis* (187,902) \$463	Multiple Sclerosis (143,123) \$866	Sexually Trans -mitted Infections (STIs) (37,316) \$10,558	Temporomandibular Muscle/Joint Disorder,* Chronic Fatigue Syndrome,* Fibromyalgia,* Candidiasis, Irritable Bowel Syndrome, Interstitial Cystitis,* HPV Infection,* Osteoporosis,* Eating Disorders
Potentially Understudied in Women	Unintentional Injuries (Including Violence Against Women)* (2,050,026)	Alzheimer’s Disease/ Dementia (1,296,376) \$2,156	Osteoarthritis (1,257,042) \$85	Endocrine, Metabolic, Blood, and Immune Disorders	Recurrent Urinary Tract Infection/ Interstitial Nephritis	HIV (118,596) \$25,936	Exogenous Hormone Use, Neuropathy Post Traumatic Stress Disorder, Overactive Bladder/Incontinence, Chronic Pain (Including Chronic Pelvic Pain)		
High Morbidity for Women	Heart Disease (3,396,660) \$472	Lower Back Pain (3,168,583) \$17	Chronic Obstructive Pulmonary Disease (2,568,947) \$449	Drug Use Disorders (2,323,237) \$967	Stroke (2,098,900) \$210	Diabetes (2,010,853) \$573	Obesity/Metabolic Disease, Influenza and Pneumonia		
*Per Manual Categorization System-Women’s Health reporting guidance, the starred RCDCs are considered particularly relevant to women’s health. Black boxes represent conditions without an RCDC category (funding estimates not available). Sources: DALYs obtained from http://ghdx.healthdata.org/gbd-results-tool ; RCDC spending obtained from https://report.nih.gov/funding/categorical-spending# .									

Due to the limitations of performing a quantitative portfolio analysis, including the lack of a standard definition of CDCW and the lack of a single RCDC category, the Chronic Debilitating Conditions Cluster of the WHC Planning Committee conducted a qualitative portfolio analysis through a query of participating ICs, which were asked to submit at least three of their highest-funded projects related to CDCW from FY 2018 to FY 2020. The category (female specific, higher morbidity for women, etc.), fiscal year, state, funding mechanism, funding amount, and activity type were provided. One-hundred eighty-four priority projects were submitted by the following 11 ICOs: NICHD, NCI, NHLBI, NIAID, NIDDK, NIDA, NIMH, NIMHD, National Institute of Dental and Craniofacial Research, National Institute of Nursing Research, and Sexual & Gender Minority Research Office. Applying the WHC framework to ICO-submitted projects demonstrates that all categories of chronic conditions relevant to women are included in ongoing NIH-supported research (Table 4). When further categorized by clinically relevant research types (prevention and screening, diagnostics, treatment and therapeutics, and health disparities), each subgroup of clinical research was represented in every category.

Table 4. Distribution of Projects Captured in the Snapshot of IC-Submitted Projects on CDCW

Category	Percent of Projects	Conditions Represented in Limited Institute and Center Provided Snapshot		
Female Specific	11%	Endometriosis and adenomyosis Fibroid tumors (uterine) Gynecological symptoms Infertility	Lymphangioleiomyomatosis Pelvic floor disorders Pelvic inflammatory disease	
More Common in Women and/or Morbidity Is Greater For Women	49%	Anorexia nervosa Asthma Autoimmune diseases Breast cancer Depression Eating disorders Interstitial cystitis Lower urinary tract symptoms	Lymphedema Maternal sleep disorder and obstructive sleep apnea Mental illness Migraine Mood disorders Post-traumatic stress disorder	Pulmonary artery hypertension Sjögren's syndrome Sexually transmitted infections Stress Temporomandibular muscle/joint disorder Traumatic stress Urinary tract infections
Potentially Understudied in Women	25%	Alzheimer's disease Contraception Chronic obstructive pulmonary disease Dementia	Health care systems HIV Intimate partner violence	Relapse Suicide and suicidal ideation Violence
High Morbidity for Women	15%	Bone health Cardiovascular disease Diabetes	Heart disease Heart failure Hypertension	Obesity Substance use (including alcohol use)

Although the distribution of projects captured in this snapshot of NIH priorities on CDCW is reassuring, several limitations of this analysis must be noted. The data do not completely represent NIH-wide priorities, because not all ICs submitted projects. The results do not represent the complete portfolio for ICOs that submitted information. Finally, the variability of chronic disease and women's health research prioritization by ICO could not be adjusted for.

Multimorbidity

In 2018, several NIH ICOs—NCI, NIA, NIMHD, the Office of Behavioral and Social Sciences Research, and the Office of Disease Prevention—held an expert panel workshop titled “Measuring Multimorbidity: Matching the Instrument and the Purpose.” From this meeting, a model and research framework for multimorbidity—depicting relationships among causal factors, disease conditions and interactions, and outcomes of multimorbidity—was developed (**Figure 20**).

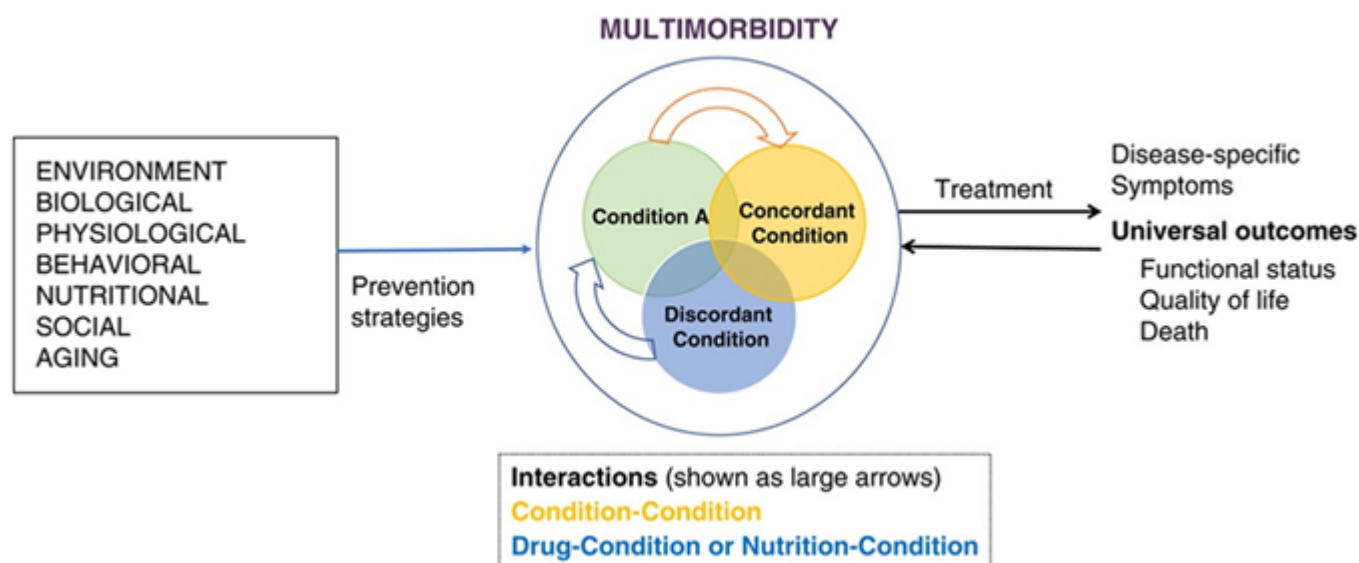


Figure 20. Conceptual model and research framework for multimorbidity, depicting relationships among causal factors, disease conditions and interactions, and outcomes of multimorbidity.

Source: Salive ME, Suls J, Farhat T, Klabunde CN. National Institutes of Health Advancing Multimorbidity Research. *Medical Care*. 2021; **59**(7): 622-24. doi: 10.1097/MLR.0000000000001565. PMID: 33900269.

This model does not consider sex and gender, yet it serves as a useful tool for conceptualizing multimorbidity.¹³⁴ NIA supports several research projects on multimorbidity; however, few projects overlap with women’s health. Five NIA-supported projects cross geroscience—the study of the intersection of aging biology and chronic disease—and the Women’s Health RCDC category: (1) [Physical Resiliencies: Indicators and Mechanisms in the Elderly Collaborative](#) (UH3); (2) [Translational Geroscience Network](#) (R33); (3) [Targeting Cellular Senescence with Senolytics to Improve Skeletal Health in Older Humans](#) (R21); (4) [Metabolic Regulation of Human DNA Methylation Clocks](#) (R01); and (5) [Cognitive Aging, Alzheimer’s Disease, and Cancer-Related Cognitive Decline](#) (R01).

Influence of Sex and Gender

Efforts are underway to advance knowledge about female-specific disorders. In fall 2021, NHLBI, ORWH, and other IC partners hosted the [Cardiovascular Risk Across the Lifespan for Polycystic Ovary Syndrome Workshop](#). The 2-day workshop reviewed the state of science on CVD across the lifespan of women with PCOS and identified knowledge gaps and opportunities in PCOS-related CVD research.

Research on the role of biological sex differences in CDCW is supported by NIH. Examples of IC-supported research include NIAMS studies that identified sex differences in phenotype and function of neutrophils that could help explain female–male divergence in immune response and risk for autoimmune diseases.¹³⁵ NIH research also has clarified the influence of sex on drug metabolism (beyond differences caused by weight differentials)—including the

effects of differences in gastric and liver enzymes, renal functioning, and body composition parameters.¹³⁶ Sex differences influence important outcomes, such as drug safety and clinical effectiveness of medications for chronic conditions (e.g., type 2 diabetes).¹³⁷

This foundational research is critical to understanding the innate factors that influence the development of CDCW and identifying evidence-based interventions specific to the health of women.

Research specific to the influence of gender on CDCW also is ongoing. For example, NIMH recently supported projects examining the associations between gender identity and eating disorders. The National Institute on Alcohol Abuse and Alcoholism supports an ongoing study of how gender differences in alcohol consumption vary across both the life course and generations.^{138,139}

Stagnant Cervical Cancer Survival

- In FY 2020, NIH invested about \$113 million in cervical cancer research, with the majority of projects funded by NCI.
- NIH research to improve cervical cancer screening and prevention efforts includes research supporting the development of novel HPV vaccines, novel surveillance and prevention models, and improved screening strategies using self-collected specimens.
- NCI-supported clinical trials networks provide infrastructure support for therapeutic clinical trials, which include studies on investigational agents to treat HPV-related precancerous lesions and novel treatment interventions.
- NCI leverages diverse data resources to examine the delivery of care.

In FY 2020, NIH invested about \$113 million in cervical cancer research, with the majority of projects funded by NCI (**Figure 21**).

NIAID, NIMHD, and NICHD also fund research on cervical cancer. Cervical cancer research represents about 1.4 percent of the overall NCI budget. Several states have NIH-funded projects related to cervical cancer, including those in the IDeA program. However, states with the largest amounts of NIH-supported research in cervical cancer do not correlate to regions with the highest burden of disease (Appalachia and Mississippi Delta). NCI-supported cervical cancer research includes research on basic biology, etiology, prevention, early detection, treatment, and cancer control. One-third of the funding mechanisms for these projects are grants (R funding); one-third are cooperative agreements (U grants); and one-third are other types of awards. NCI funds multiple clinical research

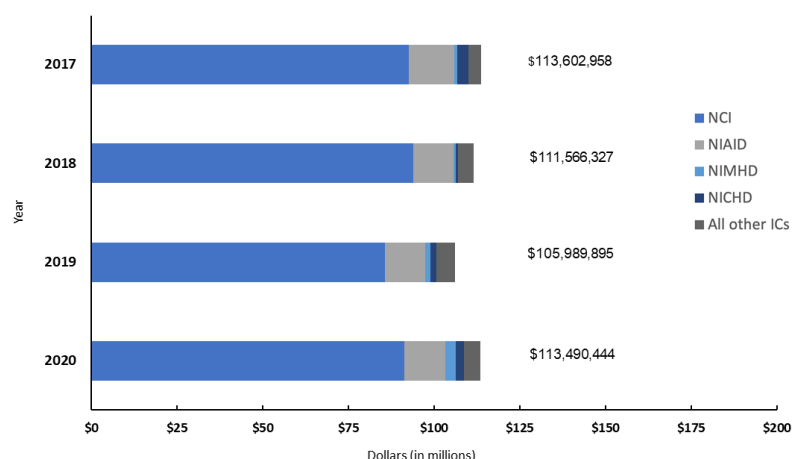


Figure 21. NIH cervical cancer funding trends, fiscal years 2017–2020.

Definitions: NCI = National Cancer Institute, NIAID = National Institute of Allergy and Infectious Diseases, NIMHD = National Institute of Minority Health and Health Disparities, NICHD = Eunice Kennedy Shriver National Institute of Child Health and Human Development, ICs = NIH Institutes and Centers.

Source: Data from Research, Condition, and Disease Categorization Categorical Spending Reporting, report.nih.gov/funding/categorical-spending#.

networks that provide extramural investigators with research infrastructure for performing clinical trials in all cancer disease sites. These research networks ([Table 5](#)) support research on prevention, screening, and treatment of all cancer types.

Table 5. NCI-Supported Clinical Research Networks

Consortium/Network/ Funding Mechanism	Type of Clinical Trials	Cancer/Precancer Focus	Geographic/Population Focus
NCI National Clinical Trials Network (NCTN)	Late phase	Cancer	United States, international
NCI Community Oncology Research Program (NCORP)	Late phase	Precancer, cancer	United States
Experimental Therapeutics Clinical Trials Network (ETCTN)	Early phase	Cancer	United States, international
AIDS Malignancy Consortium (AMC)	Early and late phase	Precancer, cancer	United States, international, people with HIV
Cancer Prevention Clinical Trials Network (CP-CTNet) (formerly, Early Phase Consortia Program)	Early phase	Precancer	United States, international
US–Latin American–Caribbean HIV/HPV–Cancer Prevention Clinical Trials Network (ULACNet)	Early and late phase	Precancer	United States, Latin America, Caribbean, people with HIV
Affordable Cancer Technologies (ACTs) Program	Early and late phase	Precancer, cancer	Low- and middle-income countries

The RCDC report for Cervical Cancer (which includes basic research, translational and clinical studies, premalignant and invasive cervical diseases, HPV biology, prevention, screening, vaccination, treatment, and related health services) was established in 2008 and is included in the broader RCDC report titled “Women’s Health.” FY 2020 cervical cancer projects classified by Common Scientific Outline codes as etiology, prevention, early detection, treatment, and cancer control are presented in [Figure 22](#).

Basic and Translational Science

Basic science is the foundation of scientific discovery, whereas translational science moves discoveries into clinical practices. One scientific challenge relevant to viral-mediated malignancies, such as cervical cancer, is discovering ways to elicit robust tumor-specific immune responses. Mechanistic studies to understand the recruitment of immunosuppressive cells to the tumor microenvironment and develop ways to generate a robust tumor-specific immune response that targets the tissue site are underway.¹⁴⁰ Research is ongoing to exploit two viral oncoproteins that drive HPV cancers—E6 and E7—as tumor-specific immune therapy.

[The Cancer Genome Atlas \(TCGA\) Program](#), a landmark cancer genomics program and collaboration between NCI and the National Human Genome Research Institute, has molecularly characterized more than 20,000 primary cancer and matched normal samples—generating a wealth of publicly available genomic, epigenomic, transcriptomic, and proteomic data on 33 cancer types. Discoveries from TCGA hold great promise for improving cervical cancer treatment as new molecular alterations are identified and available to be exploited as therapeutic targets.¹⁴¹

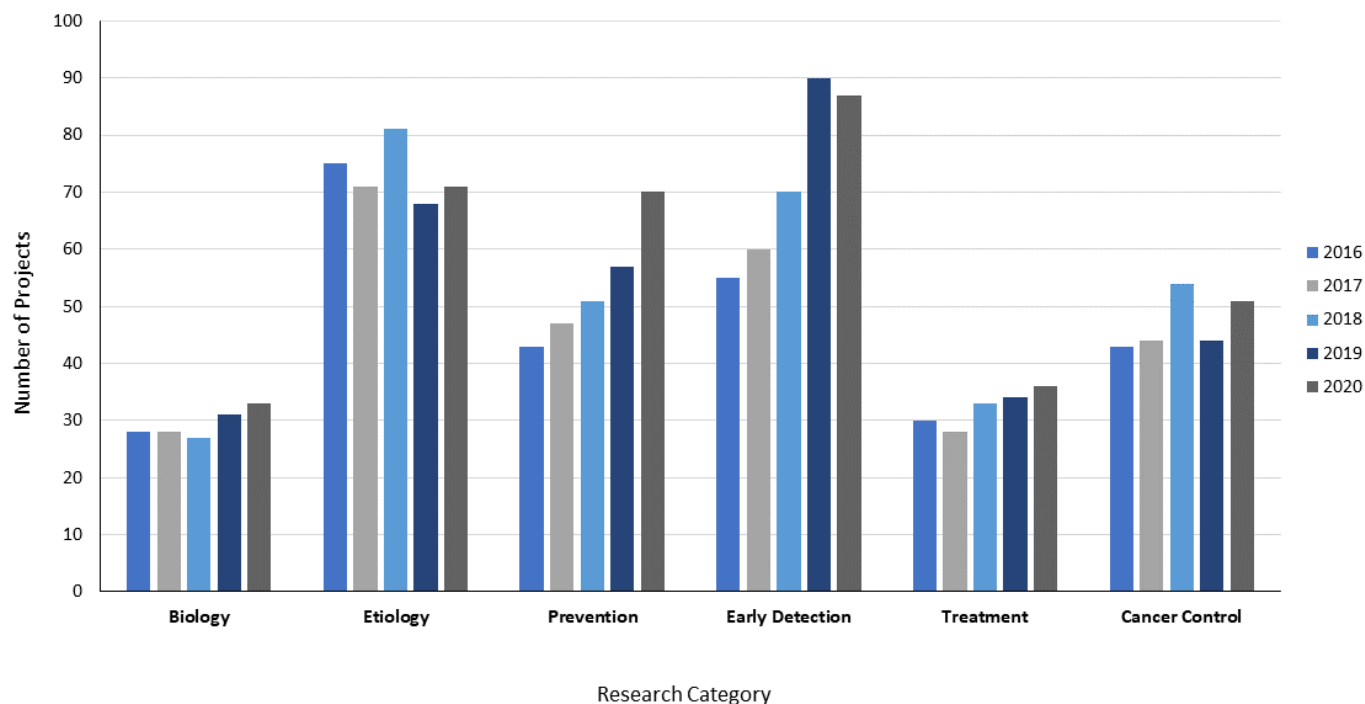


Figure 22. NIH funding categories for cervical cancer research from the fiscal year 2020 Research, Condition, and Disease Categorization Cervical Cancer category.

Projects were assigned to International Cancer Research Partnership Common Scientific Outline classifications using a dimensions machine learning process. Individual projects can be assigned to multiple categories. Not all projects are classified, and unclassified projects have been excluded from the data shown.

An important NCI initiative is the [Specialized Programs of Research Excellence \(SPORE\)](#). Each of these programs is designed to rapidly translate basic research into clinical practice. NCI funds one SPORE specific to cervical cancer, within which three projects aim to develop novel HPV vaccines. In the first project, researchers are developing and testing a heat-stable HPV vaccine designed for global use. Investigators working on the second project are examining the safety, virologic outcomes, and disease outcomes for a candidate therapeutic and preventive HPV vaccine in women with and without HIV in whom both HPV 16 and high-grade cervical dysplasia have been detected. In the third project, researchers are investigating a therapeutic protein-based vaccine in patients receiving conventional chemoradiation therapy and its potential concurrent use with checkpoint blockade.

Screening and Prevention

NCI has a robust portfolio of studies to improve test characteristics of cervical cancer screening in the United States. The [Improvement of Risk-Informed Screening \(IRIS\)](#) cohort study will evaluate the performance of several promising biomarkers head to head in 70,000 women screened for cervical cancer (storing “discard” cytology and HPV test specimens). The cohort will be a resource for ongoing and future etiologic work on HPV-related cancers—particularly the work on HPV viral and host genetics, epigenetics, and the cervicovaginal microbiome. A partnership among NCI, The University of Mississippi Medical Center, and the Mississippi State Department of Health (the [STudying Risk to Improve DisparitiES of cervical cancer in Mississippi \[STRIDES\] Study](#)) evaluates risk of cervical precancer and studies novel biomarkers in women undergoing cervical cancer screening in a state with a high burden of disease. NCI’s [Study to Understand Cervical Cancer Early Endpoints and Determinants \(SUCCEED\)](#) aims to assess biomarkers of risk for progressive cervical neoplasia and validate promising biomarkers that can distinguish those patients at highest risk of developing cervical cancer from those with benign infection. SUCCEED investigators

will prospectively validate the most promising biomarkers by assessing their predictive values for key outcomes related to progression (HPV persistence, diagnosis of precancer) or non-progression (HPV clearance).

NIH has provided support to the [New Mexico HPV Pap Registry \(NMHPVPR\)](#). This novel model for public health surveillance and prevention was established in 2006 as the first population-based, statewide cervical screening registry in the United States. The NMHPVPR includes address-level data on health care facilities that provided cervical screening (Pap or HPV testing), diagnostic testing (colposcopy), excisional precancer treatment (loop electrosurgical excision procedure or cone biopsy), and linkages to HPV vaccine administrative data. Data can inform statewide progress and reveal unanticipated or adverse events related to changes in screening and HPV vaccination practices.

Improving cervical cancer screening strategies using self-collected specimens could expand women's access to care in both high- and low-resource settings. The feasibility of testing self-collected samples for HPV DNA methylation on certain genes as an assay for cervical cancer is under investigation. NCI sponsors the [Last Mile Initiative](#), a public-private partnership to examine cervical screening self-sampling and inform the relevant regulatory approvals. NCI's [Population-based Research to Optimize the Screening Process \(PROSPR\)](#) project aims to understand ways to improve the cancer screening process (including recruitment, diagnosis, and referral for treatment) in community health care settings. These efforts are intended to expand access to cervical cancer screening and ensure that the service is available to underserved women and in low-resource settings.

NCI scientists contributed significantly to the development of HPV vaccines.¹⁴² Efforts continue to improve HPV vaccination rates. The [ESCUDDO \(Estudio de Comparacion de Una y Dos Dosis de Vacunas Contra el Virus de Papiloma Humano\)](#) is co-funded by NCI and the Bill & Melinda Gates Foundation, with support from the International Agency for Research on Cancer, to study whether one dose of the HPV vaccine is as effective at preventing infection as two. If one dose of the HPV vaccine is found to be sufficient to reduce cervical cancer burden, the feasibility of operating vaccination programs at an overall lower cost will increase. Low-cost vaccination programs could lead to more widespread vaccine uptake in the United States and around the world.

The NCI clinical trials portfolio includes secondary prevention approaches using investigational agents to treat HPV-related precancerous lesions, reversing the HPV-driven malignant transformation. Ongoing trials of immunologic agents include [NCT04131413](#), a Phase 1 single-arm trial on the safety and tolerability of a vaccine in women with and without HIV with biopsy-confirmed high-grade cervical pre-cancers; [NCT02481414](#), a Phase 2B clinical trial of a therapeutic HPV E6 peptide vaccine with or without a Candida skin-testing reagent to treat high-grade pre-malignant cervical lesions; and [NCT03284866](#), a Phase 3 trial of HPV vaccine therapy to reduce high-grade cervical lesions in patients with HIV and HPV. An additional clinical trial, [NCT03196180](#), is a Phase 1 trial assessing self-applied 5-fluorouracil with clinician-applied once-weekly imiquimod as a topical agent for women with high-grade cervical pre-cancers before excisional biopsy. Additional trials of topical, intralesional, or immunologic agents are focused on men and women with HIV and HPV in other disease sites (anus and vulva).

Clinical Research and Research to Improve Therapeutic Options

Strategic priorities related to cervical cancer are outlined in the [2021 Gynecologic Cancers Strategic Plan](#), ratified by the NCI Gynecologic Cancer Steering Committee at the annual review meeting on July 15, 2021. The identified goals for clinical cervical cancer research include (1) investigation of immunotherapy combination treatment and predictive biomarkers at all phases of disease life cycle, (2) molecular stratification for treatment decisions, and (3) development of combination (multimodality) interventions for newly diagnosed and recurrent cervical cancers. In 2018, NCI supported a [clinical trials planning meeting](#) with the goals of identifying novel experimental strategies, optimizing radiotherapy as a DNA damage and repair regulator, and designing clinical trials for primary and recurrent therapies for metastatic cervical carcinoma.¹⁴³

NCI supports research to improve cervical cancer treatment through its previously mentioned ([Table 4](#)) support of clinical trials infrastructure within academic and community oncology sites. The Experimental Therapeutics Clinical Trials Network (ETCTN) supports public–private partnerships for the early clinical evaluation of innovative cancer therapies. The National Clinical Trials Network (NCTN) is a collection of organizations and clinicians that coordinates and supports cancer clinical trials at more than 2,200 sites across the United States, Canada, and internationally, providing infrastructure for NCI-funded treatment and primary advanced imaging trials. The NCI Community Oncology Research Program (NCORP) is a national network that includes 46 community oncology sites, 14 of which are designated as minority/underserved sites. The NCORP network designs and conducts clinical trials in the following focus areas: cancer prevention, screening, supportive care and symptom management, surveillance, health-related quality of life, and cancer care delivery. The NCORP network also participates in treatment and imaging clinical trials conducted by the NCTN.

An ongoing trial in cervical cancer within the ETCTN, [NCT02595879](#), is a Phase 1 bioavailability study of oral triapine (a ribonucleotide reductase inhibitor) combined with concurrent chemoradiation for locally advanced cervical cancer and vaginal cancer. The NCTN is running the following trials in cervical cancer: (1) [NCT01101451](#), GOG-0236, evaluating radiation therapy with and without chemotherapy in patients with Stage I–IIA cervical cancer who previously underwent surgery; (2) [NCT02466971](#), NRG-GY006, evaluating the addition triapine to the usual chemotherapy treatment (cisplatin) during radiation therapy for advanced-stage cervical and vaginal cancers; and (3) [NCT00980954](#), evaluating postoperative chemotherapy in treating patients with high-risk, early-stage cervical cancer following a hysterectomy. The NCORP is running a research trial—[NCT01649089](#), GOG-0278—studying the physical functioning and quality of life before and after surgery in patients with Stage I cervical cancer.

Immunotherapy has revolutionized cancer treatment over the past decade, and research to apply this novel therapeutic approach to cervical cancer is ongoing. Although the PD-1 inhibitor pembrolizumab has proven effective in this disease site, the benefits of this class of drugs in cervical cancer treatment are less pronounced than in other malignancies (e.g., lung, melanoma). Intramural NCI investigators have pioneered the use of tumor-infiltrating lymphocyte therapy for HPV-related malignancies, which have shown encouraging response rates in patients treated so far.¹⁴⁰ An NCI-sponsored clinical trial found that among patients who received tumor-infiltrating lymphocyte therapy followed by systemic high-dose aldesleukin, patients with cervical cancer showed a higher percentage of tumor regression (28%) than those with other types of malignancies (18%).¹⁴⁰ Therapeutic HPV vaccines that activate the immune system by targeting these proteins are an exciting potential avenue for cervical cancer treatment. Additional research on therapeutic HPV vaccines focuses on the tumor microenvironment and increasing the immunogenicity of T-cell responses. NIH-funded researchers have tested a variety of delivery systems in a range of patients—from individuals with preinvasive, intraepithelial disease to those with end-stage cancers.¹⁴⁴

Health Services Research

Access to care influences when a patient can get diagnosed, which affects the cancer stage, comorbidities at the time of diagnosis and the likelihood of treatment completion. NCI leverages diverse data resources—such as various SEER Program linkages, the National Survey of Precision Medicine in Cancer Treatment, the Health Information National Trends Survey, household surveys, and information on cancer care in community settings—to examine delivery of care. Additionally, NCI’s Cancer MoonshotSM supplements are accelerating cervical cancer control by helping Federally Qualified Health Centers (FQHCs) in North Carolina plan for implementing self-collection. In another Moonshot project, the Cancer Intervention and Surveillance Modeling Network (a consortium of NCI-sponsored investigators) is modeling older women’s risks to determine when to stop cervical cancer screening. Four NCI-Designated Cancer Centers are examining HPV vaccine hesitancy, with the aim of increasing uptake.

Research Gaps on the Health of Women in the Current NIH Portfolio

The process of responding to the congressional request (i.e., the focused assessments, portfolio reviews, and discussions in preparation for the WHC) led the ACRWH to propose, rank, and approve a list of research gaps in each of the topic areas. That process and the discussions at the WHC informed the following recommendations that were proposed, ranked, and approved as opportunities for future NIH-funded research.

Women's Health Research

Research to improve the health of women is embedded in the work and mission of all NIH ICOs. ORWH coordinates this research and ensures that sex and gender are integrated into an interdisciplinary scientific framework at NIH and throughout the broader scientific enterprise. Additionally, ORWH is the only organization within NIH to specifically support scientific inquiry on sex differences in health research.

The ACRWH identified the following gaps related to women's health research:

- availability of data collection systems that host clinically meaningful data relevant to the health of women
- medical and interprofessional education on sex and gender, including person-centered and culturally appropriate language
- research on intersectionality and the health of women
- concordance of data and definitions of women's health research across ICs
- research on menopause, gynecologic diseases, and other female-specific conditions

Although the MCS-WH was updated in 2019 to estimate current NIH investments in research focused on women's health, difficulties persist in capturing this research. Within each IC, attention to definitions of women's health research and prioritization of research relevant to the health of women varies. Although race, ethnicity, and sex and gender reporting of Phase 3 clinical trials now is required, there is no data capture system to identify the study of overlapping populations (e.g., Black women), limiting research on intersectionality. Sex and gender currently are reported as "either/or" categories, limiting the ability for researchers to understand the distinct influences of sex and gender on health. Uniform NIH-wide definitions of sex, gender, and what research is categorized as women's health research limits this data collection, thereby limiting the development of science poised to directly address the needs of women.

The NIH portfolio on sex differences in health and disease currently is coordinated within ORWH and has varying priority within ICs. The [SABV policy](#) has led to preclinical and discovery knowledge of relevant diseases that affect women. Despite this policy, gaps remain in basic and translational understanding of how sex differences influence health. Understanding basic biologic differences in male and female physiology and disease pathogenesis is fundamental to translating preclinical findings into interventions to improve the health of women.

ORWH was created with the purpose of improving the inclusion of women in NIH-supported clinical research. In the decades since, clinical trials enrollment of women across NIH has improved dramatically, such that half of participants in clinical research are women. Historical and structural factors have resulted in large research gaps in such areas as basic physiology of the uterus and menstruation that influence researchers' ability to develop

interventions to improve the health of women. Research on female-specific conditions and diseases has been and remains limited. Scientific inquiry on subjects with such conditions as menopause, endometriosis, or fibroids does not clearly fall under the purview of a single IC, and NIH receives fewer unsolicited investigator-initiated grant applications addressing these female-specific conditions than other NIH-supported research topics. Without this foundational knowledge, gaps remain in providing high-quality, evidence-based care for women.

Many of these gaps stem from a historic lack of emphasis on education on sex and gender within medical school and other biomedical scientific educational training programs. The lack of professional education in sex and gender is bidirectional: Without research, education is incomplete and uninformed.

Maternal Morbidity and Mortality

There is an ongoing need to reduce known maternal health risk factors; improve care to effectively manage pregnancy-related and underlying comorbidities; improve the identification and management of severe morbidity; and expand comprehensive, interdisciplinary research to reduce preventable maternal deaths and improve health for women during and after delivery.

The ACRWH identified the following gaps related to NIH-supported research on MMM:

- research on how to overcome structural barriers, including limited access to high-quality care, for patients from underrepresented communities, rural communities, and sexual and gender minority populations
- standard data collection and quality measures related to pregnancy outcomes that include social determinants of health
- understanding of the underlying physiology of pregnancy and pathophysiology of pregnancy disorders so that the effect of pregnancy on the life course of women can be better understood
- clinical research networks with the capacity to enroll pregnant people of all risk levels and answer research questions specific to pregnancy
- implementation research to study interventions known to improve pregnancy outcomes that are risk specific

During the past few decades, NIH maternal–child health research has focused largely on fetal and newborn outcomes rather than maternal health. Such endpoints as preterm birth and premature labor are easier to measure and obtain in shorter time frames. Currently, clinical trials infrastructure for research on pregnancy (MFMU) is concentrated in tertiary care, including academic sites without requirements to include community or minority-serving hospitals. Research on maternal health is geographically concentrated in the Northeast and needs to be expanded to IDeA states in the West, the South, and the central part of the United States. These weaknesses limit the capacity for clinical trials on pregnant patients with pregnancy-specific endpoints. Non-obstetrical clinical trials (e.g., for COVID-19 and chronic diseases) that include pregnant women also are greatly needed, and grant applicants must be required to justify the exclusion of pregnant women. Large data sets that follow women from pre-pregnancy through pregnancy to the postpartum period and beyond also are lacking. The absence of big data or “virtually warehoused” data that include granular, pregnancy-specific measures—such as proteinuria and blood pressure—limit the availability of knowledge on how events during pregnancy affect health later in life.

Despite marked progress, there continues to be missing surveillance data on MMM, which does not include suicide, homicide, and substance use disorder. Half of deaths associated with pregnancy occur after delivery before 1 year postpartum, yet these events currently are not well captured in the PMSS. Similarly, there remains a need to

improve longitudinal data resources. There is a need for research that includes long-term follow-up and linking pregnancy studies to ongoing pediatric cohorts. These studies need to incorporate patient-reported outcomes and quality-of-life measures. A relative lack of granular, representative data sets from diverse patient populations has led to challenges in identifying and understanding the effects of structural racism and discrimination—as well as environmental exposures (e.g., pollution, stress)—on risk for SMM. Little research on the effects of implicit bias is ongoing, although bias can negatively affect patient–provider communication (e.g., counseling on options), as well as the interventions that women receive during maternity care (e.g., analgesics).¹⁴⁵

Additional basic and translational research is needed to better define the effect of pregnancy on medical conditions (e.g., diabetes, COVID-19) and the pathogenesis of pregnancy-specific disorders (e.g., preeclampsia, preterm birth). The root causes and underlying mechanisms of specific common causes of maternal death (e.g., infection and hemorrhage) warrant greater attention and might be addressed by research that stratifies maternal mortality by etiology and pathogenesis. Fundamental, basic, and translational knowledge on what causes the initiation of labor is lacking. Similarly, although rates of preeclampsia and pregnancy-associated hypertension have increased in the last decade, the underlying cause of preeclampsia remains unknown.

More than half of MMM events occurring in the United States are preventable, meaning that best practices are available but not universally applied. Implementation research on how best to apply evidence-based, high-quality care—such as those described in safety bundles—to all pregnant people is a critical gap. To bring science to the women most affected by MMM, NIH must seek input and guidance from communities, where health begins and ends, and support research that emphasizes prevention and wellness.

Chronic Debilitating Conditions

The disaggregation of clinical research data by sex and gender, as well as race and ethnicity, is necessary for understanding their influence across all chronic debilitating conditions. These details can better inform clinical care, health communication, and future lines of scientific inquiry. A historic overreliance on male clinical research subjects left gaps in our current evidence base regarding CDCW. To produce interventions that meet the needs of all women, researchers must consider women when designing studies—which means addressing inequities in care for women who are members of underserved or understudied populations, including but not limited to underrepresented racial and ethnic groups, women living in rural communities, and women of low socioeconomic means. The paradigm of “one patient–one disease” no longer fits the medical necessities and needs of most patients with chronic diseases, and a more holistic, patient-centered perspective is needed.

The ACRWH identified the following research gaps related to CDCW:

- research to enhance our understanding of disease presentation, diagnosis, and treatment specific to women
- standardized definitions of CDCW
- communication, coordination, and consistency of reporting of research activities on CDCW
- understanding of the implications of gender in CDCW (e.g., access to care, health care system interactions, health outcomes)

Basic and preclinical models that incorporate sex are needed to improve the understanding of CDCW, including the influence of hormonal and nonhormonal mechanisms. In-depth knowledge of the cellular and molecular processes underlying pathophysiology would enhance our understanding of female-specific chronic conditions and may be broadly applicable to studying SABV. An important related research gap for CDCW is the assessment of biomarkers

(e.g., genetic, proteomic, metabolomic) that influence the development of disease. Information is needed on how specific environmental and behavioral exposures can lead to female-specific phenotypic manifestations of disease.

The portfolio analysis of current NIH research on chronic debilitating conditions was complicated by a lack of consistent definitions, both in the medical literature and—as a consequence—within the NIH RCDC. A framework for the consideration of CDCW was not available and was created in response to the congressional inquiry leading the WHC and this report. Utilizing this framework demonstrated that current research funding for chronic debilitating conditions is not reflective of the CDCW disease burden or the concerns of the public (as measured by the conference RFI).

Nearly all ICs support some research on chronic debilitating conditions, and the prioritization of NIH support for research on women's health varies significantly by IC. Little is known about the effects of chronic conditions specific to women on functioning, quality of life, and mortality across the life course. Studies that provide detailed clinical outcomes data—tied to such critical life course windows as menarche and menopause—from a diverse population of women are needed to support this important work.

Because women have higher rates of multimorbidity compared with men, challenges for research on multimorbidity have greater impact on the health of women. Research gaps include studies to understand which subpopulations are affected disproportionately; population-level distributions of chronic diseases, particularly those specific to women; and studies that evaluate the interactions of multiple CDCW specifically. Without attention to multimorbidity, given that women are affected disproportionately by multiple chronic conditions, women then may be excluded disproportionately from clinical research because morbid conditions (e.g., chronic kidney disease) influence eligibility (**Figure 23**).

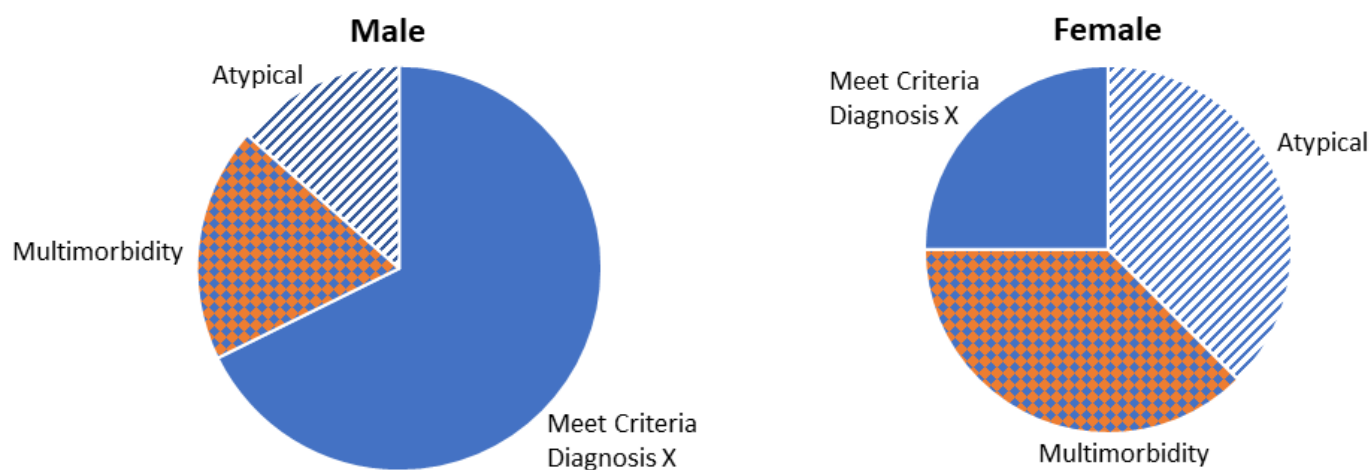


Figure 23. Exclusion of subjects with multimorbidities decreases the validity and generalizability of research throughout the pipeline.

Disparate funding is a telescoping problem: The relevance of new data is focused on the population that we already know the most about; important disease-relevant, mechanistic information revealed by studying across populations is missed.

Race, ethnicity, and other social determinants of health influence the health of women differently than the health of men, so the influence of gender on these factors must be considered. The complexity of overlapping social factors and how these features influence therapeutic responses within diverse populations remain understudied.

Stagnant Cervical Cancer Survival

Despite high-quality screening and prevention methods, invasive cervical cancer remains prevalent among certain populations within the United States. Access to screening, prevention, and treatment are ongoing issues that have hampered cancer control in this disease site.

The ACRWH identified the following research gaps related to cervical cancer:

- clinical research that addresses specific screening and prevention needs of communities with high burdens of disease
- research on improving linkages to care for people with positive screening results
- implementation research on interventions that will improve screening and prevention, treatment, and access to care in populations with high burdens of disease (non-HIV)
- research on treatments in advanced and metastatic disease that are feasible for specific populations with high burdens of disease
- research on treatment for patients with cervical cancer and comorbid medical conditions

Gaps in the areas of primary and secondary prevention relate primarily to the implementation of best practices. Vaccination and screening rates remain less than ideal within many U.S. communities, particularly in geographic regions with high burdens of HPV infection and cervical cancer. Research on self-sampling and ways to enhance the screening process may help reduce disparities in screening rates but may alleviate barriers only for patients already receiving current screening and prevention interventions without expanding the reach of this intervention. Specifically, innovative health services research is needed to help improve HPV vaccination rates among U.S. adolescents (e.g., by better understanding vaccine hesitancy, consideration of alternate vaccination sites). Additionally, novel interventions and incentives are needed to improve cervical cancer screening and follow-up for historically underserved groups.

Imaging results and biomarkers predictive of relapse currently are not available and represent an urgent, unmet need in both basic and translational research. Enhancing basic research in such areas as genomics and imaging biomarkers most likely would facilitate personalized medicine approaches in cervical cancer prediction, diagnosis, and treatment on par with other disease sites. Research is needed to identify whether new targeted agents—such as DNA damage response inhibitors and metabolic targets—can be used as cervical cancer treatments. Such research would further reveal different growth-regulating pathways and expand our understanding of cervical cancer types as they relate to HPV variants. Improved multidisciplinary research that includes basic research in the biology and etiology of cervical cancer is needed to translate basic research into improved diagnostic and treatment options for patients.

NCI-sponsored research historically has produced the formative advances on treatment of cervical cancer. Following the 2010 Institute of Medicine (IOM) report, [*A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*](#), the legacy Gynecologic Oncology Group joined with the Radiation Therapy Oncology Group and the National Surgical Adjuvant Breast and Bowel Project Foundation (NSABP) to form NRG Oncology. Intentionally smaller clinical trials than in past decades—with a shift toward the Phase 2/3 design—based on biomarker hypotheses have replaced larger Phase 3 trials to improve efficiency and accelerate approval of effective drugs. However, gynecologic cancer clinical trials were affected by the restructure. Disproportionately low NIH funding to gynecologic cancers compared with other cancer disease sites has been

described.^{3,146,147} Recent FDA drug approvals in this disease site (including cemiplimab, tisotumab vedotin, and pembrolizumab) have resulted from industry-supported research. The practice-changing GOG-240 trial that demonstrated a survival benefit of adding bevacizumab to chemotherapy closed to patient accrual in 2010; a replacement trial in the advanced and/or metastatic setting, where mortality is highest, has not been opened. Clinical trials specific to innovative, novel therapeutics, drug sequencing, and drug dosing for patients with advanced and metastatic invasive cervical cancer are needed.

The populations at risk for cervical cancer and those needing treatment for cervical cancer have been traditionally underserved by health care systems. Often, patients with cervical cancer are diagnosed and managed outside of settings where clinical trial enrollment is available. Research on innovative treatments has, as a result, rarely focused on the needs of the majority of patients with the disease—such as modifications to radiotherapy (e.g., hypo-fractionated external radiation, brachytherapy, radiopharmaceuticals) and antibody–drug conjugate therapies. Investigations into treatments that are practical and feasible for the majority of patients with cervical cancer are a critical need. Given the burden of disease of cervical cancer in resource-poor settings, studies using multilevel, multisite, multimodal, multilingual, and multicultural techniques and optimizing technology to improve outcomes will be of particular benefit to patients with this disease. Large numbers of patients with advanced and metastatic cervical cancer have comorbidities (e.g., renal dysfunction) that limit their eligibility for clinical trials. Clinical trials that investigate personalized dose and schedule intensification are needed, particularly in low-resource settings where transportation, housing, and food security are challenges. Industry funding for research on surgical, imaging, and radiation therapy is unlikely, so these topics could be prioritized by NIH.

The structural factors driving health disparities in cervical cancer survival are well defined, yet there are few interventional implementation projects currently underway to alleviate related inequities. Research is needed to assess the impact of structural and interpersonal racism on outcomes in the cancer care continuum and will particularly benefit patients with this disease. Gaps exist in the quantitative and qualitative evaluation of bias and exclusion in biomedical cancer research. All areas of cervical cancer research—but especially research to reduce disparities—would benefit from a diversified workforce, particularly among clinical research professionals. Personnel (e.g., patient navigators) and resources (e.g., non-English language patient information and consent forms) are not universally available but would allow more diverse enrollment into clinical research.

Research Opportunities on the Health of Women in the Current NIH Portfolio

Women's Health Research

Increasing investment in research on the health of women has been demonstrated to produce significant societal returns.¹⁴⁸ The [2019–2023 Trans-NIH Strategic Plan for Women's Health Research](#) sets out an ambitious vision for a world where the biomedical research enterprise thoroughly integrates sex and gender influences; every woman receives evidence-based disease prevention and treatment tailored to her own needs, circumstances, and goals; and women in scientific careers reach their full potential. However, intentional interventions are needed to achieve that vision.

The ACRWH identified the following opportunities to strengthen NIH-research on the health of women:

- Perform a granular and comprehensive evaluation of the NIH-wide research portfolio dedicated to the health of women.
- Identify women's health research leads in each IC with authority to direct and coordinate women's health research.
- Create intentional funding opportunities for topics on the health of women aligned with the *2019–2023 Trans-NIH Strategic Plan for Women's Health Research*.
- Enforce the NIH SABV and other inclusion-across-the-lifespan policies.
- Create standing study sections to evaluate research focused on the health of women and include women's health experts on all applicable standing study sections.

Given the limitations of the portfolio analysis performed leading up to the WHC, the ACRWH recommended a granular and comprehensive NIH-wide review of current NIH support of research on women's health. This review would include a focused review of NIH priorities in female-specific conditions and diseases, as well as a review of the prioritization of research specific to women in non-sex-specific conditions and within clinical studies. The performance of such a review would provide the opportunity to identify specific areas of need and allow focused, intentional research programs where gaps exist. Given the NIH structure of organ- and disease-specific ICs, this will require collaboration with a dedicated champion for women's health research within each IC. Providing an IC representative with the authority to identify and support research where gaps have been identified is critical to the success of filling in historic gaps in the evidence base of prevention, diagnosis, and treatment of women's health.

The SABV policy has had success at increasing investigations of sex differences; however, more must be done to improve adherence to the SABV and other inclusion policies across all studies. Continued attention to and enforcement of the SABV policy will lead to further understanding of how sex influences physiology and pathophysiology, allowing improvements in disease prevention and treatment strategies in the multitude of conditions that present differently in women and require different treatment in women and men.

Intentional funding opportunities can improve NIH-wide support of research on women's health to overcome the disproportionately low number of women's health- and female-specific unsolicited investigator-initiated NIH-funded projects. NIH also must solicit research with hypotheses centered around the health needs of women to address those prevention, diagnosis, and treatment interventions where sex- and/or gender-specific knowledge is

insufficient. Intentionally funding and leveraging existing NIH resources—such as cohorts, biobanks, and bioinformatics—can advance a robust research agenda on the health of women.

The creation of standing study sections on sex differences and women's health research and the inclusion of researchers with women's health expertise on other study sections could help overcome the bias that discourages research on women's health. Standing study sections on women's health also would signal to the extramural community that NIH is interested in supporting this research and would generate more extramural research funding applications.

Maternal Morbidity and Mortality

The ACRWH identified the following opportunities to strengthen NIH research related to MMM:

- Enhance clinical research on structural barriers for patients from underrepresented communities, including but not limited to underrepresented racial and ethnic populations, rural communities, and sexual and gender minority populations.
- Develop standard data collection measures and quality metrics related to pregnancy outcomes.
- Encourage research that improves the understanding of the impact of pregnancy and pregnancy complications on the life course of women.
- Increase clinical research network capacity to enroll pregnant women of all risk levels and answer research questions specific to pregnancy.
- Support implementation research to identify methods to apply interventions known to improve pregnancy outcomes.

Given the contribution of structural inequities on the quality of preconception, antenatal, and postpartum care, research on reducing disparities in MMM rates is critical. The defined timeline of pregnancy and the utilization of a single health care delivery site (labor and delivery units) make pregnancy an ideal condition for researching interventions to prevent discrimination. A disparity database could capture information on deliveries across birth settings (e.g., birth centers that employ midwives, intention of birth site, provider racial and ethnic concordance) and help researchers analyze quality measures for groups at higher risk for negative outcomes, providing much-needed prospective data to study meaningful interventions.¹⁴⁹ Efforts that promote diversifying the maternal health research workforce also would help improve maternal health. Research on workforce strategies (e.g., implicit bias training; inclusion of nontraditional providers, such as doulas) to reduce discrimination not only can improve outcomes in pregnancy but also can potentially be extended to other health care settings. NIH could offer training, mentorship, and access to diversify the research teams it supports and include physicians (from disciplines besides obstetrics/gynecology), physician assistants, nurses, midwives, doulas, community health practitioners, and data scientists as investigators.

Current efforts to identify gaps in knowledge and research on safe and effective therapies for pregnant women, such as [PRGLAC](#), can be supported and expanded. The enrollment of pregnant women in clinical trials and support for research with large and diverse enrollment (by race, ethnicity, socioeconomic status, geography, and health care setting) will advance knowledge that ultimately can make pregnancy safer.

Maternal health research would benefit from expanding networks (or creating new networks) to enroll pregnant patients and answer pregnancy-related outcome questions. Such networks must encourage participation from

diverse practice settings, such as FQHCs, community practices, and minority-serving hospitals. Additional capacity for clinical trials in pregnancy could provide new knowledge about pregnancy and its effects on later health by incorporating a life course approach—that is, gathering information on experiences from childhood (and even *in utero* exposures) and following dyads longitudinally to assess long-term outcomes.

For all clinical research regarding pregnancy to be successful, data collection and quality metrics that relate to pregnancy outcomes that include social determinants of health must be standardized. Measurable, consistent, quantitative definitions of factors—such as low-risk versus high-risk pregnancy—must be developed and agreed to within the research community. Pregnancy-associated morbidity and mortality from overdose, suicide, or other mental health conditions must be captured and available for researchers to identify and test potential interventions.

In implementation science, there are opportunities to build new models for optimizing pre-pregnancy health and providing perinatal care (e.g., patient navigators and case management). Care delivery research must focus on improving care beyond the hospital—including in the outpatient setting, home, and neighborhood—and across pre-pregnancy, pregnancy, and postpartum. The prenatal care electronic medical records, for example, contain universal data (e.g., blood pressures, ultrasound findings) that are well suited for data set creations from medical records. Artificial intelligence and informatics techniques from other disciplines (e.g., oncology) can be leveraged to produce publicly available, rich data sources to produce hypothesis-generating, real-world data. In addition to examining maternal and infant health outcomes, investigators could use implementation science platforms to investigate multilevel models that improve care quality and patient satisfaction and address disparities. Research on new care delivery models also would provide an opportunity to promote culturally tailored and patient-centered interventions.

The development of a rapid-cycle maternal–infant data system would support projects to advance both equity and clinical quality improvement (QI). There is an opportunity to change the culture around maternal health care with a series of large-scale, data-driven QI projects (e.g., safety bundle implementation). Building electronic health record analytics might facilitate both QI and research on maternal health improvement. To further support innovation in maternal health and health disparities reduction, NIH research also might contribute to interventions to improve the education and training of clinical service providers and staff to mitigate health care inequalities. Tools to promote shared decision making, cultural competence, bias awareness, and patient advocacy, as well as the dissemination of health education content to communities most affected by the U.S. maternal health crisis, could all benefit the health of pregnant people.

A broad range of public, private, and community partnerships will be essential to NIH's efforts to fill these gaps with research focused on health equity and reducing MMM. To that end, NIH must collaborate with other HHS agencies, such as the Indian Health Service, FQHCs, community hospitals, and the Migrant Clinicians Network. NIH cooperation with these organizations and facilities would bolster community-partnered studies and outcomes-driven research. NIH engagement in collaborations within HHS and public–private partnerships would help disseminate evidence-based research findings and advance policies for implementation.

Chronic Debilitating Conditions in Women

The ACRWH identified the following research opportunities related to CDCW:

- Develop definitions and a framework specific to CDCW—consider partnering with the National Academy of Sciences (NAS).
- Support clinical research aligned with the needs of women (e.g., study objectives and endpoints).

- Increase research activity on female-specific diseases, menopause, and aging in women.
- Support clinical research specific to chronic diseases in women through existing clinical research networks or by creating new networks.
- Encourage research on multimorbidity in women.

Although a framework to consider CDCW was developed in preparation for the WHC, a structured, expert review of this topic could enhance our understanding of the current clinical needs and outline a future research trajectory. Convening a workshop with the NAS was suggested as a potential mechanism to achieve this goal. Adopting a definition of chronic debilitating conditions within the NIH RCDC system would codify this variable within applicable databases and allow the tracking of funding and the alignment and overlap of research on chronic debilitating conditions with women's health research. Creating an RCDC category for menopause would allow the tracking of funding for chronic diseases across the life course of women.

Specific and intentional attention to research design, analysis, and reporting by sex and gender is critical to the mission of alleviating the burden of CDCW. As part of the 21st Century Cures Act implementation, all applicable Phase 3 clinical trials must report results of valid analyses in the NIH database [ClinicalTrials.gov](https://clinicaltrials.gov) by sex, gender, race, and ethnicity. Improved adherence to this policy could provide much-needed disaggregated data on sex differences in response to interventions, allowing the development of novel treatments specific to women with chronic debilitating conditions.

In response to the limited research portfolio on female-specific disorders, NIH has an opportunity to pilot multiple-IC funding opportunities on gynecologic disorders that then could be applied to other disciplines and studies of women. The creation and application of standard data elements related to menses and menopause would allow prospective investigation of how these life course events influence health and disease in multiple categories of chronic conditions that affect women. Prospective NIH-wide collection and analysis of female-specific tissue (e.g., endometrial tissue) and relevant data (e.g., state of the menstrual cycle and menopausal status) would benefit the health of women beyond gynecology. NIH might leverage longstanding prospective cohorts for existing banked biospecimens and electronic medical or other virtually warehoused data to promote investigation of female-specific conditions.

Clinical research that is specifically and intentionally centered on women, equipped to design trials that answer questions specific to women, and able to enroll women into studies could be created through existing research networks or by founding new networks specific to women's health. Cohort studies of women with chronic debilitating conditions might likewise begin to fill some of our gaps in understanding the specific pathophysiology of women with such diagnoses.

Lastly, due to the outsized burden of multimorbidity in women, specific attention to basic, translational, and clinical research that encompasses more than one chronic condition would benefit the health of women. Expanded eligibility criteria within clinical research to allow the inclusion of patients with comorbidities would make clinical research in chronic conditions more applicable to the population in need of novel therapies and ensure representative enrollment of women onto clinical trials. Novel clinical trial designs, "big data" studies that utilize population health records, and the incorporation of advances in disease modeling all could be utilized toward this goal.

Stagnant Cervical Cancer Survival

The ACRWH identified the following research opportunities related to cervical cancer:

- Support research to develop and implement novel interventions to improve screening and prevention in communities with historically low uptake.
- Support research to identify interventions to translate screening abnormalities into earlier diagnosis and treatment.
- Continue to align and incentivize clinical research questions with patient care needs (e.g., reduced toxicity, shortened courses of treatment, improved survival in advanced and metastatic disease).
- Encourage psychosocial support for nontreatment needs (e.g., housing, transportation) in historically under-resourced communities to actively engage in the trust-building necessary for diverse clinical trials enrollment.
- Promote research to reduce disparities in Cancer Center catchment areas.

Generally, research gaps might be filled by considering invasive cervical cancer as a rare disease. As in other rare diseases, heightened NIH-wide and international collaboration would help fill gaps in cervical cancer research. When considered as a rare disease within the United States, cervical cancer could benefit from the creation of national data sets that leverage information from support groups and electronic medical records.

Enhanced basic and translational cervical cancer research could result from facilitating the development of *in vivo* models and biospecimen availability for studies of HPV-related premalignant lesions, as well as invasive disease. Further study of HPV genotypes, gene expression, and proteomics might be translated into better outcome prediction and targeted treatments that could benefit patients with any HPV-related malignancies. Knowledge of subtype-specific molecular or genetic drivers that might direct responses to therapy could allow subtype-specific treatment algorithms, rather than our current one-size-fits-all therapies. TCGA results could be leveraged to study HPV genotypes and HPV gene expression, as well as the role of mRNAs, microRNAs, and lncRNAs. Work also must focus on improving basic and preclinical research models (e.g., 2D co-cultures, 3D cultures, patient-derived xenografts, genetically engineered mouse models) relevant to human disease. NIH can facilitate biobanking from clinical research and expand real-time data sharing such that specimens from clinical research can be used secondarily for novel basic and translational discovery. For rare diseases, this is particularly important because single- or multi-institution cohorts might not have adequate banked samples to assess predictive and prognostic biomarkers meaningfully.

Novel approaches are required for implementation research to scale up effective screening and prevention interventions at the population and community levels. Lessons learned from the COVID-19 pandemic could be applied broadly to overcoming vaccine hesitancy and outreach to communities at high risk for disease. Such programs as CDC's [Prescription Drug Monitoring Program](#) and [COVID vaccination data collection](#), as well as the NMHPVPR, can be utilized to design linkage systems to track and monitor individual patient-level adherence to cervical cancer screening and prevention interventions. Database solutions to identify in real time whether patients have or need vaccination, HPV testing, or cytology could help patients access what they need across multiple health care settings. Research on how to improve linkages to care for people with positive screening results would fill one of the largest gaps in care that determines stage at diagnosis and defines survival. Research on prevention and screening efforts can be focused on how to move beyond office-based interventions toward community-based

interventions to better serve populations with historically low uptake. Innovative models of service delivery (e.g., nontraditional provider delivery, self-sampling at community venues) must be investigated.

Access to health care and specialty care are structural factors that drive stagnant cervical cancer survival rates, and additional investments are needed in health services research addressing these issues. Targeted queries within the SEER database specific to cervical cancer and an NIH investment in building information systems (at the state, regional, and national levels) would bolster research in this area. Quality of care (e.g., brachytherapy receipt) could be measured within such databases as SEER to inform population-level adherence to guidelines and allow the measurement of interventions. Research on multilevel approaches to achieving equitable representation of historically understudied populations in cancer-related clinical trials also could provide critical information to inform cervical cancer treatment.

Gynecologic cancer treatment research must be prioritized based on the burden of disease within our communities. Endpoints for cervical cancer clinical trials must be aligned with patient needs—such as reducing toxicity and shortening courses of treatment—and endpoints to evaluate disparities can be included in outcomes. Expanding access to clinical trials that focus on improving available therapeutics and testing novel agents is another important opportunity for NIH and would be helped by participation in international collaborations, particularly considering the global burden of disease. NCI efforts to expand eligibility criteria and create novel clinical trial designs to include older patients and patients with comorbidities will benefit patients with cervical cancer. Because cervical cancer typically affects patients with multiple barriers to care (e.g., poverty, lack of health insurance, low English-language proficiency), these patients often receive care at sites where clinical trials are available at lower rates than patients with other malignancies.

Research can be encouraged on methods that promote linkages to care and access to treatment and clinical trials to patients who historically are underserved. Extending relationships among institutions receiving infrastructure awards and minority-serving and safety-net hospitals would extend the reach of NCI-supported clinical trials in cervical cancer and diversify their patient population enrollments. Research could support such questions as how practical assistance and nontreatment support (e.g., housing) can alleviate barriers to care and improve adherence to long courses of treatment (e.g., external beam pelvic radiation). Equity research must be grounded in theories and frameworks of how race, gender, and health intersect within our society, because such interventions are needed to overcome barriers related to race, English proficiency, poverty, and geography that overlap for many patients with this disease.

NIH could enhance efforts to improve the diversity of the research workforce and provide training in the delivery of complex multidisciplinary care. The number of gynecologic oncologists in the United States remains small (fewer than 1,200 physicians¹⁵⁰), as is the number of radiation and medical oncologists trained in the management of cervical cancer. Training opportunities could be targeted toward oncologists with niche expertise. Ensuring that gynecologic oncologists and radiation oncologists with cervical cancer expertise are present on review committees and study sections would help prioritize this and other research on gynecologic malignancies.

Existing and future partnerships between NIH and other HHS agencies (e.g., CDC, CMS, HRSA), as well as third-party payors and health maintenance organizations, will encourage the use of evidence-based interventions that could reduce mortality from cervical cancer. Such partnerships must continue to be leveraged to increase the number of women who receive, for example, follow-up from abnormal screening tests and guideline-adherent care (e.g., brachytherapy) and the efficacy of NIH-supported interventions.

Conclusion

Improving the health of women benefits all members of our society.¹⁰ Increasing research on the health of women has been demonstrated to [produce significant returns on investment](#). The [2019–2023 Trans-NIH Strategic Plan for Women’s Health Research](#) sets out an ambitious vision for a world in which the biomedical research enterprise thoroughly integrates sex and gender influences; every woman receives evidence-based disease prevention and treatment tailored to her own needs, circumstances, and goals; and all women in scientific careers reach their full potential.

Broad support for increased prioritization of research on women’s health was expressed by members of the public, NIH stakeholders, ACRWH members, and the participants of the WHC.

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- Neel Shah, M.D., M.P.P., Assistant Professor, Department of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School; Senior Advisor, Delivery Decisions Initiative, Ariadne Labs
- Melissa A. Simon, M.D., M.P.H., Vice Chair for Research, Department of Obstetrics and Gynecology; Director, Institute for Public Health and Medicine; Director, Center for Health Equity Transformation; George H. Gardner, MD, Professor of Clinical Gynecology; Professor of Obstetrics and Gynecology (General Obstetrics and Gynecology)/Preventive Medicine and Medical Social Sciences; Feinberg School of Medicine, Northwestern University
- Kimberly J. Templeton, M.D., Professor of Orthopedic Surgery; McCann Professor of Women in Medicine and Science; Director, Orthopedic Surgery Residency Program, University of Kansas Medical Center; Past-President, American Medical Women's Association

Ad Hoc Members

- Haywood L. Brown, M.D., M.P.P., Professor of Obstetrics and Gynecology; Vice Dean of Faculty Affairs and Associate Dean of Diversity, Morsani College of Medicine, University of South Florida (USF); Senior Associate Vice President of Academic Affairs, USF Health
- C. Neill Epperson, M.D., Robert Freedman Endowed Professor and Chair, Department of Psychiatry, University of Colorado School of Medicine Anschutz Medical Campus; Executive Director, Helen E. and Arthur Johnson Depression Center; Professor, Department of Family Medicine, University of Colorado School of Medicine Anschutz Medical Campus
- Linda Griffith, Ph.D., School of Engineering Teaching Innovation Professor of Biological and Mechanical Engineering, Massachusetts Institute of Technology (MIT) School of Engineering; Director, Center for Gynepathology Research, MIT
- Charles Kunos, M.D., Ph.D., Medical Officer, Markey's Clinical Research Office and Investigational Drug Branch, Cancer Therapy Evaluation Program, the National Cancer Institute; Professor of Radiation Medicine, University of Kentucky College of Medicine
- Charles A. "Trey" Leath, III, M.D., M.S.P.H., Director, Division of Gynecologic Oncology; Professor, Department of Obstetrics and Gynecology, The University of Alabama at Birmingham
- C. Noel Bairey Merz, M.D., FACC, FAHA, FESC, Director, Barbra Streisand Women's Heart Center; Director, Linda Joy Pollin Women's Heart Health Program; Director, Preventive and Rehabilitative Cardiac Center; Professor of Cardiology, Cedars-Sinai Medical Center

Appendix A: Conference Agenda

The National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) presents:

Advancing NIH Research on the Health of Women: A 2021 Conference

Date | Wednesday, October 20, 2021, 9:00 a.m.–4:30 p.m. EDT

Welcome | Samia Noursi, Ph.D., ORWH

Introduction | Janine Clayton, M.D., FARVO, ORWH

Women's Health Matters: When, Where, & Why | Chloe Bird, Ph.D., RAND Corporation

How Stereotypes Underpin Inequities for Women in Academic STEM & Advancements in Women's Health | Molly Carnes, M.D., University of Wisconsin–Madison

The U.S. Maternal Health Care Crisis | Elizabeth Howell, M.D., M.P.P., University of Pennsylvania Health System

Impact of Chronic Disease: The Sex & Gender Gap | Marjorie Jenkins, M.D., M.E.H.P., University of South Carolina School of Medicine Greenville

Cervical Cancer: How Can We Overcome Our History | B.J. Rimel, M.D., Cedars-Sinai Medical Center

Concurrent Sessions

Maternal Morbidity and Mortality <i>Moderator:</i> Yoel Sadovsky, M.D., University of Pittsburgh	Chronic Debilitating Conditions <i>Moderator:</i> Judith Regensteiner, Ph.D., University of Colorado Anschutz Medical Campus	Stagnant Cervical Cancer Mortality <i>Moderator:</i> Wendy Brewster, M.D., Ph.D., The University of North Carolina School of Medicine
Maternal Morbidity and Mortality: Tip of a Lifecourse Iceberg Janet Rich-Edwards, Sc.D., M.P.H., Brigham & Women's Hospital	Prevention of Chronic Conditions in Women to Advance Health and Function Across the Lifespan Heidi D. Nelson M.D., M.P.H., MACP, FRCP, Kaiser Permanente Bernard J. Tyson School of Medicine	The Future of Cervical Cancer Prevention in the United States: The Realities of Evidence Beyond Innovation Cosette Wheeler, Ph.D., The University of New Mexico Health Sciences Center
Harnessing the Power of Research: Optimizing Infrastructure to Optimize Maternal Outcomes Uma Reddy, M.D., M.P.H., MFM, Yale School of Medicine	The Impact of Chronic Debilitating Conditions on Women Kimberly Templeton, M.D., University of Kansas Medical Center	A Path Forward Toward Accelerating Cervical Cancer Eradication Diana S.M. Buist, Ph.D., M.P.H., Kaiser Permanente Bernard J. Tyson School of Medicine
Opportunities in Clinical Research to Reduce Maternal Morbidity and Mortality Cynthia Gyamfi-Bannerman, M.D., University of California, San Diego, School of Medicine	The Case of Fibroids as a Female-Specific Chronic Debilitating Condition William Catherino, M.D., Ph.D., Uniformed Services University of the Health Sciences	Improving Treatment for Cervical Cancer: What Can Tumor Biology Tell Us? Julie Schwarz, M.D., Ph.D., Washington University School of Medicine in St. Louis
Expanding Maternal Morbidity and Mortality Research Within and Beyond Our Hospital Walls Mary D'Alton, M.D., Columbia University Irving Medical Center	Fortifying Opportunities to Advance Female-Specific Chronic Disease Research Stacey Missmer, Sc.D., Harvard T.H. Chan School of Public Health	Translating Science into Improved Patient Care for Women with Cervical Cancer Janet Rader, M.D., Medical College of Wisconsin

Maternal Morbidity and Mortality <i>Moderator:</i> Yoel Sadovsky, M.D., University of Pittsburgh	Chronic Debilitating Conditions <i>Moderator:</i> Judith Regensteiner, Ph.D., University of Colorado Anschutz Medical Campus	Stagnant Cervical Cancer Mortality <i>Moderator:</i> Wendy Brewster, M.D., Ph.D., The University of North Carolina School of Medicine
How Can Research Findings Be Translated into Reduced Maternal Morbidity and Mortality? Elliott Main, M.D., Stanford University	What We Do and Do Not Know About the Leading Killer of Women and What We Should Do About It! C. Noel Bairey Merz, M.D., Cedars-Sinai Medical Center	The Future of Clinical Research in Cervical Cancer Treatment Charles Kunos, M.D., Ph.D., University of Kentucky
You Are What You Love: Prioritizing Women's Health Research for a Healthier Society Maeve Wallace, Ph.D., Mary Amelia Center for Women's Health Equity Research	Using Cardiovascular Disease as a Framework for Thinking About Chronic Diseases in Women Judith Regensteiner, Ph.D., University of Colorado Anschutz Medical Campus	NCI Clinical Trials in Gynecologic Cancer: A Changing Landscape Robert Mannel, M.D., The University of Oklahoma College of Medicine
Root Causes of Maternal Health Outcomes and Research Justice Joia Crear-Perry, M.D., National Birth Equity Collaborative	Integrating Biopsychosocial Determinants of Health to Develop and Implement Culturally Sensitive Care for Women Cheryl Giscombé, Ph.D., RN, The University of North Carolina at Chapel Hill	The Urgent Need for Crosscutting Anti-Racist Approaches to Cancer Disparities Research Kemi Doll, M.D., University of Washington
Opportunities for Research to Reduce Disparities in Maternal Mortality and Morbidity Stacie Geller, Ph.D., University of Illinois College of Medicine	Beyond Sex as a Biological Variable: Addressing Chronic Debilitating Conditions Among All Women Melissa Simon, M.D., M.P.H., Northwestern University Feinberg School of Medicine	Clinical Trials in Cervical Cancer: Can They Be All That We Want Them to Be? Charles A. "Trey" Leath, III, M.D., M.S.P.H., The University of Alabama at Birmingham

Innovation Through the Lens of Women's Health Research: A Rising Tide Lifts All Boats | Linda Griffith, Ph.D., Massachusetts Institute of Technology

Key Findings

- Of the topics specified in the RFI, 42 percent (104/247) of comments addressed MMM, 73 percent (182/247) discussed CDCW, and 10 percent (27/247) addressed cervical cancer. Women's health topics not specified in the RFI were raised in 44 percent (109/247) of comments ([Figure B2](#)).
 - Comments focused on CDCW most frequently addressed female-specific conditions (83%), conditions that occur in both sexes and are potentially understudied in women (71%), and conditions that are more common in women or have higher morbidity in women (71%).
- Comments were categorized by sender organization and affiliation, and some comments mentioned multiple topics. Researchers or research groups submitted the largest share of comments (N = 56), followed by members of the public (N = 49), patients (N = 40), awareness or advocacy groups (N = 36), and health care providers (N = 34). Comments also were received from government agencies, pharmaceutical and technology companies, and professional societies.
- The ten most frequently identified keywords from the manual coding were as follows: (1) MMM, (2) racial disparities, (3) access to care, (4) provider training, (5) mental health, (6) Black or African American women, (7) screening, (8) quality of care, (9) time to diagnosis, and (10) social determinants of health.

Methodology for properly defining women's health research ... will enable NIH to accurately categorize its research and stakeholders to work more effectively with ORWH and NIH Institutes and Centers to fill existing research gaps and advance women's health.

—Women First Research Coalition

Methods

ORWH analyzed the RFI data on the three congressionally specified topics. Comments submitted in response to the RFI were delivered to ORWH via electronic mail (N = 260). After excluding 13 duplicates, 247 comments ultimately were included in the analysis.

To build a codebook, the full set of comments were open-coded, and a master list of 150 keywords was created. Each comment then was independently coded by two reviewers using the keyword master list, commenter type, and RFI topic. Comments addressing CDCW were categorized further using the conceptual framework developed by NIH as female specific; more common in women or morbidity is greater for women; occur in both sexes, potentially understudied in women; or high morbidity for women. All comments also were reviewed and coded for clinically relevant elements: screening, prevention, treatment, basic research, implementation, and disparities. The coding team consolidated individual reviews; when discrepancies existed between two reviewers' coding, the team discussed and determined final codes by consensus. ORWH staff described themes and trends in the public comments and synthesized the recommendations provided by commenters.

An additional quantitative analysis of comment text was performed using [ProSuite](#), a content analysis software ([Figure B2](#)). ProSuite counted the number of times words and phrases appeared in the correspondence. The word frequencies then were sorted to highlight terms and phrases used most often, excluding common English words (e.g., "and," "but," "or"). This analysis was used to verify the choice of keywords.

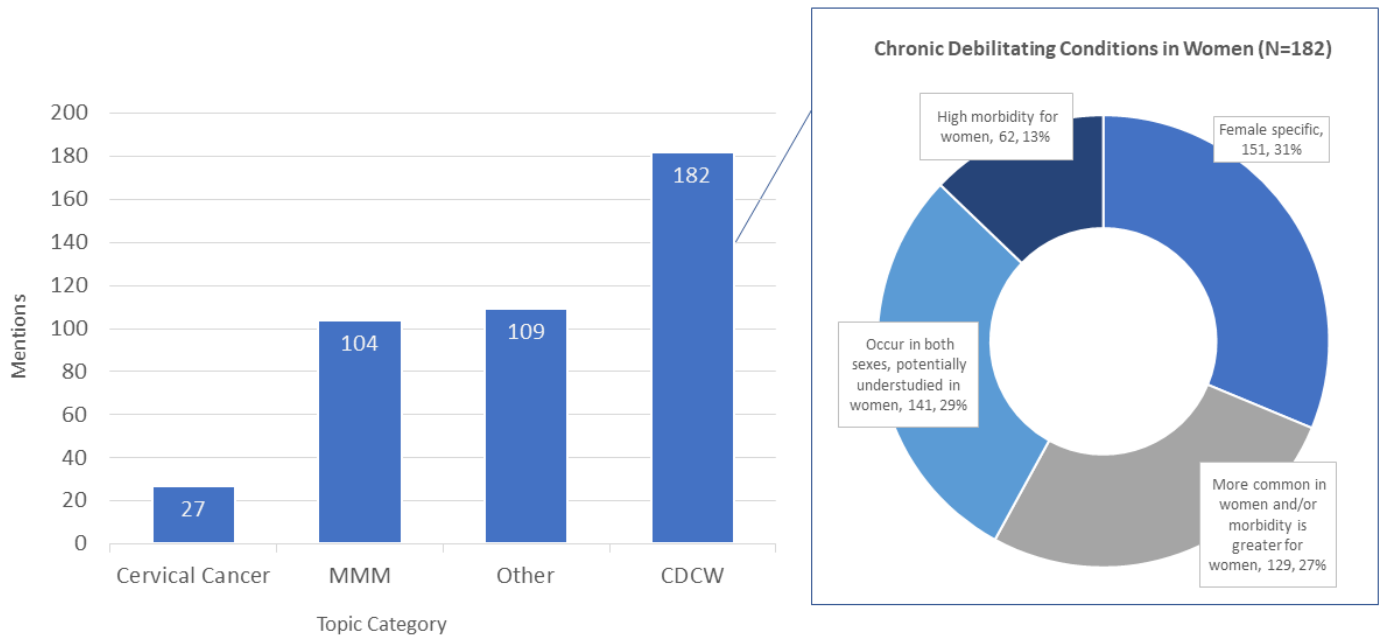


Figure B2. Request for Information topics and other emergent themes

Definitions: CDCW = chronic debilitating conditions in women; MMM = maternal morbidity and mortality

Maternal Morbidity and Mortality

Forty-two percent (104/247) of comments addressed MMM. These comments identified gaps in the care of pregnant women and birthing people; called for new research and programs to provide solutions to the MMM crisis; and articulated the importance of holistic, community-based care to help fix entrenched racial disparities in MMM. Specifically, commenters recommended the need for new research to address the higher rates of MMM in women who are Black, Indigenous, People of Color (BIPOC) and in pregnant people.

I will never forget learning about Sha-Asia and her family and what has happened to so many other Black women and other women of color. As a Black woman ... and a 26-year-old who dreams of having children someday, I fear this may also be my reality. This reality must change.

—Commenter

MMM-related comments called for centering health equity, referencing increasing rates of MMM and corresponding poor health outcomes in women of color. Indeed, improving the health of pregnant people “requires a comprehensive consideration of the many factors that influence women’s health, such as sex and gender, race and ethnicity, and a host of other internal and external factors,” as outlined in the multidimensional framework set forth in [Advancing Science for the Health of Women: 2019–2023 Trans-NIH Strategic Plan for Women’s Health Research](#).

Comments calling for increased attention to prenatal, postnatal, and infant care for pregnant Black women and birthing people outlined numerous avenues for future research and align clearly with ORWH programming, such as those focused on [understudied, underreported and underrepresented populations](#) of women. For example, a joint

comment from the Society for Birth Defects Research and Prevention and the Organization of Teratology Information Specialists called for research on “Trans/inter-generational trauma, adverse experiences leading to fetal/maternal programming of HPA [hypothalamic-pituitary axis], stress, [and] chronic conditions later in life,” consistent with a life-course perspective.

Comments related to pregnancy and labor focused on labor induction, managing labor, and addressing complications. Eight comments cited the benefits of doulas during pregnancy, birth, and postpartum. As noted by AccessMatters, “Doulas have been found to have a protective effect on pregnant, birthing, and parenting people during pregnancy and childbirth, reducing the potential outcomes of infant mortality and the deaths of birthing people.” Doulas and community-based birth support were mentioned in the context of the health of women of color, and commenters specifically identified the importance of doula care for Black women, who are at [higher risk for pregnancy-related complications and death](#) than White women. Researchers at the University of Minnesota School of Public Health urged for research on interventions aimed at increasing cultural congruence in birth teams and “access to midwives, doulas, and freestanding birthing centers, all of which have demonstrated superior care and outcomes for Black birthing people.”

Another commenter, a board-certified obstetrician gynecologist working as an inpatient obstetric hospitalist at a tertiary care academic, urban hospital in the Midwest, raised the importance of racial and cultural congruence between patients and providers, noting, “Many of my patients lack access to care or engagement with care due to a history of racism, but **seeing a health provider that looks like them could make the difference.**”

My patient population is a majority Black and deeply [affected] by racial inequities in health care and environmental health from a system of institutionalized racism. I see how this negatively [a]ffects their obstetric care every day ... [I] would love to see funding that addresses the lack of health providers that are culturally congruent with the population. Many of my patients lack access to care or engagement with care due to a history of racism, but seeing a health provider that looks like them could make the difference. I would love NIH funding to research doulas and pregnancy health navigators who are from the same communities as our patients and see the differences in obstetric care and outcomes. Many other complex conditions, like cancer, have health navigators that help someone through a complex health system to make sure appointments, diagnostics, and treatments aren't missed.

—Health Care Provider

Further describing the need for increased and improved provider training around MMM, AccessMatters noted, “Many medical conditions disproportionately impact Black pregnant and birthing people. Addressing implicit bias in medicine—through trainings and by centering the voices of BIPOC organizations, professionals, and patients—is a critical component of improving health outcomes for BIPOC people and eliminating racial disparities in pregnancy-related outcomes. AccessMatters encourages intentional action ‘to support implicit bias training for all health care providers and support staff.’”

Contraception access was cited as another element of health equity, allowing women to manage and space pregnancies and improve birth outcomes. Commenters described the value of readily available contraception, in multiple forms, so that women have access to what is easiest and best meets their individual needs and preferences.

Finally, safe and legal abortion was highlighted as an important option for pregnant people in the United States, for both medical and elective motivations. As noted in a comment from the Society for Academic Emergency Medicine, the United States saw a reduction in deaths from abortion following *Roe v. Wade*, and in the absence of safe and legal abortion, “pregnant women may resort to unsafe means to end unwanted pregnancy.”

Chronic Debilitating Conditions in Women

Nearly three-quarters of commenters (182/247, 73%) discussed CDCW. These comments spanned the categories defined within the CDCW framework of chronic diseases in women as relevant to women: (1) female specific, (2) more common in women and/or morbidity is greater for women, (3) potentially understudied in women, and (4) high morbidity for women.

More research is needed to inform clinical practice and improve diagnosis and treatment. Both my sisters and I were misdiagnosed for YEARS when we were suffering from endometriosis (my two sisters) and recurrent ovarian cysts (me). We were told the pain was “normal,” told it was kidney stones, told it was IBS, etc., etc. My sister was only diagnosed once she experienced ovarian torsion and underwent surgery and almost lost her right ovary. In all three of our cases, providers told us there just isn’t enough evidence to understand the conditions and lead to more accurate and timely diagnoses and treatment.

—Patient Testimony

Female Specific

More than 150 comments addressed female-specific chronic debilitating conditions (**Table B1**). Endometriosis, uterine fibroids, menstruation, menopause, diethylstilbestrol (DES) exposure, fertility, and pelvic floor issues were the most cited female-specific conditions in the public comments. An independent researcher submitted a comment describing [their recent work](#) to characterize sex disparities in NIH spending. Per this investigator, “There are roughly three times as many diseases whose funding pattern favors males (the disease affects mainly women and is underfunded or affects mainly men and is overfunded) as there are diseases whose funding pattern favors females; funding is measured relative to disease burden. The degree of funding bias for diseases that favor males is roughly twice as great as that for diseases that favor females. In other words, not only are there roughly three times as many diseases whose funding is biased toward males, but the degree of funding bias for those diseases is roughly twice as great.”

Similarly, the Androgen Excess and Polycystic Ovary Syndrome (PCOS) Society called for increased funding, commenting, “The underpinnings of the pathology of PCOS, its genetic and epigenetic origins, as well as the appropriate treatments require additional focus and investigation, as **there is a significant funding gap in research fostering our understanding of the etiology of the condition and in the generation of new effective therapies.**”

Table B1. Number of Mentions for Female-Specific Conditions

Condition	Number of Mentions
Endometriosis	22
Fibroids	17
Menstruation	15
Menopause	15
Diethylstilbestrol (DES)	13
Fertility	12
Pelvic Floor	10
Polycystic Ovary Syndrome (PCOS)	9
Postpartum Depression	8
Hysterectomy	7
Pregnancy Loss	5
Vaginal Health	4
Abortion Research	3
Cancer: Endometrial	3
Vulvodynia	3
Premenstrual Syndrome	1
Vaginal Bleeding	1
Vulvar Dysplasia	1

I am a DES daughter. My mother took the drug diethylstilbestrol when she was pregnant with me in 1960/1961. I have had long-lasting effects, including infertility, premature births, extremely painful menstrual periods, and the fear of what else will happen as I age.

—Patient Testimony

More Common in Women and/or Morbidity Is Greater for Women

Forty-six commenters raised mental health as a key priority for women's health and women's health research, making it the most common condition within this sub-category (**Table B2**). In this category overall, 18 specific conditions were noted. After mental health, the most frequently raised conditions were autoimmune disease; human papilloma virus (HPV); trauma and post-traumatic stress disorder (PTSD); breast cancer; and sexually transmitted infections (STIs), including herpes simplex virus.

Commenters described the co-occurrence of mental health conditions, substance use disorders, and violence and discussed the intersections of mental health and pregnancy, MMM, and the postpartum period. Untreated mental health conditions, as multiple commenters noted, are associated with MMM and must not be viewed as separate concerns. Commenters also noted significant barriers that many women face when seeking to access care for mental health and substance use, including that mental health and substance use programs are often expensive, underfunded, or not covered by insurance.

Table B2. Number of Mentions for More Common in Women and/or Morbidity Is Greater for Women

Condition	Number of Mentions
Mental Health	46
Autoimmune Disease	26
Human Papilloma Virus (HPV)	13
Trauma/Post-traumatic Stress Disorder	13
Cancer: Breast	11
Sexually Transmitted Infections (STIs)	8
Lupus	8
Osteoporosis	7
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome	7
Fibromyalgia	6
Sjögren's Syndrome	6
Rheumatoid Arthritis	5
Migraines	5
Herpes	4
Intimate Partner Violence	4
Thyroid Disease	2
Eating Disorder	1
Temporomandibular Muscle/Joint Disorder (TMJ)	1

I am the mother and part-time caretaker of a recently diagnosed daughter with ME/CFS who has endured decades-long suffering in search of compassionate and evidence-based treatment for this horribly disabling and stigmatized disease."

—Patient Testimony

Occur in Both Sexes, Potentially Understudied in Women

The RFI comments addressed 16 conditions that occur in both sexes but are potentially understudied in women. The most common condition was pain (including chronic pain and pain treatments), followed by environmental exposures (including climate change), COVID-19, infections, osteoarthritis, and Alzheimer's disease. Comments described gaps in screening/diagnosis, prevention, and treatment for these conditions. For example, the Treatment

Action Group advocated additional research on women and HIV, noting the scarcity of data on pre-exposure prophylaxis (PrEP) in cisgender women: “The development of biomedical HIV prevention interventions has lagged for women compared to men, with the most egregious example being [a pharmaceutical company’s] drug for [PrEP] ... which was only approved for use in men because the company failed to conduct a study in women.”

Commenters also noted racial, geographic, and socioeconomic disparities in many conditions within this category, including chronic pain. In making their recommendations to NIH, the nonprofit National Pain Advocacy Center articulated, “**Women are not a monolithic population**, and many conditions that disparately affect women are more dominant in women of certain races: rheumatoid arthritis, for example, unequally affects women of color (especially Black and Latina women); fibroids disproportionately affect Black women; Asian women have a higher incidence of endometriosis; and Native American women are at higher risk for migraine.”

While there are numerous gaps in research related to sex and gender with regards to pain, we write to request that NIH prioritize research in three specific areas: disparities and inequities in the diagnosis and treatment of painful conditions in women across the age spectrum; sex-based differences in the role of immune cells in pain signaling, progression, and chronicity (in humans); and persistent pain examined from a systems biology perspective that concurrently considers neurologic, immune, and endocrine influences.

—National Pain Advocacy Center

High Morbidity for Women

Four conditions with high morbidity for women were noted specifically: heart disease, substance use, hypertension, and obesity. Public comments about conditions with high morbidity for women urged the advancement of holistic, multidimensional approaches and engaging diverse and underrepresented populations of women in research. For example, the advocacy group WomenHeart: The National Coalition for Women with Heart Disease encouraged ORWH to “incorporate women’s lived experiences and stories into your work, whether that be through **more qualitative research studies and other unique study designs, as well as through how you communicate the results and impact of the research you lead.**”

Narratives are compelling, and stories can often provide a more complete picture of a woman’s health than a single data point. The Office of Research on Women’s Health is uniquely positioned to consider research that is not limited to one organ system or disease state, but rather considers myriad factors that impact health and well-being and multiple diagnoses. As a patient-centered advocacy organization, WomenHeart encourages ORWH to incorporate women’s lived experiences and stories into your work, whether that be through more qualitative research studies and other unique study designs, as well as through how you communicate the results and impact of the research you lead.

—WomenHeart

Multimorbidity

Underscoring the utility of multidimensional, life course approaches to understanding CDCW, many commenters described their experiences living with multimorbidities and the frustrations and challenges with receiving appropriate diagnoses, treatments, and care. For example, one patient testimony chronicles decades of inadequate care, writing “My rheumatologist in the 1990s told me I had Sjögren’s. He told me that I would have dry mouth, dry eyes, and would probably want to use estrogen cream. I have had Parkinson’s for 3 years. My neurologist and arthritis doctor tell me that most of my aches and pains are from the progression of Sjögren’s. All my Parkinson’s contacts tell me there is very little research being done on that disease.”

My rheumatologist in the 1990s told me I had Sjögren’s. He told me that I would have dry mouth, dry eyes, and would probably want to use estrogen cream. I have had Parkinson’s for 3 years. My neurologist and arthritis doctor tell me that most of my aches and pains are from the progression of Sjögren’s. All my Parkinson’s contacts tell me there is very little research being done on that disease. I hope more can be done about stopping the progression and find a cure.

—Patient Testimony

Members of the biomedical research community and advocacy groups similarly called for increased focus on co- and multimorbidity in women across condition category. For example, the American Urogynecologic Society calls for increased NIH attention to the “impact and interactions of comorbidities and biomechanical forces on pelvic floor tissues and the lower urinary tract,” and a global health research group identified environmental exposures and co-morbidities as key considerations in maternal morbidity.

Cervical Cancer

Twenty-seven comments mentioned cervical cancer, focusing on survival rate, treatment, screening, support, and HPV. All 27 mentioned the importance of making improvements to cervical cancer prevention, diagnosis, or treatment: 24 specifically mentioned treatment, 14 emphasized screening, 11 mentioned vaccinations, and 13 referenced access to care.

BD recommends advancing self-sampling and reporting extended genotyping as policies that can begin to counter the stagnant cervical cancer survival rates ... We recommend that NIH and CDC partner to advance a cervical cancer registry that will enable health care providers, researchers, and policymakers to monitor the prevalence of HPV genotypes in order to close gaps in care.

—Becton, Dickinson and Company (BD)

In reference to the survival rate of cervical cancer, concerns were raised by the Association of Clinical Oncology and its affiliated organization, the American Society of Clinical Oncology (collectively known as ASCO) regarding persistent racial disparities in cervical cancer survival rates: “Although Black women have seen a decrease in cervical cancer incidence and mortality overall, they continue to have a higher incidence than non-Hispanic Whites. Hispanic women also continue to have a higher incidence rate than [non-Hispanic] Whites. The causes of these disparities

remain elusive but are likely driven by multiple factors. An important component of efforts [to increase cervical cancer screening and HPV vaccination] is **increased attention to social determinants of health and their impact on cancer incidence and mortality, cervical cancer screening, and HPV vaccination practices in historically excluded and marginalized populations.**”

Additional Topics

Table B3. Count of Keywords

Keyword	Count
Gender Inequity	6
Sex Differences	5
Menstruation	5
Sex and Gender Disparities	5
Sex as a Biological Variable	4
Patient Engagement	3
Diversity in Research	3
Provider Training	3

Forty-four percent of comments (109/247) raised issues of relevance to the health of women other than the three topics specifically named in the RFI. Within these comments, 48 keywords were identified. The keywords appearing most frequently in this subset of comments were gender inequity, sex differences, menstruation, and sex and gender disparities (**Table B3**).

Patient testimonies submitted in response to the RFI added nuances and depths to the comment portfolio (**Figure B3**)—many of the most common topics in patient testimonies were not well represented in comments from other groups, suggesting an opportunity for additional engagement with the public to set research priorities for women’s health. Commenters

described frustrations at care systems for having ignored or dismissed their symptoms, and many expressed strong desires to contribute to setting research priorities, given that their suffering had gone unrecognized. One commenter, a Ph.D. student and endometriosis patient, shared her experience as a patient and researcher, writing, “I am an epidemiology PhD student at [a midwestern university] researching endometriosis. I am also an endometriosis patient. I chose this research because I was met with constant roadblocks, poor information, and stonewalling while trying to get my own diagnosis which took 15 years of consistent requests for help, at least 20 doctors, and invasive testing before finally getting surgery and a diagnosis. My story is not unusual. **I felt unheard and like this topic has received little attention from researchers. I want to change that, and I hope the NIH will also recognize that this disease affects so many people who go into clinician offices everyday just to be told that the symptoms are all in our head if birth control pills don’t work.**”

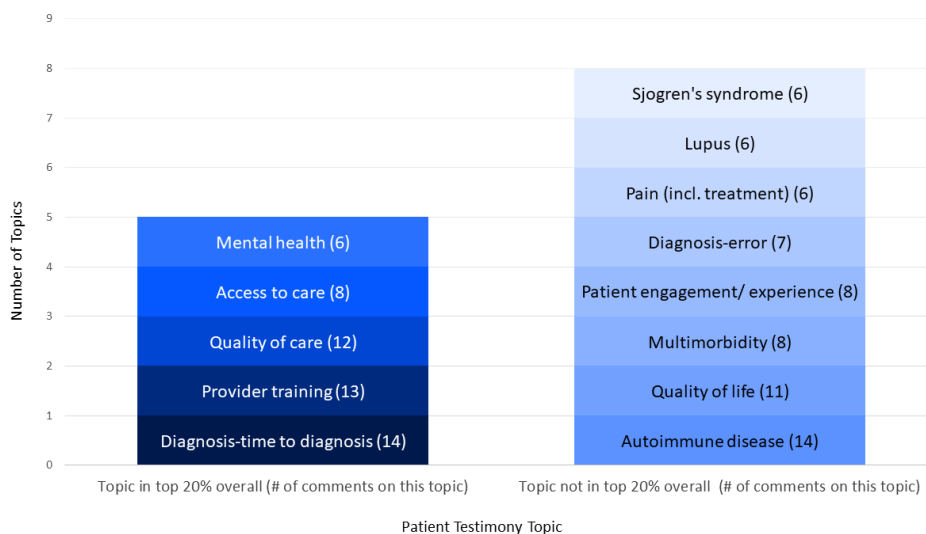


Figure B3. Patient testimony added unique perspective

I am an epidemiology Ph.D. student at [a Midwestern university] researching endometriosis. I am also an endometriosis patient. I chose this research because I was met with constant roadblocks, poor information, and stonewalling while trying to get my own diagnosis, which took 15 years of consistent requests for help, at least 20 doctors, and invasive testing before finally getting surgery and a diagnosis. My story is not unusual. I felt unheard and like this topic has received little attention from researchers. I want to change that, and I hope the NIH will also recognize that this disease affects so many people who go into clinician offices everyday just to be told that the symptoms are all in our head if birth control pills don't work.

—Ph.D. Student

Gender Inequity

Commenters urged structural changes to correct gender inequity in NIH funding patterns (e.g., the underfunding of research in female-specific conditions) and the NIH women's health research agenda (e.g., increased funding for gender-based conditions, such as intimate partner violence). Comments from researchers emphasized that a longstanding lack of funding for research on gender's influences on health has inhibited scientific progress and upheld gendered health disparities. A multinational research team noted, "The mechanisms by which gender influences health are, to date, minimally understood. Indeed, despite the clear influence of social factors on health—as evidenced by cross-national (and intra-national) disparities—there has not been systematic investment on the part of the NIH and ORWH into examining the effects of gender across biomedical research topics."

In failing to properly address gender as a fundamental health influence, NIH is missing ripe, low-hanging fruit for remedying women's health disparities.

—Researchers at the Chicago Medical School, Rosalind Franklin University, and
l'Université de Lausanne

The landmark 2016 [Sex as a Biological Variable \(SABV\)](#) policy was noted as an important step in understanding sex differences; commenters recommended that NIH develop additional gender-related policies modeled after SABV. For example, researchers at the Chicago Medical School, Rosalind Franklin University, and l'Université de Lausanne recommended that NIH "develop a gender-focused NIH-wide policy equivalent to SABV (i.e., Gender as a Sociocultural Variable, GASV) [as part of an] intersectional approach for addressing gendered health disparities."

Including sex as a biological variable is an important step in redressing this funding gap but does not address the deficit of funded research specific to the unique biological, psychosocial, and social-political health experiences of women and girls, who constitute half the U.S. population. We urge NIH to radically expand funding on women's health.

—Pacific Institute for Research and Evaluation

Increased investment in women's health research was cited repeatedly as essential to improving the health of all women. For example, Women's Health Access Matters (WHAM) recommended that NIH "prioritize funding in areas with disproportionate sex- and gender-based disparities. Targeted funding opportunities are critical to minimizing gaps in research practice, translational advances, and patient care by providing researchers with the resources necessary to address research questions in areas that have been historically understudied or deprioritized for a myriad of reasons."

As noted in one patient's testimony, the "continual use of White men at certain ages for research has show[n] a total lack of caring for women and people of color whose needs according to age is so different."

Provider Training

One public commenter raised this point: "[M]ale doctors and female patients may not communicate as effectively as non-male doctors (female and transgender doctors) and female patients. What gets communicated between the doctor–patient dyad might affect the care levels administered and received, respectively. For instance, male doctors may often pathologize women's symptoms as psychological in nature when they are seeking physiological care for heart attack risk or stroke risk factors and assessments. The female–female doctor–patient dyad might work better under such conditions because (a) female doctors may understand the needs of female patients better, and (b) male doctors may not have been trained to deal with their potential implicit or explicit biases against female patients."

Several comments centered around the need for enhanced awareness of the roles of sex and gender on health and disease by students, clinicians, and investigators. A family member who submitted a comment had this to say about care provision regarding lupus: "Since there are many doctors who don't see people with lupus regularly, **clinical practice guidelines that explain the heterogeneity of lupus and provide guidance for treatment that focus[es] on the individual needs of each patient**, might help others avoid what my daughter had to endure."

Advocacy groups similarly argued for expanded and enhanced provider training. WHAM suggested that "**dedicated resources and training mechanisms should be developed to engage the next generation of leaders in science and medicine who are cognizant of both the biological and social determinants of health imparted by sex and gender**. By cultivating a robust workforce which can address sex- and gender-based research questions, we will be able to minimize gaps in research practice and health care and generate new discoveries and real-world innovation."

The NIH should identify and provide new opportunities for trainees and young investigators to engage in research related to sex- and gender-specific conditions. In addition to providing targeted funded resources for women's health research, we must also consider the human capital required to address sex- and gender-based health disparities. In order to create a sustainable pipeline for women's health research, dedicated resources and training mechanisms should be developed to engage the next generation of leaders in science and medicine who are cognizant of both the biological and social determinants of health imparted by sex and gender. By cultivating a robust workforce which can address sex- and gender-based research questions, we will be able to minimize gaps in research practice and health care and generate new discoveries and real-world innovation.

—Women's Health Access Matters

Intersectionality

Commenters also raised the concept of intersectionality, or how socially determined categories—such as race and gender—overlap and interact to create disparate outcomes for individuals and communities. Structural racism, implicit bias, provider bias, and racial disparities were mentioned in RFI comments as areas of concern for women’s health, as well. Specifically, the needs of Black women were referenced in 24 comments and the needs of women of color in 16 comments. Racism was explicitly referenced in 18 comments as a factor preventing women from accessing care, being screened for certain diseases, and having their health concerns taken into consideration.

RFI comments also advocated for improvements to care settings, specifically with respect to freedom from bias for members of the LGBTQ+ community, and for improved data collection to better serve these populations. As noted in a comment from signatories affiliated with The Williams Institute at the University of California, Los Angeles, “sampling and measurement in maternal health and mortality research that includes sexual and gender minority women” is an unmet need related to data collection.

Location of U.S. Commenters

RFI responses were received from 36 U.S. states. Comments also were received from Sweden and Switzerland. Of the U.S. comments, 22 came from California, followed by 16 from New York, and 15 from Maryland. **Figure B4** presents location information of commenters who provided their city, state, and ZIP code. The location of 111 comments was not disclosed and therefore are not accounted for in **Figure B4**.

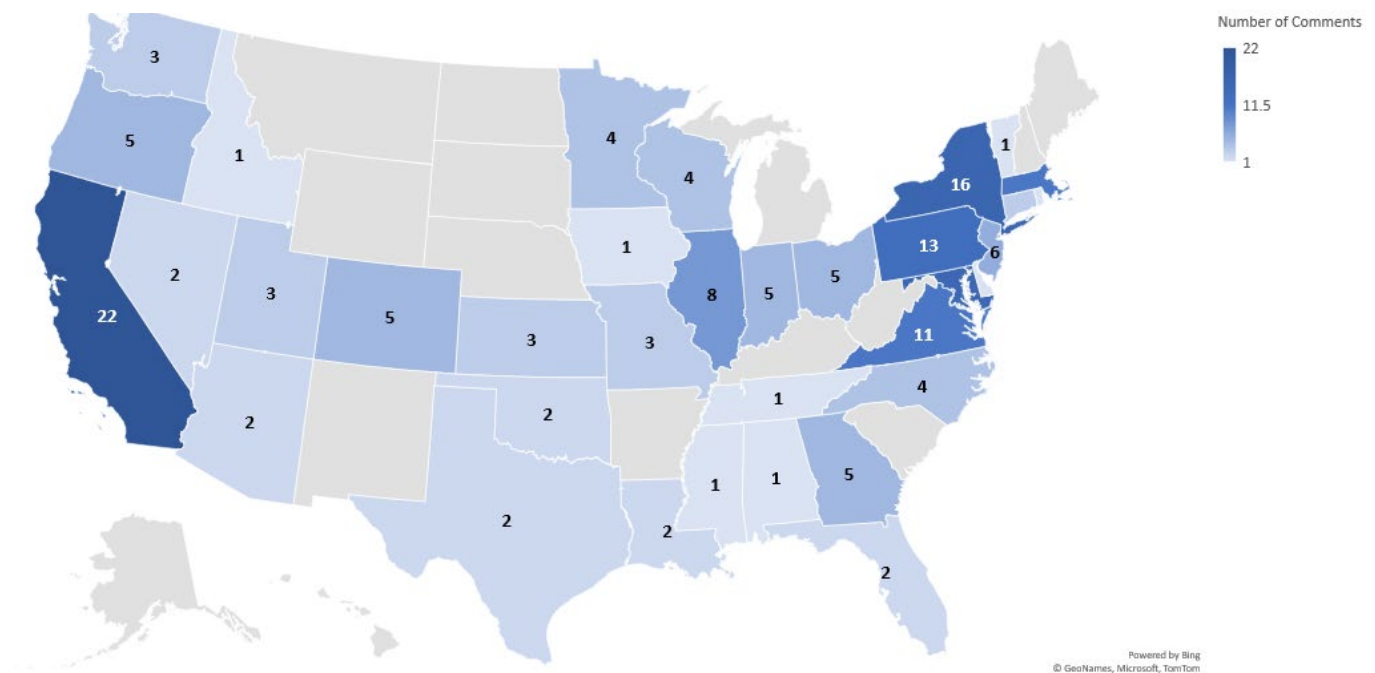


Figure B4. Map of responses throughout the United States

Commenter Categories

Table B4 presents the number of individual commenters in each category:

Table B4. Number of comments per commenter category

Commenter Category	Number of Comments
Researcher/Research Group	56
General Public	49
Patient Testimony	40
Awareness/Advocacy Group	36
Health Care Provider	34
Professional Society	13
Pharmaceutical/Technology Company	10
Government Agency (State, Local, or Federal)	8
TOTAL	247

Conclusion

Comments returned to ORWH in response to an RFI ([86 FR 35099](#)) soliciting comments in advance of the Women's Health Conference demonstrate a broad range of concerns related to the health of women, including MMM, CDCW, and cervical cancer. A wide array of commenters included patients, advocacy groups, and academic and professional organizations, originating from geographically diverse locations. These comments reflect a strong desire from the public for prioritization of research on the health of women.

Keywords

<p> Abortion research Access to care Aging Animal testing Attention deficit hyperactivity disorder Autoimmune disease Birth process Bleeding Breastfeeding Cancer: breast Cancer: cervical Cancer: endometrial Cancer: other Cancer: ovarian Cardiac care Care delivery site Childhood screening Clinical trials Community-based participatory research (CBPR) Comorbidity Contraception COVID-19 Data collection Dementia/Alzheimer's disease Dental care Diethylstilbestrol (DES) Diagnosis: error Diagnosis: time to diagnosis Dissemination Distrust Diversity in research Doula Drug development Eating disorders Emergency care Employment impacts (of disease) Endometriosis Environmental exposures (including climate change) Epigenetics Eye health Fetal alcohol spectrum disorder Fertility Fibroids Fibromyalgia Fracture prevention Gender differences in quality of care Gender inequity Gender roles Genetic disorders Genome Health care costs </p>	<p> Health care simulation Heart disease Herpes HIV/AIDS Hormones Human papilloma virus (HPV) Hypertension Hysterectomy Implementation Implicit bias Infection Intersectionality Invasive treatment Intimate partner violence (IPV) Institutional review board (IRB) Lactation Life-course perspective Lipedema Long-acting reversible contraceptives Lung health Lupus Lymphedema Mammogram Mastectomy Maternal morbidity and mortality (MMM) Myalgic encephalomyelitis/chronic fatigue syndrome Medicaid expansion Medication-assisted treatment Medication use Menopause Menstruation Mental health Migraines Multidisciplinary approach Multimorbidity Musculoskeletal disorders Nicotine use NIH funding structure Nontraditional medicine, including diagnostics Obesity Opioid prescribing Osteoarthritis Osteoporosis Other condition Parenting Patient engagement/experience Patient-focused education Patient–physician concordance Pelvic floor Polycystic ovary syndrome (PCOS) </p>	<p> Postpartum depression Postpartum hemorrhage Precision medicine Pregnancy Pregnancy loss Premenstrual syndrome (PMS) Preterm birth Provider health Provider training Quality of care Quality of life Racial disparities Radiation Rheumatoid arthritis Rural medicine Screening Sepsis Sex and gender disparities Sex as a biological variable (SABV) Sex differences Sexual health and sex education Sexually transmitted infections (STIs) Sickle cell Sjögren's syndrome Social determinants of health Standardized treatment guidelines Stigma Structural racism Substance use Telehealth Thyroid disease Temporomandibular muscle/joint disorder (TMJD) Tocolytics Trauma-informed care Trauma/post-traumatic stress disorder (PTSD) Treatment of pain Trial design Vaccines Vaginal bleeding Vaginal health Vulvar dysplasia Vulvodynia Women: American Indian or Indigenous Women: Black or African American Women: Hispanic or Latinx Women: immigrant Women: incarcerated Women: sexual minority Women: transgender </p>
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List of Commenter Organizations and Institutions

This list is limited to organizational/institutional affiliations for comments submitted from awareness/advocacy groups, government agencies, health care providers, pharmaceutical/technology companies, professional societies, and researchers/research groups.

2020 Mom	The Fibroid Foundation
AccendoWave	Focused Ultrasound Foundation
AccessMatters	GHD EMPHNET
Advanced Tactile Imaging, Inc.	Harvard Medical School
Agency for Healthcare Research and Quality	HealthyWomen
Albert Einstein College of Medicine	Herpes Cure Advocacy
American College of Obstetricians and Gynecologists	Indiana Hemophilia and Thrombosis Center, Inc.
American Medical Women's Association	Indiana University School of Nursing
American Society for Bone and Mineral Research	Infectious Diseases Society of Obstetrics & Gynecology
American Society for Reproductive Medicine	Ingram Screening, LLC
American Society of Clinical Oncology	IPQ Analytics, LLC
American Urogynecologic Society	Johns Hopkins University
Androgen Excess and PCOS Society	Karolinska Institutet
Aspira Women's Health	Kean University
Banner University Women's Institute	Looms for Lupus
Becton, Dickinson and Company (BD)	The Lundquist Institute
Binghamton University	Lupus Research Alliance
Birth Justice Defenders	March of Dimes
Boston University School of Public Health	Maternal Mental Health Leadership Alliance
Breast Cancer Prevention Partners	Mayo Clinic Alix College of Medicine
Brigham and Women's Hospital	<i>Med</i> (Journal)
Brodar Chiropractic Office	Medical College of Wisconsin
Butterfly Walkers, Inc. Alliance of Hope for Lupus	MedShadow Foundation
Case Western Reserve University	Memorial Sloan Kettering Cancer Center
Cefaly	Metrodora Institute
Center for Antiracism Research for Health Equity, University of Minnesota	Milken Institute School of Public Health, George Washington University
Center for Endometriosis Care	Mineta Transportation Institute at San Jose State University
Center for Evidence and Practice Improvement, Agency for Healthcare Research and Quality	National Black Justice Coalition
Cerus Corporation	National Hemophilia Foundation
Chamberlain University	National Institute of Environmental Health Sciences, NIH
Chicago Medical School	National Pain Advocacy Center
Coalition to Expand Contraceptive Access	Naval Medical Center San Diego
Columbia University	Nurse-Family Partnership and Child First
Contraceptive Development Program, <i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development, NIH	NYC H+H Simulation Center
David Geffen School of Medicine at University of California, Los Angeles	Office of Disease Prevention, NIH
DES Action	The Ohio State University
Emory University	Oregon Health & Science University
Endocrine Society	Organization for the Study of Sex Differences
Endometriosis Association	Organization of Teratology Information Specialists
Environmental Health Center of Martha's Vineyard	Osteoarthritis Action Alliance
FHI 360	Pacific Institute for Research and Evaluation
	Pediatric Endocrinology Children's Hospital Colorado
	Peggy and Charles Stephenson Cancer Center
	Pfizer Biopharmaceutical Group
	Pitt Public Health

Princeton Perinatal Institute, LLC
 Rainbow Babies and Children's Hospital
 RAND Corporation
 RTI Global Gender Center
 Rutgers Robert Wood Johnson Medical School
 Sage Therapeutics
 The Sickle Cell Reproductive Health Education Directive
 Silent Spring Institute
 Society for Academic Emergency Medicine
 Society for Birth Defects Research and Prevention
 Society for Women's Health Research
 Society of Gynecologic Oncology
 Society of Toxicology
 Solve M.E.
 Stanford University
 TEGA Therapeutics
 Texas Children's Hospital | Baylor College Medicine
 The TMJ Association, Ltd.
 Treatment Action Group
 Tufts University School of Medicine
 Tulane School of Public Health

Turner Syndrome Global Alliance/RareKC
 Two Rivers Midwifery, Oregon Midwifery Council
 U.S. Preventive Services Task Force Program
 University of Delaware
 The University of Iowa
 The University of Kansas
 University of Minnesota Medical School
 The University of Mississippi Medical Center
 University of Nevada, Reno School of Medicine
 The University of Oklahoma Health Sciences Center
 University of Pittsburgh
 The University of Utah
 Virginia Polytechnic Institute and State University
 The Warren Alpert Medical School of Brown University
 Wasatch ObGyn Intermountain Healthcare
 Washington University School of Medicine in St. Louis
 Women First Research Coalition
 WomenHeart: The National Coalition for Women with
 Heart Disease
 Women's Health Access Matters
 Women's Health Innovation Coalition

Appendix C: National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) Advancing NIH Research on the Health of Women: A 2021 Conference October 20, 2021

Opening Session

Introduction and Welcome

Dr. Samia Noursi—Associate Director for Science Policy, Planning, and Analysis at ORWH and Executive Secretary of the Advisory Committee on Research on Women's Health (ACRWH)—formally opened the meeting. She explained that ORWH convened the conference in response to a request in a congressional significant item. The U.S. Congress believes that more focus on research related to obstetrics and gynecology is required to address (1) rising rates of maternal morbidity and mortality (MMM), (2) rising rates of chronic debilitating conditions in women (CDCW), and (3) stagnant cervical cancer survival rates. Congress instructed NIH to convene a consensus conference to evaluate current women's health research priorities. ORWH will work with ACRWH to prepare a conference report identifying priorities in research on the health of women and areas for additional study by December 2021. The October 20 Women's Health Conference (WHC) was held in conjunction with the 55th meeting of the ACRWH, which was held on October 21. The WHC served as a forum for robust discussion on the current and future state of research on the health of women. Dr. Noursi noted that biographical sketches of speakers were available on the [WHC webpage](#).

Dr. Janine A. Clayton, Associate Director for Research on Women's Health at NIH and Director of ORWH, welcomed participants to the meeting. In light of Dr. Francis S. Collins' recent announcement that he is stepping down as NIH Director, Dr. Clayton acknowledged his leadership and commitment to women's health and women's health research. Dr. Collins' leadership allowed NIH to implement policies that ensure that sex is considered in the research it funds, and Dr. Clayton wished him all the best in his future endeavors on behalf of ORWH. Dr. Clayton also expressed gratitude to the members of the Coordinating Committee on Research on Women's Health (CCRWH), ACRWH, and all the working groups that helped plan the WHC. They played an important role in raising important questions and helping to gather foundational information for the conference, which will inform future directions for women's health research. Public comments in response to NIH's request for information also informed planning for the conference.

Since the 1960s, there have been many milestones in the field of women's health, and progress has accelerated. Dr. Clayton reflected that it was 31 years ago when ORWH was formed in response to congressional concern about the lack of inclusion of women in clinical research and the lack of clinical research on the health of women. With the congressional significant item's focus on current research and contemporary gaps in knowledge about the health of women, the WHC serves as another launching point for a robust future centered around women's health. As women's health is critical to our Nation's health, more women should be enrolled in clinical trials and more females included in preclinical research.

Acknowledging all the individuals and organizations that built the field of women's health research, Dr. Clayton remarked on the movement away from a default human model of women being seen as small men, as well as paternalistic and protectionist attitudes. Additionally, there has been progress away from using mostly male animals in preclinical research, which provided a unidimensional picture of physiology and generated knowledge that applied only to males, with a lack of understanding about female biology. To address the situation, NIH and Congress require the inclusion of women and other understudied populations in clinical trials. Currently, the women's health research commitment is a relatively small portion of the overall NIH budget. To address gaps in

knowledge, collaboration among all 27 NIH Institutes and Centers (ICs) to advance research on the health of women is essential.

Dr. Clayton briefly reviewed the broad input through converging paths that informed the planning of the WHC. ORWH obtained input on the three priority areas from experts in women's health, members of the public, and representatives from NIH (ICs) and other Federal agencies. ORWH formed and guided the CCRWH WHC Planning Committee and assembled, guided, and participated in the ACRWH WHC Working Group. The CCRWH WHC Planning Committee and ORWH established four subcommittees, or group clusters, each co-led by a subject matter expert from ORWH and another expert from an IC. The clusters provided updates to the ACRWH Women's Health Consensus Conference Working Group. To inform the planning of the WHC and development of the report, the four cluster groups focused on (1) MMM, (2) cervical cancer (emphasis on survival), (3) CDCW, and (4) data harmonization (among the three priority topic areas). The clusters reviewed the NIH research portfolios in the three focal areas and categorized the most prevalent diseases and conditions into four areas for further study. They summarized recent research trends, the current state of NIH-funded studies, and gaps in the NIH portfolio. Findings from the clusters were shared with CCRWH and ACRWH, which helped shape the conference agenda. This information, as well as discussions from the WHC, will be summarized in the December report to Congress.

ORWH and the NIH-Wide Strategic Plan promote a focus on the health of women across the life course and the biomedical research continuum. Incorporating sex and gender across the research continuum—from basic and preclinical studies to translational research to all phases of clinical trials—advances rigor, discovery, innovation, and equity. The information can contribute to further research, health policy, health care, and interprofessional education. ORWH also encourages the adoption of the multidimensional framework into the consideration of the health of women across the life course. This framework considers women in context and the interaction of external factors that influence their lives (such as policies and social determinants of health) and biological internal factors (such as genetics) that influence health and well-being. An integrated life course perspective—with particular attention to pregnancy as a stress test and menopause as a time of heightened risk and opportunity for intervention—is required to understand the health of women. Bodily systems are all connected, as is seen with the links between hypertension and mental health and the links between heart disease and depression. Multisystem perspectives must be considered, which requires multidisciplinary research and convergent scientific approaches, to advance science for the health of women.

In such an approach, researchers and clinicians consider context of events prior to a condition (e.g., overall health and traumatic experiences) and what may occur afterward (e.g., increased risk for a chronic disease). But there is a need to move beyond the concept of lifespan. Although women live longer than men on average, they often experience more years with chronic disease and disabilities. Therefore, the biomedical research enterprise needs to ensure that the health span matches the lifespan. Dr. Clayton emphasized that ORWH will work with partners representing all disciplines and sectors who share that vision. The WHC is an opportunity to seize this moment to advance the health of women, and ORWH asks the following questions:

- How do we move beyond policy and programs to drive fundamental change?
- What checks and balances need to be built into the research ecosystem?
- How can we incentivize cross-sector innovation to drive discovery?
- Which part are you going to play?

Women's Health Matters: When, Where, and Why

Dr. Chloe Bird, Senior Sociologist at the RAND Corporation, noted that women make up the majority of the U.S. population and nearly half of the workforce. They are responsible for 85 percent of consumer spending, make more than 85 percent of health care decisions, control 60 percent of personal wealth, and are more likely to be caregivers. The health of women matters, not only because of the diseases and conditions that impact only them but because many diseases that affect women and men have different presentations, prevalence, and trajectories in women. Women experience considerable disease burden from conditions such as cardiovascular disease—the No. 1 killer of women—yet they are only a third of clinical trial participants in this area of research. The majority (78%) of the estimated 50 million Americans with autoimmune disease are women. Similarly, women are three-quarters of the patients with Alzheimer's disease. The No. 1 cause of cancer-related death among women is lung cancer, and more women die of lung cancer each year than die of breast, ovarian, and uterine cancers combined. Twice as many women as men suffer from depression in the United States, and this is the leading cause of disability among women.

The [2019–2023 Trans-NIH Strategic Plan for Women's Health Research](#) sets out an ambitious vision for a world where the biomedical research enterprise thoroughly integrates sex and gender influences; every woman receives evidence-based disease prevention and treatment tailored to her own needs, circumstances, and goals; and women in scientific careers reach their full potential. However, the world is a long way off from achieving that vision. Dr. Bird focused on a study that compared the proportion of articles that included both sexes across nine biological science disciplines in 2019 with the results of similar research in 2009. Although the proportion of articles that included both sexes across all nine disciplines increased, in eight of the disciplines there was no change in the proportion that included data analyzed by sex. Moreover, the majority of single-sex studies and studies that did not perform sex-based analysis did not provide a rationale for their lack of focus on both sexes. Those that did provide such a rationale relied on misconceptions surrounding the hormonal variability of females.

Current NIH policies related to the inclusion of women in clinical trials and the consideration of sex as a biological variable (SABV) are making a difference but lack teeth. Dr. Bird emphasized that the inclusion of women in clinical trials is not the same as studying women. The SABV policy—which outlines NIH's expectation “that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies” unless a strong justification for a single-sex study exists—is not a requirement for funded researchers. The SABV policy is not fully implemented or accepted, as some scientists perceive that it is politically, rather than scientifically, motivated.

WHAM (which stands for “Women's Health Access Matters”) commissioned the RAND Corporation to assess the societal impact of increasing investment in research on the health of women in a series of studies, the results of which are described in [the WHAM Report](#). The effects of accelerating sex- and gender-based health research on women, their families, and the economy were assessed via microsimulation of return on investment (ROI) for rheumatoid arthritis, coronary artery disease, and Alzheimer's disease. Doubling NIH funding for research on Alzheimer's disease and related dementias among women pays for itself threefold (with a conservatively estimated annualized ROI of 4%). Doubling the funding for other diseases leads to even higher annualized ROIs—16.4 percent for coronary artery disease and 28.3 percent for rheumatoid arthritis.

Women are the majority, but they are not yet the norm in scientific research. The current evidence base was built disproportionately on studies of men's health. This is particularly important for diseases that have a greater prevalence in women, as the male-skewed evidence base leads to the erroneous categorization of women's presentation as “atypical” or women's symptoms being dismissed by clinicians. The male-skewed evidence base has colored measurement (what is counted), diagnosis, and testing—as they are fitted to a male norm. It can also influence the comparison of disease incidence and prevalence when the focus is on age-adjusted prevalence for diseases that men die from earlier than women (such as cardiovascular disease). Such a focus leads to the

assessment of those diseases as having a higher impact among men. Although earlier onset and death is important, there are other dimensions of disease burden that could be considered.

Achieving evidence-based care for all women will require additional funding to address the knowledge gaps, which have a high cost to society. Challenges include the fact that the lack of an evidence base on women can be a self-fulfilling prophecy, leading to researchers not studying them. Additionally, women's health is not valued sufficiently in grant reviews or by journals. For example, an NIH analysis indicated that research on the health of women is less likely to be funded in general study sections than in special emphasis panels. To achieve evidence that is based on women, the field needs to clarify and distinguish what has been assumed and what has and has not been studied. The research agenda should be informed by an understanding of the extent and consequences of the existing knowledge gaps. Policies are needed that require research to look for and report indications of sex and gender differences. Scoring rubrics for grants should acknowledge that addressing gender gaps in the evidence base is both innovative and scientifically significant. And funding should level the playing field, not just achieve evidence that is "a little better." In conclusion, women's health matters today not because it would be nice or good or equitable but because biomedical science is getting it wrong and it is costing lives and health and the economy.

How Stereotypes Underpin Inequities for Women in Academic Science, Technology, Engineering, Mathematics, and Medicine (STEMM) and Advancements in Women's Health

Dr. Molly Carnes, the Virginia Valian Professor and the Founder and Director of the Center for Women's Health Research at the University of Wisconsin–Madison, explained that our knowledge of gender stereotypes (even if we do not believe them) gives rise to overt and unintentional ("implicit") gender bias. People are aware of common stereotypes about men (e.g., they're strong, decisive, and stubborn) and women (e.g., they're caring, nurturing, and family-oriented), even if they do not believe them. Men's stereotypical characteristics are agentic—that is, they require individual human agency—whereas women's are communal. Similarly, stereotypes about racial groups are well known (even if one does not believe them), and ones about Black and Latino groups can be painful to acknowledge, as they are mostly negative. Cultural stereotypes are responsible for overt discrimination and implicit bias against minoritized groups at the institutional, interpersonal, and internalized levels.

People also hold stereotypes about leaders—who are perceived as being competitive, self-confident, aggressive, ambitious, powerful, and decisive—such that men (agentic) are seen as fitting this role and women (communal) are not. Dr. Carnes reviewed research supporting this hypothesis, and there seems to be a disconnect between what people say they believe about women (e.g., their characteristics do not exclude them from leadership roles) and what the gender stereotypes are. Moreover, there are societal penalties for breaking gender "rules" (i.e., not conforming to stereotypical characteristics). Evidence suggests that transformational leaders have the positive stereotypical qualities of both genders, which can put them in a difficult position. Women are more likely to display this style than men. The lack of fit between stereotypical female characteristics and those of a leader may lead to bias in grant review. This hypothesis was supported by a Canadian study that showed government grants were equally likely to be awarded to women on the basis of the science proposed but less likely than men when the scientist was the basis of the funding. The new NIH R01 (Type 1) award rate is the same for applicants of both genders, but for renewals (Type 2)—when applicants are both scientists and leaders—success rates were consistently lower for women until 2020. Dozens of experimental studies have documented that evaluators rate women and non-White individuals (as deduced by name) lower on performance- and employment-related variables than men and White individuals, even when the work or application is identical. This pattern holds for the evaluation of identically qualified postdoctoral candidates in physics and biology. Male candidates were perceived as being more competent and better to hire than female applicants. White and Asian candidates were perceived as being more competent and better to hire than Black and Latinx applicants. Therefore, objective data can be filtered through stereotypes subconsciously.

Abundant evidence affirms that a lower societal value is placed on women and their roles and work than is placed on those of men. This has been the case for centuries, and such effects are seen today despite progress. For example, a study found that reimbursement for 42 of 50 surgical procedures performed in men (usually by male urologists) was higher than matched procedures performed in women (usually by female gynecologists). Women have been largely excluded from important biomedical studies—such as those on cardiovascular prevention and normal human aging. Women often work at the lower echelons of organizations, and there is a strong correlation between the percentage of women in a medical field and the salaries of those in that field. In medicine, there is a strong relationship between average salary in a specialty and the percentage of women in that specialty. The conflation of gender and status predicts that health conditions unique to or more common in women will be seen as less important. Women in STEMM are more likely to study issues that affect the health of women, but gender bias may impede publication, research funding, willingness to resubmit, and attainment of leadership positions. Gender bias can reduce investment in research to improve the health of women directly and by impeding women's career advancement in STEMM.

There may be a publication bias against research conducted in women, as shown by a study that had the pretext of developing a new journal and testing whether a review could be done from an abstract alone and with blinding to authors' identities. Reviewers were randomly assigned one of three versions of the abstract—conducted in women, men, or “individuals”—and evaluated scientific rigor and the contribution to medical science and then made a recommendation to publish. Research in women was perceived to make greater contributions to science. The rigor of research in women was equal to that of studies in men, but despite that fact, reviewers were almost twice as likely to recommend publishing research when conducted in men. Dr. Carnes emphasized that negative performance expectations for women in STEMM are not borne out by actual performance. For example, patient satisfaction scores in a large HMO were significantly more negative for female and non-White physicians than male and White physicians, even though they had the same objective quality metrics. A study that used natural language processing of nearly 1.2 million dissertations found that those from women and non-White men had less future impact on science despite having more novel ideas. Another study found that women received lower scores than men on research proposals but outperformed men in securing NIH grants and publishing in top journals after receiving the grants.

In conclusion, Dr. Carnes explained that female investigators are more likely to conduct research on women and that some areas of research on diseases in women are underfunded relative to their lethality and compared with diseases in men. Additionally, manuscripts describing research conducted in women are less likely to be recommended for publication. Combined with the bias against women as authors, this may lead to female faculty members having lower research productivity and visibility in the scientific community than their male counterparts. This may be linked to the lower likelihood of female faculty members being promoted to leadership in academic medicine, where they can advance women's health research, education, and clinical care. Ultimately, these factors mean that less research is conducted to improve the health of women.

Individuals at all levels of STEMM must work hard to break their own bias habits, because policy is not sufficient to overcome gender bias. One of the few proven strategies for changing behavior in response to stereotype-based bias is known by multiple terms, including “breaking the bias habit.” Breaking the bias habit takes more than good intentions and is a process of awareness, motivation, self-efficacy, positive outcome expectations, and deliberate practice. A cluster randomized trial of gender bias habit-reducing intervention found that among 92 STEMM units at the University of Wisconsin–Madison, faculty members assigned to intervention showed an increase in awareness, motivation, self-efficacy, positive outcome expectations, and action. Participants also reported that their departments were more inclusive in the university's faculty work–life study, and departments had greater diversity in new faculty hires compared with the control units. A large-scale investigation of this approach was taken in the Bias Reduction in Internal Medicine (BRIM) Initiative, a cluster randomized study of 3-hour bias habit-reducing

workshop in 19 departments of medicine across the country. Divisions were randomly assigned to receive the workshop early (Group 1) or later (Group 2), and the researchers measured self-reported equity-promoting behaviors, perceptions of department climate, and burnout. Preliminary results are promising. Dr. Carnes remarked that this approach may be effective because it engages those responsible for organizational norms, incorporates strategies shown to be effective in fostering sustained intentional behavioral change, relies on voluntary participation, and enables social diffusion by targeting the entire department and division. Individuals can break their own bias by adopting a growth mindset that applies hard work to overcome the influence of stereotypes on judgment and decision-making and by perceiving variability in groups—i.e., acknowledging that a characteristic does not always apply to a member and that others may also have it.

Questions and Answers

In response to a question about how to achieve fundamental change outside of policy, Dr. Bird noted it depends on the definition of “outside of policy.” Inertia impedes progress. A policy mandate should be followed by funding to conduct research on women’s health. A doubling of the overall NIH budget would benefit the health of men and women and science. Research on sex and gender leads to breakthroughs that can improve interventions for the benefit of men’s health, as including women allows investigators to have insights not available if only men are studied. Replying to questions about stereotypes in the context of structural racism that reinforces them and the role of intersectionality, Dr. Carnes remarked that the persistence of stereotypes is really the root cause and gives rise to structural racism and sexism. Most professionals in academic STEM want to be fair but do not realize that passively acquired cognitive habits undermine that goal. Regarding advocacy for gender-diverse individuals, Dr. Carnes noted that people would not perceive them as different or discriminate if society did not have binary gender stereotypes. Dr. Bird commented that the extent to which the United States underinvests in health research is surprising. Investments in research have great ROIs through effects on health and health care utilization. Policies and additional funding should help fill gaps in research on women’s health, the fill the workforce shortage, and enhance women-related patents and interventions.

Congressional Significant Item Request Focal Area Presentations

Please note that participants who discussed maternal health referred to “women” to describe pregnant individuals but recognized that people of various gender identities (including some transgender males, nonbinary individuals whose sex is female, and cisgender females) can give birth and receive maternity care.

The U.S. Maternal Health Care Crisis

Dr. Elizabeth Howell, Chair of the Department of Obstetrics and Gynecology at the University of Pennsylvania’s Perelman School of Medicine, noted that the U.S. maternal health crisis has gotten media attention. The majority of maternal deaths are preventable, and there are significant racial disparities in maternal mortality. Hospitals and the health care system are failing women. Dr. Howell reviewed the Centers for Disease Control and Prevention (CDC) definition of maternal mortality: “the death of a woman while pregnant or within 42 days of termination of pregnancy,” excluding deaths from accidental or incidental causes. CDC also uses the term “pregnancy-related death,” which is the death of a woman while pregnant or within one year of the end of a pregnancy from any cause related to or aggravated by the pregnancy or its management, but not from an accidental or incidental cause. This definition is used to calculate the pregnancy-related mortality ratio, an estimate of the number of pregnancy-related deaths for every 100,000 live births. The distinction between pregnancy-related causes of death and pregnancy-associated deaths—that is, a maternal death that is attributable to a condition unaffected by the pregnancy, even if it occurred within one year of it—is important. It means that deaths of pregnant women from suicide, homicide, and drug overdose are currently considered pregnancy-associated rather than pregnancy-related and are not included in maternal mortality statistics. However, maternal mortality review committees (MMRCs) can include those deaths in their data.

Regardless of the metric used, there is a maternal mortality crisis in the United States. In 2018, the maternal death rate was 17.4 per 100,000 live births in the United States, for an international ranking of 55th. Pregnancy-related mortality increased from 13.2 deaths per 100,000 live births in 1999 to 16.9 in 2016. The leading clinical causes of pregnancy-related mortality are cardiomyopathy and other cardiovascular conditions, and deaths from these causes have increased over the past decade. Maternal deaths related to self-harm (e.g., suicide and overdose) must be addressed, although they are underreported. Among new mothers, suicide is a leading cause of death. Risk factors for maternal death by suicide include major depression, substance use disorder, and intimate partner violence. According to a report from nine MMRCs, common themes among maternal deaths related to mental health causes include inadequate assessment of risk; failure to screen; ineffective treatment; delay in diagnosis, treatment, and follow-up; and lack of coordinated care and communication.

There is a marked racial and ethnic disparity in maternal deaths in the United States, as shown by many personal stories and data. Black mothers have been more likely to die than their White counterparts since these data began being recorded, and healthier living conditions and medical advances have only increased the Black–White gap. Maternal mortality disparities are more pronounced in some cities. Pregnancy-related mortality ratios (2007–2016 data) were 40.8 among Black, 29.7 among American Indian, 13.5 among Asian and Pacific Islander, 12.7 among White, and 11.5 among Latinx women. Importantly, education does not mitigate the Black–White gap—as Black women with a college degree or higher are five times more likely to have a pregnancy-related death than their White counterparts. The leading causes of maternal deaths also differ by race and ethnicity (cardiomyopathy for Black women and mental health conditions for White women). A recent analysis of 2016–2017 data that also examined the actual text written on death certificates found that maternal mortality and late maternal mortality rates among Black women were higher than previously thought—3.5 times those of White women. This study also found that Black women had five times the rates of eclampsia, preeclampsia, and postpartum cardiomyopathy than White women and more than double the rates of obstetric embolism and obstetric hemorrhage.

The timing of pregnancy-related deaths provides insight into interventions to reduce maternal mortality. More than half of deaths occur postpartum. The intersection of timing and cause of death is also instructive. During pregnancy, non-cardiovascular medical conditions and cardiovascular conditions are the leading causes of death. Deaths on delivery day are most frequently from hemorrhage or amniotic fluid embolism, whereas hemorrhage and hypertension are leading causes one to six days after delivery. Maternal deaths seven to 42 days postpartum are most frequently from infection or other (not cardiomyopathy) cardiovascular conditions, and cardiomyopathy is the leading cause of deaths 43–365 days after delivery.

But for every maternal death, many more women experience severe maternal morbidity (SMM), the term for having a life-threatening diagnosis or requiring a lifesaving procedure. As with maternal deaths, Black and American Indian/Alaska Native women have higher rates of SMM conditions. More than 60 percent of maternal deaths are preventable, and the factors (at the patient, community, clinician, and system levels) contributing to SMM and maternal mortality have been identified. All these factors jointly shape the health status of women when they become pregnant and interact with the health system. Quality of care is a major lever to reduce SMM and maternal mortality. In New York City, hospital performance on SMM varies widely (sixfold to sevenfold differences), and Black and Latinx deliveries are more likely to occur in high-SMM hospitals. Qualitative interviews with chairs of obstetrics departments, frontline and head nurses, and others at hospitals with low and high rates of risk-adjusted SMM reveal some important distinctions between the two. Hospitals with high rates of SMM have nurse staffing issues and wide variation in quality measurement and improvement. Importantly, these hospitals tend not to analyze data on the care provided across race, ethnicity, or insurance source. In contrast, hospitals with low rates of SMM are more likely to have stronger focus on standards and standardized care, nurse–physician communication or teamwork, and sharing of performance data with nurses and other frontline clinicians. These hospitals also have greater awareness that disparities and racism might be present and could lead to differential treatments. Focus groups of women with

SMM who delivered at these hospitals revealed that they had experienced trauma and subtle discrimination, among other issues. Black and Latinx women had higher levels of SMM, even after insurance and other factors were taken into account. A contributing factor to high-SMM hospitals is the racial and economic segregation by ZIP Code.

The life course perspective is crucial when considering the levers to reduce MMM. To address the U.S. maternal health crisis, the field must engage the community to promote contraception, optimize pre-pregnancy health, and implement new models of antenatal care. Delivery and hospital care quality improvement efforts, standardization, safety bundle implementation, and training are among the methods to reduce SMM and maternal deaths. Communication should be enhanced to improve postpartum care, and new models (e.g., patient navigators and case management) can help eliminate bias.

Dr. Howell recommended that NIH consider establishing an institute for women's health, expand research on pregnant women and long-term health outcomes, and invest in health services research and implementation science. It will also be important to enroll pregnant women in clinical trials and to expand research on structural racism and other root causes of inequities in women's health, as well as conducting gynecological studies. Finally, research on women's health would be advanced by diversifying the NIH staff and principal investigator workforce to include more obstetricians and gynecologists.

Impact of Chronic Disease: The Sex and Gender Gap

Dr. Marjorie Jenkins, Dean of the University of South Carolina School of Medicine Greenville and Chief Academic Officer of Prisma Health-Upstate, emphasized the importance of terminology. She mentioned the U.S. Department of Health and Human Services (HHS) 2010 definition of chronic illnesses: "conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living." This definition incorporates elements of duration, medical requirements, and functional status. The HHS Strategic Plan also uses "multiple" to describe two or more concurrent chronic conditions, which is often called multimorbidity. An NIH-wide definition of CDCW does not currently exist.

"Sex" (a biological classification of living things) and "gender" (a social construct related to a person's self-representation) are unique terms, and it is important not to interchange them. The frequency of interchanging "sex" and "gender" has increased, even in basic and translational science, since about 2002. This represents a cultural shift that is reflected in scientific journal practices. Using "sex" and "gender" interchangeably conflates the science and makes it difficult to aggregate data. Scientists are taught to control all but the experimental variable, so they often control for sex, which has led to a lack of information on the health of women.

Chronic diseases have a great influence on the health of people in the United States and a significant economic impact. Six in 10 adults have a chronic disease, with four in 10 having two or more. Women are more likely to have multimorbidity. The leading causes of death mostly overlap for men and women, with a few differences. Dr. Jenkins stressed that research needs to intentionally address women's mortality because of the domino effect that their deaths have on families and society. Evidence to support women's health is provided through well-designed, well-conducted, and optimal reporting of research that has appropriately considered sex and gender. Additionally, health care is evidence-based, as data drive solutions in women's health. The end users of this research are patients, who bear the burden of more than three decades of sex bias in research on infectious diseases, autoimmune conditions, and nonreproductive cancers. Additionally, the traditional research pipeline—discovery (NIH), product development (industry), and approval/post-market (U.S. Food and Drug Administration [FDA])—is biased, with more male study subjects even though females are 80 percent of health care consumers. Research environments and expenditures directly impact the burden of chronic diseases. Research silos prevent the benefits of synergistic efforts. Industry should be encouraged to analyze data for sex and gender differences.

Dr. Jenkins reviewed a timeline of health policies that enable the understudy and underreporting of sex and gender differences—including the 1977 FDA policy that no women of childbearing age were allowed in early-phase clinical trials. Although the policy pertained only to early phases of drug development, the participation of women in all phases was affected in practice. The 1985 NIH policy on inclusion in clinical trials had only encouraging language (“consider the inclusion of women” and “general differences should be noted”). A 1990 General Accounting Office (GAO) study concluded that the NIH policy on inclusion of women in clinical trials was not well communicated or understood within NIH or the greater research community. The policy was applied inconsistently among institutes and only to extramural research. Additionally, there was “no readily accessible source of data on the demographics of NIH study populations,” so it was impossible to determine whether NIH was enforcing its own recommendations. In 1993, FDA guidance encouraged the inclusion of women in Phase I and II studies and expected their inclusion in efficacy studies, as well as data analysis, regarding race, age, and gender. But it became clear that patients were bearing the consequences of the Government’s inability to enforce the intentional study and publication of sex differences.

The NIH Revitalization Act of 1993 created the Office of Research on Women’s Health, which had been established by NIH in 1990, in statute. Additionally, the act mandated that women and minorities be included in clinical research and researchers ensure that valid scientific analysis can be performed to determine whether differences exist between women and men and among study subjects of different races and ethnicities. The law covers the inclusion of both sexes in adequate numbers to ensure data can be analyzed for the effects of gender on safety and efficacy of proposed interventions and drugs. The 1998 FDA Demographic Rule requires sponsors to tabulate the trial population by age group, sex, and race in investigational new drug (IND) applications and to analyze safety and efficacy by age group, sex, race, and other variables as appropriate. Despite these changes, a 2000 GAO study of NIH found a number of issues. Although women were included in clinical trials at rates proportional to their numbers in the general population, NIH lacked protocols to enforce the mandate to perform and report valid scientific analysis of sex differences in late-stage (Phase III) clinical trials and lacked adequate data tracking of women and minorities enrolled in trials. It was noted that the lack of compliance could significantly affect the ability to apply sex differences research to clinical management and outcomes. Also, in 2000, FDA gained the ability to place a clinical hold on an IND application if men or women with reproductive potential are excluded from participation only because of the risk or potential risk of reproductive or developmental toxicity associated with use of the investigational drug.

A 2015 GAO (whose name had changed to the Government Accountability Office) study found that 57 percent of NIH-funded clinical trial subjects in 2014 were women. However, NIH had not tracked whether funded studies included plans for analysis by sex. There was also a lack of summary data to identify potential sex differences, and the report noted that this limited the assurance that NIH was supporting research that could inform medical practice for both women and men. In 2016, the SABV policy took effect. The article presenting the policy to the field noted that the consideration of sex may be critical to the interpretation, validation, and generalizability of research findings. It also stated that the appropriate analysis and transparent reporting of data by sex may therefore enhance the rigor and applicability of preclinical biomedical research. In the SABV policy, NIH outlined its expectation that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. A strong justification from the scientific literature, preliminary data, or other relevant sources must be provided for applications proposing to study only one sex. NIH strongly encourages investigators to discuss these issues with NIH program staff members prior to submitting applications. Dr. Jenkins remarked that it is not enough to “expect” these actions from investigators. A five-year progress report from NIH noted that although there has been some advancement, uptake of the SABV policy has been inconsistent, and ORWH is developing resources to help investigators consider sex as a biological variable in their research.

Women's health faces a research crisis regarding the exclusion of pregnant women and lactating women in clinical trials. The 21st Century Cures Act (Public Law 114–255) established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). In 2018, [PRGLAC released a report and recommendations](#), but the lack of human data was striking. An FDA audit of 575 prescription drug and product labeling changes found that 414 products (72%) did not have human data about pregnancy or lactation. As has been said often, the field continues to protect women from research instead of with research.

In conclusion, Dr. Jenkins remarked that ORWH cannot advance the health of women alone. Achieving true progress requires change across many organizations and institutions, and she identified multiple points of engagement for integrating sex and gender into research, education, and clinical care. Although more women are participating in research, without marked progress in outcomes and clinically meaningful knowledge of sex and gender differences, the field cannot advance. NIH and FDA must strengthen the language of their policies, as researchers opting out causes disparities. Dr. Jenkins' call to action is for all to advocate for the appropriate use of sex and gender terminology within their spheres of influence. NIH and FDA should revise health policies to include specific language that mandates research design, analysis, and reporting by sex and gender. They should periodically report objective progress in advancing the health of women. NIH should adopt a definition of "chronic debilitating conditions in women" and allow tracking of its funding by codifying this variable within applicable databases. Congress and the pharmaceutical industry are crucial environments that require strategic and continual engagement and advocacy.

Cervical Cancer: How Can We Overcome Our History?

Dr. B.J. Rimel, Vice Chair of the Protocol Review and Monitoring Committee at the Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute and the Associate Director of Gynecologic Oncology Clinical Trials at Cedars-Sinai Medical Center, reviewed a brief history of cervical cancer screening. Dr. Georgios Papanicolaou and Dr. Aurel Babeş determined that cervical cancer can be detected by inspecting cervical cells. Dr. Papanicolaou, under the supervision of Dr. Charles Stockard, presented his findings and his Pap test at the third Race Betterment Conference, in 1928. Dr. Rimel acknowledged Dr. Papanicolaou's wife, Andromahi Papanicolaou, who collaborated with her husband at the Cornell pathology laboratory. Pap testing increased from 1943 into the 1950s after a few key publications. In 1976, Dr. Harald zur Hausen postulated that human papillomavirus (HPV) was the cause of cervical cancer, driving forward the viral oncology concept that would change the face of screening. By 1995, HPV 16 and 18 had been sequenced and were determined to be absolutely pathogenic. The link between HPV and carcinogenesis was clearer than that between smoking and lung cancer. Liquid cytology replaced glass slide Pap tests in the 2000s. Gardasil was released in 2006. In the last two decades cervical cancer incidence has decreased by 45 percent. However, the death rate from cervical cancer did not decrease proportionately, and 5-year survival rates remained steady. With the best cancer screening tool ever, how has associated mortality not declined?

In the United States, there are more cases of cervical cancer and higher mortality rates in Black, Latina, and American Indian populations than in White and Asian populations. Treatment for advanced stage disease remains largely palliative. Clinical trials of novel agents (e.g., cemiplimab, tisotumab vedotin, and pembrolizumab + platinum/paclitaxel +/- bevacizumab) suggest that improved treatment is possible. Dr. Rimel noted that these studies were funded by pharmaceutical companies and not the National Cancer Institute. A multidrug treatment regimen will be more costly and have more potential toxicity.

How can we address both equity and quality of therapy, and why haven't we already? Cervical cancer study populations are not racially representative. Opportunities for improving clinical trials include the following:

1. Treat cervical cancer like a rare disease. As a rare disease, cervical cancer may warrant large, national, annotated data sets that leverage information from support groups and electronic medical records.

2. Address structural racism in the design of clinical trials. The geographic distribution of patients with cervical cancer and of members of underserved racial and ethnic groups overlap. Low English fluency is also a barrier.
3. Create opportunities for patients with low socioeconomic status to participate in trials. The geographic distribution of patients with cervical cancer and populations living in poverty overlap. Poverty and racial geographic distributions overlap as well.
4. Acknowledge that rural and urban locations require different solutions. Travel times, Wi-Fi access, and other challenges create difficulties with including patients from rural areas.

Dr. Rimel reviewed issues related to structural feasibility (e.g., Where are patients with cervical cancer? Where do they receive care? Do these clinics participate in clinical trials? Are there recruitment issues related to trust, insurance, or language?) and trial-specific feasibility (e.g., Do inclusion criteria exclude representative populations? Are multiple visits required? Are there roles for smaller or broader studies?).

Dr. Rimel concluded by encouraging conference participants to reimagine cervical cancer as a disease of patients who are historically underrepresented due to race, language, poverty, and location; to recognize that cervical cancer is rare disease; and to consider clinical trial designs that improve equity (e.g., allowing smaller enrollment numbers per site; promoting non-English fluent patients to participate; compensating patients for their travel; and/or providing them with technology to allow for off-site monitoring).

Questions and Answers

In response to a question about the professionals who care for pregnant women and the effects of workforce issues on MMM, Dr. Howell noted that the United States (unlike many other countries) does not have a system for training midwives. Incorporating midwives and doulas into the U.S. maternity care workforce would likely improve the maternity experience—that is, reduce intervention and enhance satisfaction. Care from these professionals has not been clearly linked to maternal health outcomes, so the field needs to build that research. She added that maternity care data do not capture provider type (and where along the continuum they provided care) very well. Better ways to reliably identify provider type and the care provided (e.g., antenatal, delivery, postpartum) are needed. She emphasized that MMM is a public health crisis for everyone. MMM affect all women regardless of race and ethnicity, although there are profound racial and ethnic disparities that must be confronted.

Dr. Rimel agreed with a participant that there are similar disparities in maternal health and cervical cancer, as both begin early in life and are influenced by access to care. There is no magic fix to these complex problems. For cervical cancer, she suggested naming the cause of the disease as HPV and emphasizing that it is the only cancer that can be prevented by vaccination; thus, it would be important to identify ways to increase uptake of the vaccine. Important issues for study include access and how people enter the health care system. Does a child have a pediatrician? Does the pediatrician offer HPV vaccination opportunities? Are parents comfortable with HPV vaccination? Potentially, such research will suggest ways to improve vaccine uptake. In Dr. Rimel's view, there are two questions: (1) How do we increase vaccination and regular screening? (2) How do we get those who have cervical cancer the best treatment and encourage their participation in clinical trials? In response to a comment that endometrial and cervical cancer have the largest racial disparities among all cancer types, Dr. Howell noted that this is the legacy of disparate treatment of women, specifically those who are Black and Brown, which is only now being highlighted.

Concurrent Breakout Sessions

Maternal Morbidity and Mortality

Moderated by Yoel Sadovsky, M.D., Executive Director, Magee-Women's Research Institute, University of Pittsburgh

Maternal Morbidity and Mortality: Tip of a Lifecourse Iceberg

Dr. Janet Rich-Edwards, Director of Research in the Division of Women's Health and Director of Lifecourse Epidemiology at the Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, discussed MMM as the "tip of the iceberg" in terms of cardiovascular disease (CVD) risk. Much of the risk is influenced by historical factors—such as discontinuous or inadequate health care, intergenerational poverty, and enslavement and colonialism. Dr. Rich-Edwards explained that prior to pregnancy, some women have subclinical risk for CVD that emerges above threshold as preeclampsia during pregnancy, which in turn, increases the likelihood of clinical risk for CVD in later life. In contrast, women with a normotensive pregnancy experience stresses and increased blood pressure that is below the detection threshold. In the larger context, reproductive health is synonymous with both women's health and cardiovascular health, although the latter was erroneously considered a men's disease for many years. Developing gestational diabetes and delivering a low birth-weight baby are among the factors that double a woman's risk of CVD, yet disciplinary silos led researchers to miss the obvious links. This is an example of the streetlight effect, or looking where you already have information (reproductive health) rather than at the actual problem (cardiovascular health). The former focus on reproductive health has been replaced by considering all diseases and conditions that affect women from head to toe, as described in the Trans-NIH Strategic Plan for Women's Health Research. But the question is how to translate this approach into practice.

The United States has been losing ground in pregnancy-related mortality, as rates have risen since 1987. The risk for maternal mortality accumulates across the life course for Black and American Indian/Alaska Native women, who have the highest rates. These data suggest that the field should take a life course approach to MMM. Risk is socially determined and inequitably distributed, as each of the leading causes of maternal death is two to five times more common for Black mothers compared with White mothers. The Black-White gap in maternal health is seen in women under age 20, which suggests unhealthy environments are an important driver. The Black-White gap in infant outcomes (e.g., very low birthweight) has been known since the mid-1990s, when Dr. Arline T. Geronimus proposed the weathering hypothesis, which states that the effects of social inequality on health compound with age, leading to growing gaps in health status through young and middle adulthood. Dr. Rich-Edwards stressed that researchers need to know about the childhood environments and health factors prior to age 15 to have a complete picture of maternal health. Similarly, violence is another factor—often conspicuously missing—that has been considered in the health of women and is underestimated as an influence on MMM.

An important driver of MMM is the increasing prevalence of pre-pregnancy chronic conditions (e.g., hypertension, asthma, diabetes, and substance use disorder), particularly among women with low income and those who have health care through Medicaid. Women with chronic conditions now make up 10 percent of deliveries. At least half of maternal mortality is related to cardiometabolic health (e.g., cardiomyopathy, thrombotic pulmonary or other embolism, cerebrovascular accidents, hypertensive disorders of pregnancy, and other cardiovascular conditions). Much of this CV risk is preventable. Thus, reproductive and cardiovascular health are not separate, and Dr. Rich-Edwards remarked that emerging omics data will only reinforce this concept. But MMM may reveal more about the health of women than risk for CVD. For example, women with hypertensive disorders of pregnancy also have increased risk for premature mortality (prior to age 70 years) from infection, respiratory, nervous system, and ill-defined causes. Dr. Rich-Edwards argued that the disciplinary silos of NIH, which often focus on particular diseases or body systems, should be broken down to gain important insights for women's health.

Dr. Rich-Edwards recommended the following to NIH:

- Support cross-disciplinary work across ICs and across other federal agencies.
- Promote the life course approach such that all RFAs and proposals consider events before and after the period under study and prioritize research on the health of girls and women (including reproductive health) across ICs.
- Promote the translation such that all proposals include both research dissemination and translation and support training in these areas (perhaps with a new K award), especially community-based research.
- Continue the move the field beyond “bikini medicine” (the erroneous assumption that women are the same as men except for their reproductive system) with increased investment in cross-disciplinary work and a coordinating body with significant resources and the mandate to ensure a holistic, translated women’s health research agenda.
 - Probably a larger role for ORWH, if not a National Institute of Women’s Health.
- Recognize that maternal health is one part of a larger women’s health agenda and that both will fail if we revert to bikini medicine.

Harnessing the Power of Research: Optimizing Infrastructure to Optimize Maternal Outcomes

Dr. Uma Reddy—Professor of Obstetrics, Gynecology, and Reproductive Sciences and Section Chief of Maternal-Fetal Medicine at the Yale School of Medicine—made the case that greater NIH funding for maternal health is needed. The 2018 NIH budget allocated \$419 million to pregnancy research, representing only 1.2 percent of the total budget. This investment simply does not correspond to the magnitude of the MMM crisis and the disease burden related to pregnancy, as has been argued by others. The development of the COVID-19 vaccine is the most recent example of how pregnant women are left out of critical research. Pregnancy research is critical for those who could become pregnant, not just those who are already pregnant.

The total NIH funding for MMM was \$223 million (with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NICHD] providing the greatest amount at \$76 million), according to an analysis conducted by ORWH. However, a greater investment in clinical research infrastructure to address the causes of MMM is needed because this work requires large sample sizes that are diverse (race, ethnicity, SES level, geographic, and health delivery system). The funding and time frame need to go beyond the scope of the typical R01 award (i.e., \$500,000-per-year direct costs) for five years.

The NICHD Maternal-Fetal Medicine Units (MFMU) Network, established in 1986, aims to reduce maternal, fetal, and infant morbidity and to provide the rationale for evidence-based, cost-effective obstetric practice. The MFMU Network comprises 12 centers (36 hospitals) that participate collaboratively in common protocols to conduct primarily randomized trials to reduce maternal and infant deaths and complications. This research network covers a large number of deliveries (165,000 annually) and offers racial/ethnic and geographic diversity. It examines important and timely questions, such as testing tranexamic acid (TXA) for the prevention of obstetric hemorrhage after cesarean delivery. An international, randomized, double-blind, placebo-controlled trial (WOMAN) found that TXA safely reduces death due to bleeding in women with postpartum hemorrhage. The MFMU TXA Trial has enrolled 11,000 women who are randomized to TXA or placebo. This trial is designed to assess efficacy of TXA for the prevention of obstetric hemorrhage. Other NIH clinical research addressing MMM includes the following:

- The NICHD Obstetric-Fetal Pharmacology Research Centers Program conducts cooperative multidisciplinary research to enhance the understanding of obstetric pharmacokinetics and pharmacodynamics of medications during pregnancy.

- The NICHD/National Heart, Lung, and Blood Institute (NHLBI) nuMoM2b is a U10 award initially set up for a single study that examines adverse pregnancy outcomes in a sample of 10,000 women, and the nuMoM2b Heart Health Study will have cardiovascular outcomes at 2–7 years.
- The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs) study is investigating whether early-pregnancy glycemia can predict gestational diabetes and adverse maternal and neonatal outcomes in a sample of 2,150 women. This study can be leveraged for longer-term outcomes.
- The NHLBI CHAP study is an RCT of antihypertension treatment compared with no treatment for mild chronic hypertension in 2,400 women with primary outcomes of preeclampsia with severe features and various fetal and neonatal events.
- The NICHD Cesarean Section Optimal Antibiotic Prophylaxis (C/SOAP) Trial is an RCT of azithromycin compared with placebo in addition to standard antibiotic prophylaxis before cesarean to decrease infection in 2,013 women. In this study, the primary outcome of infection was reduced from 12 percent to 6 percent.

Noting that these are high-impact studies on MMM outcomes, Dr. Reddy stated that clinical research in this area requires the large sample sizes these studies feature. She recommended that NIH invest more in clinical research site infrastructure for maternal health research by increasing the MFMU or a similar network funding to expand site diversity and recruitment capacity. Instead of starting a new network, NIH can better leverage existing infrastructure to promote critical studies across ICs and investigators and tie funding opportunities to use of the network. NIH needs to establish an NIH Obstetric Research Consortium (using the example of the NIH Pediatric Research Consortium) to prioritize research on pregnancy, generate a catalog of research across NIH, identify gaps, and coordinate research. NIH should target RFAs to research gaps and promote the life course approach and enhance research training.

Coordinated NIH research on MMM is ongoing in the Implementing a Maternal health and PRenancy Outcomes Vision for Everyone (IMPROVE) Initiative. IMPROVE addresses the leading causes of MMM by building an evidence base for improved care and outcomes. NIH provides administrative supplements for existing grantees to add or expand research focused on maternal mortality. To date, NIH has funded 37 awards totaling \$7.2 million, but sustained funding is needed to target specific gaps. The ultimate goal is for NIH to lead the agenda in this field and not only track maternal health research. To do so, it needs to be empowered to direct how the maternal health funding is used, with concomitant annual reporting on priorities and activities. But addressing MMM will require collaboration across HHS through a committee with representation across agencies, as well as single-agency coordinating and tracking maternal health research across the department to determine how best to leverage resources. An important need is a program for encourage the study of therapeutic products in pregnant women (equivalent to the one for children), as recommended by the PRGLAC to the HHS Secretary in 2020.

To drive priority maternal health research objectives, NIH can do the following:

- Create a standing Center for Scientific Review study section specific to women's health to include reviewers with expertise in obstetrics/gynecology, internal medicine, adolescent medicine, epidemiology, health equity, and implementation science.
- Increase funding targeted to investigators who are members of underrepresented racial and ethnic groups and geographically diverse institutions.

- Boost the funding of physician scientists who focus on maternal health (e.g., individual K grants and bridge funding).
- Promote a single institutional review board process for efficiency.
- Fund translational research of all types.
- Incorporate a “Patient Voice Core” component to funding opportunities to ensure that investigators have expertise and support to include patient-reported outcomes and appropriate quality of life measures.
- Add a community-based participatory research (CBPR) component to funding opportunities (NIMHD’s CBPR program offers a model).

Opportunities in Clinical Research to Reduce Maternal Morbidity and Mortality

Dr. Cynthia Gyamfi-Bannerman—Chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Diego School of Medicine—noted that severe maternal mortality has increased in the past two decades and is higher among Black, Hispanic, and Asian/Pacific Islanders women compared with White women. The question is what to do about it. RCTs are one option, and they have the advantage of being the gold standard in medical research, as they limit bias in selection, offer a direct comparison between two groups, and can establish causation. However, the strict inclusion criteria of RCTs limit their generalizability. In general, there are two categories of clinical trials in pregnant women: (1) tests of interventions to improve pregnancy outcomes (e.g., preterm birth and preeclampsia) and (2) tests of interventions for common medical conditions that co-exist with pregnancy (e.g., hypertension, diabetes, and COVID-19). The latter type presents more challenges for including diverse women. Clinical trials in obstetrics can be performed as investigator-initiated studies or through the MFMU Network.

Dr. Gyamfi-Bannerman focused on a small clinical trial conducted in the OPRU Network that is studied pravastatin for the prevention of preeclampsia in high-risk women. The trial’s primary question was this: What are the pharmacokinetic properties and maternal and fetal safety profiles of pravastatin when used as a prophylactic daily treatment in pregnant women at high risk of preeclampsia? Although this was only a pilot study (10 women in each group), the findings were remarkable and showed that no women in the pravastatin arm developed preeclampsia. Pravastatin lowered blood pressure and decreased indicated pre-term birth. An RCT is pending, and the MFMU Network is nimble enough to conduct this research. Research from the MFMU network has changed lives, as shown by the example of antenatal corticosteroids in women at risk for preterm delivery.

Although RCTs are crucial, Dr. Gyamfi-Bannerman stressed that it is important for the field to leverage different study designs. Design variety is needed to address the top three causes of maternal mortality, which have changed over time (from hemorrhage, preeclampsia, and venous thromboembolism in 1987 to cardiovascular conditions, cardiomyopathy, and sepsis/infection between 2014 and 2017). Therefore, the data have shifted the emphasis from implementing hemorrhage safety bundles to addressing cardiovascular risk. The frequency of various pregnancy complications among nulliparous women is valuable information that should affect practice and implementation.

Dr. Gyamfi-Bannerman identified the following ways to address gaps in the current approach:

- Develop centers with infrastructure to enroll pregnant women (of all risk levels) to answer pertinent research questions.
- Leverage electronic health records (EHRs) to gather and analyze data on a general, large-scale population of pregnant individuals.

- Identify and address barriers to research in underrepresented groups.
- Leverage implementation science to study proven interventions in groups in whom the outcomes can be improved.

Research opportunities need to be diversified, as MMM continues to increase. With only a single obstetrics research network that has limited funding, additional research is needed to focus on pregnancy complications either through MFMU investigator studies or additional future research networks in response to a funding opportunity. There is an opportunity to develop an infrastructure for a nimble response to priority research areas. Once infrastructure is established in multiple settings, researchers can conduct the needed studies. A second opportunity is to conduct clinical research in community settings that would engage community clinicians in research, offer training, mentorship, and access. These relationships can be leveraged to enroll a more diverse population in clinical trials. A third opportunity is to expand traditional research mechanisms to allow for follow-up studies. Traditional R01 funding for clinical trials provides 5 years to study a pregnancy intervention and outcomes related to that intervention but does not allow for long-term infant or maternal (beyond 6 weeks postpartum) follow-up. Researchers need to study the life course that is the continuum of pregnancy, postpartum, fetal programming, infant and childhood outcomes, and subsequent pregnancy. To do this, they need to maintain prospective cohorts and incorporate detailed pregnancy questions into ongoing pediatric cohorts. A fourth opportunity is to move beyond the RCT and to consider multilevel clinical trials that affect at least two levels of influence—for example, the patient and the health care provider. Such research usually includes community input and implements economies of scale to study interventions on target populations. A disadvantage is that these trials allow for variables of interest to interact, which makes interpretation of findings more challenging.

A major opportunity is to include pregnant people in non-obstetric clinical trials. The need for this was highlighted by the exclusion of pregnant individuals in the COVID-19 trials. NIH requires that women and underrepresented groups be included in clinical trials (or that researchers justify their exclusion). However, the exclusion of pregnant women requires no justification. Once inclusion of pregnant people should be considered, nonpregnancy interventions would be studied in pregnancy. This reduces the need to replicate findings in pregnant populations and is the ethically correct solution. Another major opportunity is to leverage EHR data, as pregnancy data are generated copiously in these datasets. Doing so requires coordination at the national level, common variables, and a variable dictionary. Epidemiologic data will help to identify morbidities, outcomes of newly introduced interventions, and implementation barriers. Researchers also need to collect data on underrepresented groups and those less likely to be involved in clinical trials.

Expanding Maternal Morbidity and Mortality Research Within and Beyond Our Hospital Walls

Dr. Mary D'Alton, Chair of the Department of Obstetrics and Gynecology and the Willard C. Rappleye Professor of Obstetrics and Gynecology at the Columbia University Irving Medical Center, remarked on her 2010 call to action that stressed the need to put “maternal” back in maternal–fetal medicine, which highlighted the increasing prevalence of chronic conditions among pregnant women. In 2012, the Society for Maternal-Fetal Medicine (SMFM) developed a plan to raise awareness along with a specific research agenda to address maternal health and outlined these in several publications. SMFM identified recommendations to address the following seven critical research gaps related to maternal care:

1. Develop standardized methods for national surveillance of maternal mortality and morbidity.
2. Define significant maternal morbidity and “near misses.”
3. Improve prediction of patient’s risk of severe morbidity and mortality.

4. Determine optimal timing of delivery to balance maternal, fetal, and neonatal risks.
5. Conduct economic analyses to show benefit of maternal care, including inter-pregnancy and postdelivery care as well as improvements in neonatal outcome.
6. Examine the effectiveness of various approaches to improve training in maternal medicine.
7. Conduct research on the impact of adverse pregnancy outcomes on long-term maternal health.

A 5-year progress report follows up on work done on the recommendations. Work on recommendations 1, 2, and 7 is in progress in the MFMU Network. The NICHD Strategic Plan 2020 also addresses research on the impact of adverse pregnancy outcomes on long-term maternal health and the need to establish a foundation for healthy pregnancies and lifelong wellness. Progress on recommendation 1 includes improved data collection and sharing. The number of MMRCs has increased, and the Prevention of Maternal Deaths Act of 2018 authorizes the CDC to provide assistance to states establishing these bodies. Dr. D’Alton remarked that the CDC has led the improvement in the quality of maternal deaths review and great progress has been made. However, there is a significant gap in reviewing maternal morbidity cases. Safety bundle implementation is part of addressing recommendation 6. Part of addressing recommendation 3 includes determining the optimal timing of referral and work to predict maternal risk 1–2 years prior to pregnancy by examining social determinants of health (SDOH). A population-based observational cohort study is addressing the long-term effects of adverse pregnancy outcomes on maternal health. NICHD-funded research on maternal health has increased, and the Institute also supports a centralized data hub and biospecimen repository for its investigators.

Moving forward, Dr. D’Alton remarked that there continues to be a gap in surveillance data, despite some progress. However, COVID-19 has accelerated the rapid aggregation of data and speed of scientific publication. Maternal health research needs a similar focus, perhaps through medical records systems. More work is needed to improve data resources and spur innovations in this area. Effectiveness research and implementation science are major gaps. In addition, the field needs to continue its expansion of the circles of relevant research and multidisciplinary collaboration. In the area of training, a question is how to sustain the principles underpinning safety bundles, especially in low-resource settings. It is crucial to understand the effect of optimal safety bundle implementation on MMM. Although most training programs include simulation and case-based learning, the field needs to consider the role of simulation, as it is expensive and time consuming. Researchers should determine the most effective types of simulation and the minimum required. Innovations in maternity care technology are lacking, although a device has been developed to stop postpartum hemorrhage that could have a significant positive impact both in the United States and in low-recourse settings that lack blood or transfusion protocols. A positive development is a partnership between the American College of Obstetricians and Gynecologists (ACOG) and the Joint Commission to scale up implementation of levels of maternal care and evaluate the effects of this approach on maternal outcomes. The optimal time to refer patients to high-risk care is often not known, especially in rural areas.

How Can Research Findings Be Translated into Reduced Maternal Morbidity and Mortality?

Dr. Elliot Main, Medical Director of the California Maternal Quality Care Collaborative (CMQCC) and Clinical Professor of Obstetrics and Gynecology at Stanford University, focused on the role of hospitals and health systems in addressing the maternal mortality crisis and shared the recent successes of the translational work of the CMQCC. Comparing the definitions of infant mortality and maternal mortality reveals that the latter is more complicated. Classification of maternal mortality requires multiple pieces of data and several judgments (i.e., whether the woman was pregnant and whether the death was pregnancy related). In addition, there are many causes of maternal death—each rare and each with many underlying causes. Dr. Main explained that each cause is connected to layers of contributing factors, including quality of care, comorbidities, social determinants, and racism. The “thickness” of each layer varies for each cause and even each instance. Racism can lead to maternal mortality through a lack of

trust in doctors and hospitals, the recurring experience of the system's "denial, delay and dismissal" of Black women's symptoms, implicit and explicit bias, weathering from toxic stress, and exposure to erosive social determinants.

It takes an average of 17 years for a national consensus guideline to be integrated into clinical practice. Hemorrhage and preeclampsia are major causes of MMM. Dr. Main commented that this is unacceptable and that the medical field must identify strategies to shorten the timeline for adoption of evidence-based practices (EBPs).

Implementation science focuses on how an EBP can be scaled up to affect the population, whereas quality improvement efforts focus on changing outcomes at a hospital.

Dr. Main described CMQCC's efforts in California, which has 450,000 to 500,000 births annually (12% of all U.S. births), with all in a single administrative unit across approximately 235 hospitals with maternity services. California is a diverse state, both in terms of race and ethnicity of residents and geographical areas that have challenges for care. CMQCC is a multistakeholder collaborative founded in 2006, launched with funding from the California Department of Public Health to address the rise in maternal mortality. An initial step was to establish an MMRC and use its findings to drive state quality efforts. Maternal Mortality Reviews to Action releases quality improvement toolkits to address causes of maternal deaths, forms large-scale quality improvement change collaboratives that engage a large number of hospitals simultaneously, partners with everyone, and houses a maternal data center. Low-burden, low-cost, high-value comprehensive and rapidly available data are the foundation of these efforts.

Prior to the CMQCC, California had maternal mortality ratios similar to the U.S. average. Since CMQCC establishment, rates have fallen significantly (5.6 deaths per 100,000 live births in 2016 compared with 21.8 for the United States overall). Hospitals that participate in the CMQCC also saw a more than 20 percent reduction in severe maternal morbidity from obstetric hemorrhage compared with 1.2 percent for a comparison group. The CMQCC also collaborated on a 2-year quality improvement effort to reduce primary cesarean births—which drive rates of transfusions and other complications—that touched every hospital in California. Rates of cesarean births fell by 14 percent overall, and initial wide variation among hospitals has subsequently narrowed. To achieve change at scale, all levers must be pulled at once. The CMQCC releases public reports and hospitals are rewarded for reducing cesarean births. A key factor in California's efforts is that multiple players speak the same message and aim at the same target. Despite these successes, racial disparities continue. Most hospitals have no idea that their outcomes differ by race. With effort, the Black-White gap in cesarean births has been narrowed.

Dr. Main observed that hospital and provider feedback can be very powerful, particularly when combined with transparency or incentives. Care decisions that have high subjectivity (labor management and care for obstetric emergencies) provide significant opportunity for bias (explicit and implicit). Providing more structure through protocols and measures reduces subjectivity and bias. The more "change levers" that can be pulled at once, the greater the effect. To scale up quality improvement, the Joint Commission standards now include the key elements of hemorrhage and hypertension National Safety Bundles for use in hospital accreditation. In addition, the Medicare Hospital Inpatient Quality Reporting Program is incorporating a new maternal morbidity structural measure. The Alliance for Innovation on Maternal Health (AIM) is funded by a cooperative agreement with the Health Resources and Services Administration's Maternal and Child Health Bureau and ACOG. AIM promotes a national, cross-sector commitment to promoting safe care for every U.S. birth and lowering the U.S. rates of preventable maternal mortality and morbidity. Supporting state teams and health systems, AIM aligns national-, state-, and hospital-level quality improvement efforts to improve overall maternal health outcomes. Forty-one states and the District of Columbia are enrolled in this Initiative (five plan to enroll), with approximately 1,900 AIM-engaged birthing facilities. Dr. Main noted that it takes about 5 to 10 years to establish momentum. CDC funds 13 State Perinatal Quality Collaboratives and may fund more this year.

In conclusion, Dr. Main identified these keys for improving care at scale:

- Use public health surveillance data and patient stories to create a “burning platform” for change and drive actions.
- Mobilize a broad range of public, private, and community partners to drive change together.
- Create a system of rapid-cycle maternal–infant data to support and sustain quality improvement projects.
- Implement a series of data-driven, large-scale quality improvement projects to change culture.
- Pull all change levers at once, both hospital and external.
- Address equity in quality improvement simultaneously with clinical quality improvement.

You Are What You Love: Prioritizing Women’s Health Research for a Healthier Society

Dr. Maeve Wallace, Associate Director of the Mary Amelia Center for Women’s Health Equity Research, made two provocative points to spark discussion. First, maternal mortality in the United States reflects our societal values. Historically embedded societal values guide decisions about who matters and which issues rise to the level of concern and warrant commitment of shared resources. As mentioned previously, maternal deaths are the highest in the United States relative to peer countries. She emphasized that maternal death rates remain relatively high despite considerable spending on medical care, technology, and efforts to address the problem. In Dr. Wallace’s view, the maternal health crisis reflects a society that does not value women, especially certain groups of women. The lack of research is a further reflection, as a society measures and studies what it values. For example, NIH funding on maternal health research has increased, investments in the study of women’s health remained relatively flat. Society has to reckon with this idea.

Second, Dr. Wallace noted that Innovative research questions approach maternal mortality as a broad indicator of population health and well-being. She encouraged participants to think beyond the biomedical model and stressed that every maternal death is inseparable from the context in which it occurs. Innovative research in this area focuses on the places where women are born, live, and work, and on the policies that shape those places as protective or harmful to health. In addition, it is important to consider the structure and functioning of a society that dictates the distribution of power and resources across people and places. The life course approach is essential, as health during pregnancy is influenced by experiences that occurred long before and affects a woman’s health for years afterward. Most women spend the majority of their lives not pregnant, if at all, and this should be recognized in research. Society must prioritize the right of every woman and girl to achieve their optimal health and well-being, regardless of the reproductive decisions they make.

Translational studies are more than a stage of research, they are crucial to saving lives and improving health. Therefore, the field must shorten the timeline from evidence to action. To improve care and health at scale, the field must pull all the levers (institutional, structural, systemic, and policy) at once. Dr. Wallace added that it is important to do so even in areas where clinical care is achieving its aims.

Root Causes of Maternal Health Outcomes and Research Justice

Dr. Joia Crear-Perry, Founder and President of the National Birth Equity Collaborative (NBEC), introduced NBEC to participants. Established in 2015, NBEC creates global solutions that optimize Black maternal, infant, sexual, and reproductive well-being. The organization aims to shift systems and culture through training, research, technical assistance, policy, advocacy, and community-centered collaboration. NBEC’s values are radical joy, reproductive and

sexual freedom, Black lives, sisterhood, anti-racism, power, and Black feminism/womanism. Its vision holds that all Black mamas and babies thrive and that all have a place of well-being.

While briefly reviewing the time frame of reproductive oppression, Dr. Crear-Perry noted the trauma Black women have experienced historically (e.g., being sold, raped, and having children taken away). She added that even after the ban on the trans-Atlantic slave trade, slavery remained legal in the United States. The gold standard of human rights—that is, all people have the right to a standard of living adequate for the health and well-being of themselves and of their families—is set by the United Nations. Dr. Crear-Perry stressed that when we speak of systems and institutions, we are still talking about people, collectively organized in a way that is based on a particular set of rules and relations.

Racism can be viewed as a SDOH. Racism affects health both directly via chronic stress and indirectly via race-based discrimination across multiple systems, which creates differential access to high-quality schools, safe neighborhoods, good jobs, and quality health care—that is, by shaping SDOH. An indicator of health (a datapoint) is not the same as a framework (a vision) for studying health that influences measurement. Dr. Crear-Perry commented on the importance of distinguishing between race and racism. Racism, not race, drives outcomes. Racism occurs at multiple levels (institutionalized, personally mediated, and internalized). She added that the risk factors are not behaviors, choices, and bodies but the racism that influences people's lives. Anthropological approaches demonstrate that race is real and matters in society, but not in the way racists think it does. Race is not a genetic cluster or a population; that is, race is not biology. However, racism has biological effects. In addition, social constructs are real for those who hold them. Anthropological approaches also distinguish among race, ethnic group, population, and ancestry. These represent four different ways to describe, conceptualize, and discuss human variation, and they cannot be used interchangeably.

The Women of African Descent for Reproductive Justice developed the concept of reproductive justice in 1994. Reproductive justice acknowledges the conditions that dictate women's and people's reproductive outcomes and affirms that all individuals have the human right to (1) decide whether/when they will have a child and the conditions under which they will give birth; (2) parent the children they already have with the necessary social supports in safe environments and healthy communities, and without fear of violence from individuals or the government; and (3) bodily autonomy. A related idea is that reproductive lives cover the full lifespan and that intersectionality influences individuals' identities. In Dr. Crear-Perry's view, NIH has contributed to harm and must counteract that harm. Research injustice is a situation where community voices and experiences are dismissed or ignored. It can also involve inaccessible information because of jargon, money, and narratives that exclude or misrepresent community experiences, and communities that lack control over the production, documentation, possession, and dissemination of their own data or stories. Dr. Crear-Perry lauded NIH's plan to confront research injustice. In June 2021, NIH Director Francis S. Collins, M.D., Ph.D., released a plan intended to eliminate a big gap between grants awarded to White scientists and grants awarded to scientists of underrepresented racial and ethnic groups and boost funding for research on health disparities. The NIH plan includes programming to recruit, mentor, and retain researchers from underrepresented racial and ethnic groups and to appoint diversity and inclusion officers at each of its 27 ICs. To help address the funding gap, NIH leaders plan to spend \$60 million on projects aimed at reducing health disparities and another \$30 million to study and address the impact of structural racism and discrimination on minority health.

Current research assumes there are no solutions or interventions for improving Black maternal health that Black women themselves do not already possess. The "shame and blame" narratives that dominate much of the discourse about data on Black mamas are not insightful or helpful and perpetuate a dangerous myth that White people serve as a default standard for the rest of the population. In addition, the current conduct of research—specifically the dissociation of social and clinical determinants of health—is both problematic and unethical.

Dr. Crear-Perry identified the following gaps in current research:

- Lack of consideration of structural factors leads to systematic underestimation or misappraisal of Black maternal clinical risk factors, and the disregard of structural factors increases risk for poorer health outcomes.
- Compounding structural determinants of health are proposed fixes to so-called “health disparities” that focus on quality improvement without equity.
- A focus on individuals who fail to acknowledge that structures of power are often out of reach for marginalized communities.

These issues are reinforced by silos in the provision of clinical health services where much of the research that drives interventions for improved health outcomes is conducted. In addition, current research must address ethical issues, such as a lack of informed consent and acknowledgment or compensation for scientific awards and discoveries. Other unaddressed ethical problems are the explicit coercion of communities of color, inflicted harm, the criminalization of pregnant people, punitive uses of various contraceptive methods, and involuntary sterilization. The Black Mamas Matter Alliance’s Research Working Group developed a conceptual framework that incorporates reproductive, birth, and research justice, as well as human rights, Black feminism, and womanism. This group has also outlined [best practices and guidelines for holistic care](#). Such care recognizes and respects the rights of Black mamas; understands the historical, sociocultural, political and economic contexts in which Black mamas live their lives; invests in Black women as researchers; funds and conducts ethical research that benefits Black mamas; honors and commits to community engagement through the entire research process; and includes health equity and social justice as key themes in research with Black mamas.

In the policy and advocacy arenas, Dr. Crear-Perry’s view is that the focus should be on upstream interventions that address power and wealth imbalances that create SDOH rather than individual interventions. She also briefly outlined a birth equity agenda, concentrating on five critical measures for ensuring that the United States has the proper infrastructure and resources to achieve equitable maternal health outcomes. In this situation, reproductive health and autonomy are promoted and protected at the highest levels of government. In addition, health is a government priority and a recognized right, and individuals and institutions are held accountable for discrimination that leads to disparate health impacts. The birth equity agenda also aims for a country in which no maternal death goes unnoticed or uncounted, and government involvement in reproductive health may not intrude on reproductive freedom, agency, and autonomy. Policy changes that advance this agenda include leveraging nurses and other staff to facilitate a culture shift to collaborative care (e.g., assessments, referrals, and relationship building). Changes in policy should also influence partner organizations to prioritize racial equity in their work and promote trainings for staff to develop more cultural competence and manage implicit bias in response to maternal experiences of racism. Policies can also promote work with community action teams to improve citywide transportation infrastructure in response to data and maternal experience. Community action teams can work to counter federal disinvestment in health and safety (e.g., Medicaid and public health infrastructure). Finally, policies can help increase community education on opioid misuse and its impact on family health. Dr. Crear-Perry closed by encouraging everyone to be anti-racists.

Opportunities for Research to Reduce Disparities in Maternal Mortality and Morbidity

Dr. Stacie Geller, G. William Arends Professor of Obstetrics and Gynecology and Director of the Center for Research on Women and Gender at the University of Illinois College of Medicine, emphasized that no single clinical intervention has substantially reduced maternal health disparities, so innovative thinking is needed. Health during pregnancy and postpartum is not isolated to medical care. Overall, health is more social and environmental than clinical. Dr. Geller argued that a paradigm shift is needed in how we deliver care in a respectful manner that establishes trust and engagement.

Chronic conditions—such as obesity, hypertension, and diabetes—can increase the risk of pregnancy complications and maternal death. However, racial disparities will continue even if obesity is reduced. Clinician shaming of overweight women is a problem, as are access to healthful food and exercise opportunities. Chronic conditions do not occur in isolation but are connected to life experiences and SDOH.

As is the case across the country, the underlying causes of pregnancy-related deaths vary by race/ethnicity in Illinois. Overall, the leading cause of maternal death was a connection to mental or behavioral issues. Black women are almost three times more likely to die than White women, and they have twice the rates of SMM as White women. The most common causes of maternal death differ by race/ethnicity. Black women are more likely to die from a medical condition (e.g., preexisting chronic disease, hemorrhage, and hypertension), whereas White women are more likely to die from a mental health condition (e.g., suicide and drug overdose). However, Dr. Geller cautioned that a research focus on leading causes of mortality may actually increase racial disparities. SDOH—such as experiencing traumatic and financial stress and food insecurity—are highly prevalent among women who died from pregnancy-related causes. This highlights the importance of evaluating and addressing women's history of trauma and improving social services (e.g., stable housing) available to families in need.

Research consistently shows that higher exposures to structural racism is associated with adverse maternal and birth outcomes among Black women. A majority (54% to 78%) of pregnant Black women report experiencing racial discrimination. In the United States, structural racism has historically been used to advantage White people over Black people through the implementation of discriminatory practices (e.g., slavery, Jim Crow, redlining, mass incarceration, and lack of intergenerational wealth). These practices have limited Black people's access to quality housing, education, employment, and generational wealth, and have marginalized them in health care. This structural racism explains why Black patients lack trust in the health care system, leading to low patient engagement and attendance in care.

Black midwives are one way to enhance trust in maternity care providers and engage Black women in prenatal care. Dr. Geller stressed that this represents a paradigm shift and a culture shift, as it meets women where they are rather than requiring their compliance. This model—Melanated Group Midwifery Care (MGMC)—is being tested in a study funded by the Patient-Centered Outcomes Research Institute (PCORI). MGMC fills a gap because there is currently no model of maternity care centered on what Black women need and inclusive of broad structural changes. Women had input into the design of the program, which is culturally adapted and patient centered. MGMC's mission is to diversify the midwifery profession and empower Black birth parents with resources and tools to successfully navigate their prenatal and postpartum care. The program vision is actively engaged in addressing the maternity health care desert and Black maternal mortality and morbidity rates on the South Side of Chicago. It aims to realize the vision by bringing together Black mothers, pregnant people, politicians, public health workers, and community activists. The unique and highly valued expertise, insight, and collaboration of these community members are crucial to building sustainable and scalable community-based models of maternity care for and by Black people. Program strategies include racial concordance, group health care, care coordination, and in-home postpartum doula support.

Dr. Geller cited the study as research that promotes structural change. She shared that the grant did well scientifically, however, the funder was concerned that because multiple strategies are being tested, the researchers would not be able to pinpoint which one made a difference. The researchers successfully argued that in this multifactorial program, the whole is greater than sum of its parts. Having the conversation with funders was crucial to obtaining financial support for the research, and Dr. Geller encouraged NIH to consider this method for engaging with investigators. Dr. Geller recommended a focus on maternal health interventions that change policies, systems, and environments rather than changing people. She also suggested that NIH partner with other federal agencies and with communities to help bring together academic and non-academic groups that aim to improve maternal health.

A focus on morbidity is inappropriate, as it does not occur in isolation. Rather than race, focus on the effects of racism.

Questions and Answers

In response to a question about expanding the impact of the MFMU to geographic areas that are underrepresented in biomedical research, particularly rural regions, Dr. Reddy agreed that this should be possible. Expanding the MFMU would help to address the lack of maternity care coverage in some regions and diversity among study participants. She added that NIH should build filling these gaps in its funding opportunities. Dr. Main was asked about states (other than California) with quality improvement collaboratives and what their data show. He commented that establishing a collaborative, building the necessary partnerships, and seeing results takes a few years. Some states have reduced rates of particular outcomes—such as SMM related to hypertension in Illinois and Washington and cesarean section in others.

Dr. D’Alton focused on the need to optimize pre-pregnancy and postpartum care. The current NIH research framework needs to be expanded to include a longitudinal approach. She added that NIH is aware of the issue. There are research opportunities in most grants to extend a study to analyze baseline data on genomics, biorepository specimens, and clinical and epidemiological characteristics. Multiple observational cohort studies prospectively collect this data, and NIH is working to share these data more widely. Dr. Rich-Edwards suggested analyzing data from cohorts of adolescent women to examine maternal health prospectively, although the sample size would need to be very large to address MMM outcomes.

In response to a comment that racial concordance in models of care is a provocative approach and the alternative is to promote ideal care for all, Dr. Crear-Perry remarked that her ideal is to have Black providers, but she believes everyone should have options. Dr. Geller added that the MGMC project provides the care that women asked for, as researchers listened to their needs. It is an empirical question whether the model is effective, as the research is ongoing. She stressed the need to remove the clinical focus on reducing obesity, which is an important factor in maternal health but will not decrease racial and ethnic disparities by itself. Obesity does not happen in isolation, and community supports are needed to prevent it. Dr. Crear-Perry emphasized the importance of engaging more midwives and doulas in research not just care, as they have expertise and knowledge. Every other peer nation has better outcomes than the United States. They also all have midwifery models and do not medicalize birth. Maternity care does need to be more robust inside health care but in her view, the sole focus should not be improving hospital care. The United States needs to address barriers in women’s ability to thrive by creating a better social safety net.

Dr. Rich-Edwards concentrated on the value of qualitative research at providing insights into the patient experience that can spur innovations in care. NIH should encourage qualitative as well as quantitative research in maternal health. Dr. D’Alton recommended longitudinal research as the best approach to accelerate research findings into societal impact. The field knows what is effective, but it is not being done. Funding for research should encourage the leveraging of EHR information and the analysis of data in real time so that clinicians can effectively respond when providing maternity care. NIH should focus on high-priority areas and continually review progress and needs. Dr. Main added that everyone has a role to play in improving maternity care, and he emphasized the importance of partnerships and breaking down silos. Improving hospital care requires a change in culture, but this is just one piece of reducing MMM—prenatal care and the life course approach are others.

Chronic Debilitating Conditions

Moderated by Judy Regensteiner, Ph.D., Director, Ludeman Family Center for Women's Health Research and Professor of Medicine in the Divisions of Internal Medicine and Cardiology, University of Colorado Anschutz Medical Campus

Prevention of Chronic Conditions in Women to Advance Health and Function Across the Lifespan

Dr. Heidi D. Nelson, Professor Emerita of Medical Informatics and Clinical Epidemiology in the School of Medicine at Oregon Health and Science University, noted that screening and prevention reduce risks for cancer (breast, cervical, colorectal, and lung), CVD, depression and anxiety, diabetes, and osteoporosis among women. Preventive services recommended by the U.S. Preventative Services Task Force and [Women's Preventive Services Initiative](#) are provided for most women with no copay or additional charges, under the 2010 Patient Protection and Affordable Health Care Act (ACA). The effectiveness of screening and prevention depends on completing the steps of the preventive service pathway. First, women need access to health care and must be correctly identified as eligible for services based on established criteria (e.g., age) to undergo the appropriate intervention. If screenings have a positive result, women need to move on to follow-up testing, diagnosis, and treatment. If screenings have a negative result, women need to be followed for periodic screening, as most recommendations for preventive services include this periodic screening following a negative screening result. Dr. Nelson stressed that societal, health system, clinician, and patient variables all influence whether women complete the steps of the pathway and, therefore, whether preventive services are beneficial.

Currently, many gaps exist along the preventive services pathway. Research related to screening and prevention typically focuses on mechanisms of disease, epidemiologic associations, development of screening technologies and tests, and treatment of conditions once identified. Dr. Nelson identified the following research to fill evidence gaps:

- Randomized trials to prove the effectiveness of preventive services on improving health outcomes (e.g., hormone trials that have demonstrated that hormone replacement does not prevent most chronic debilitating conditions)
- Modeling to develop clinically relevant risk prediction methods
- Examination of barriers and facilitators of implementation of preventive services in different populations
- Consideration of potential harms of preventive services including the impact of false negative and false positive screening and testing results as well as complications of procedures

Dr. Nelson illustrated how evidence gaps might be addressed by considering specific examples. Screening is effective in reducing deaths related to cervical, colorectal, lung, and breast cancer. Of these, breast cancer has the highest incidence among women, while lung cancer has the highest death rate. Overall, there are seven total preventive services proven effective at reducing cancer incidence and death. Currently there are four recommended preventive services for cancers specific to women (three are related to breast cancer, one cervical cancer). Those are:

- Breast cancer screening: mammography every two years for women aged 50 and older and for women ages 40 to 49 as indicated by individual factors
- Risk assessment, genetic counseling, and genetic testing for breast cancer: assess for family history of cancers associated with breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations and provision of genetic counseling and testing as indicated

- Medications to reduce breast cancer risk: offer risk-reducing medications (tamoxifen, raloxifene, or aromatase inhibitors) for women aged 35 and older with increased risk for breast cancer and low risk for adverse effects
- Cervical cancer screening: screen ages 21 to 65; screening interval dependent upon type of test

The following three preventive services are for cancers not specific to women:

- Colorectal cancer screening: screen ages 45 to 75; screening interval dependent upon type of test
- Lung cancer screening: screen (yearly with low-dose computed tomography) ages 50 to 80 years with a 20 pack-year smoking history and currently smoke or have quit within the past 15 years
- Tobacco smoking: ask about tobacco use, advise smokers to quit and provide behavioral interventions and pharmacotherapy

Dr. Nelson emphasized that underuse of preventive services limits their effectiveness and impact. For example, low rates of lung cancer screening and a lack of data specific to women and lung cancer limits the impact of this intervention. In addition, clinical practice has low uptake of assessing family history of breast cancer, genetic counseling, and mutation testing for women at risk for this disease. There is also low uptake of medications to reduce breast cancer risk and smoking cessation efforts in clinical practice.

It is also important to recognize that economic disparities influence differences in cancer screening rates among women. Research indicates that the largest differences in screening rates for colorectal, breast, and cervical cancer are related to income (no data are available for lung cancer screening). Screening rates vary widely, but the highest rate of zero screening occurs in the population at the greatest poverty level. A similar pattern of screening rates is apparent for insured versus uninsured status. Dr. Nelson suggested that using the preventive services pathway, research can be targeted to address these gaps. Research to address cancer screening gaps includes clinical trials to increase screening rates. For example, some clinical studies compare patient navigation interventions to standard-of-care in populations experiencing disparities (primarily low-income women). Navigation services were tailored to overcome barriers (e.g., education, scheduling, transportation, assistance with referrals, and reminders for screening tests). A review of these studies found higher breast cancer screening rates with patient navigation, with greatest effects among patients who had never been screened before. Results were similar for colorectal and cervical cancer among low-income and disadvantaged groups. Dr. Nelson commented that studies such as this are important to identifying effective methods of increasing screening uptake.

In a second example of research to address evidence gaps, Dr. Nelson focused on prevention of depression, anxiety, and violence against women. Experiences of violence, depression, and anxiety are common and occur more frequently in women than men. All three conditions are typically underdiagnosed and underreported, and many researchers believe the actual prevalence of these conditions is double the published rates. Currently, there are three preventive service recommendations to address depression, anxiety, and violence. The following recommended interventions include both behavioral and medical therapies for depression and anxiety and ongoing support services for intimate partner violence (IPV):

- Depression screening: screen for depression including pregnant and postpartum women; refer for appropriate therapy
- Anxiety screening: screen for anxiety in adolescents and adult women including pregnant and postpartum women; refer for appropriate therapy

- IPV: Screen for intimate partner violence and provide or refer women who screen positive to ongoing support services

All these preventive services are covered under the ACA mandate, and research has demonstrated that detection and intervention improve these conditions. These conditions are often not addressed in health care but are often interrelated. IPV may be detectable through physical injuries, but can also lead to the other two conditions, which may appear to be the primary manifestation of symptoms. Often, physicians may look for and address these one at a time, but identification of one can help lead to detection of the others when considered as connected. Research can address evidence gaps by

- Developing accurate screening instruments for both anxiety and depression
- Considering connections between the three to help us understand the relationships between conditions
- Considering life stage and reproductive stage to help to focus on ways to improve early detection and treatment

Dr. Nelson noted that the four-item patient health questionnaire (PHQ-4) for anxiety and depression is simple and confers minimal burden yet is often not included in health assessments. She suggested that preventive approaches focus on aspects of women's health as interconnected conditions, which is listed in the WPSI Well-Woman Chart. Prevention of chronic conditions in women depends on effective screening and prevention measures. Evidence gaps limit prevention recommendations, so these gaps need to be filled with appropriate research. Additionally, research improves screening and prevention in women. In order to fill evidence gaps, research should include personalized approaches that address patient needs. Studies must also recognize the inter-related nature of some of the conditions unique to women and the effects of these conditions on health and function across the lifespan. Dr. Nelson recommended conducting research that specifically addresses gaps in the preventive services pathway and shifts the focus from high-tech innovations with low impact to some of the low-tech, women-centered interventions that have a high impact on preventing chronic conditions.

The Impact of Chronic Debilitating Conditions on Women

Dr. Kim Templeton—Professor of Orthopedic Surgery and Vice Chair for Diversity, Equity, and Inclusion at the University of Kansas Medical Center—noted that osteoarthritis is an example of a chronic debilitating condition that occurs in both men and women but has a more significant impact on disability and reduced quality of life (QOL) in women. The overall incidence of OA in the United States is 25 percent (approximately 30% for women and 20% for men). In every age group over 25, women are more likely than men to have arthritis, and self-reported joint pain is more common among women than among men in all joints except the shoulder and elbow. OA of the knee accounts for 80 percent of the disease burden of OA in the total population. The incidence of OA is expected to continue to increase. Globally, OA of the knee increases with age in all countries, and prevalence and incidence are greater in females than males across the world.

Sex and gender differences in OA prevalence are affected by various genetic, metabolic, and biomechanical factors related to sex-based differences. The exact cause of sex differences in knee OA is unclear and requires elucidation to improve preventive strategies and patient care. Differences noted in literature include acquired risk factors (e.g., injury and patterns of overuse). Women are more likely than men to sustain knee injuries, especially anterior cruciate ligament (ACL) injuries, which are associated with significantly higher risk of OA at a younger age, even after reconstruction in both women and men. Researchers do not yet know the reasons underlying these differences. They may relate to difference in cartilage, the inflammatory response, or some other factor. The increasing number of women participating in competitive sports means ACL injury and related OA will increase.

The inherent risk factors for OA include anatomy, gait pattern, impact of estrogen, and muscle strength. Knee anatomic risk factors can affect alignment and alter forces around the knee that could influence the development of OA. Sex-based differences in gait patterns and forces and movements around the knee, in both those with and without OA, are believed to increase medial compartment loading among women. Key research questions include how does this influence the development of OA and are there preventive measures that can be instituted? In people without OA, MRI evidence shows men have significantly larger knee cartilage volumes even after correcting for body and bone size. Men have more articular cartilage to begin with, which might mean it takes longer or more significant injuries to damage the cartilage enough for men to develop symptomatic OA.

Sex hormones may also influence OA, as there are estrogen receptors on cartilage cells and estrogen has an impact on cartilage metabolism. However, the effect of estrogen on the development of OA is not clear. In a study using a mouse model of induced OA of the knee, mice that underwent ovariectomy experienced more rapid progression of initial cartilage injury, lessened somewhat by supplementary estrogen. These findings provide some evidence that loss of estrogen may lead to more rapid cartilage loss. As women age, they are more likely to develop OA, and this is especially true after menopause. It is not clear whether this is due to loss of bone or direct effects of estrogen on cartilage. Another study that examined cartilage volume (using MRI) in men and women with OA found that in men, cartilage volume had no relationship with sex hormone levels but in women, cartilage volume was positively associated with serum progesterone levels and decreased levels of serum estradiol led to more changes in adjacent bone.

Quadriceps strength is important to limit loading of the knee and reduce impact on articular cartilage and is required to maintain mobility. A study assessing quadriceps strength in a series of women with and without OA (diagnosis based on x-rays) found that the greater the degree of OA, the lower the level of quadriceps strength. In this study, only approximately half of women with OA experienced OA-related pain; any decrease in quadriceps strength was not due to pain but underlying decreased strength. Another study found a greater degree of central quadriceps activation failure in women with grade 1 (asymptomatic) OA than those without this condition, suggesting that quadriceps strength loss occurs first and may influence development of OA. Longitudinal studies of loss of strength and relationship to radiographic studies on the progression of OA are needed to determine the sequence of events in the development of this condition. In addition, intervention studies are needed.

In the area of inflammatory responses, obesity can lead to increased risk of developing OA. The degree of influence of obesity on OA differs between men and women—the effect of obesity is greater in women than men for severe (grades 2 and 4) OA of the knee. The prevalence of OA in obese females increased more significantly in women than men. In addition, women are more likely to demonstrate a connection between metabolic syndrome and OA. The effects of obesity on OA are partially due to increased weight on articular cartilage. There is also an increased risk of OA of the hand in obese patients, especially women, suggesting increased risk is not just due to more weight on cartilage. There may be an impact of low-grade inflammatory response in patients with obesity, possibly mediated by leptin, leading to low-grade chronic inflammation. It is important to note that women demonstrate greater inflammatory responses in other conditions. Therefore, more research is needed to examine sex differences in the association between OA and obesity.

Currently, most studies of OA focus on pain. Both sex and gender influence the perception and expression of pain. But it is not clear how much of the identified sex differences in OA are based on differences in damage that occurs at joint level versus how pain is experienced and expressed. Sex-based differences in pain are related to genetic differences, neurochemical differences, the impact of sex steroids, systems-level differences (e.g., inflammation, cortical connectivity, midbrain-brainstem connectivity), and psychological differences (e.g., depression, anxiety). Gender-based differences are related to psychosocial differences (e.g., coping, self-efficacy), sociocultural

differences (e.g., gendered expectations, gender role), and experiential differences (e.g., abuse, intimate partner violence, familial history).

Prior to joint replacement therapy, women have more frequent episodes of care, are more likely to receive opioids, non-opioid medications, injections, and physical therapy than do men. Dr. Templeton noted that these observations lead to many questions about the underlying reasons. Following joint replacement therapy, both women and men improve but, at every timepoint, women have significantly more pain and poorer function than men. In patients with end-stage OA waiting for knee or hip replacement, women have significantly poorer health-related QOL, self-efficacy (e.g., confidence in management of pain fatigue), and function. When these are factored into postoperative assessments of pain and function, most gender-based differences disappear. Preoperative issues may explain most of the issues women have after surgery. Researchers need to understand why women have more pain and worse function than men before surgery before attempting to influence outcomes. At one point, gender-specific knee implants were used to try to improve differences in outcomes. There is no evidence these led to better outcomes, underscoring the need to know why differences exist before attempting to design interventions. Women are also more likely than men to experience higher rates and severity of metal hypersensitivity, leading to painful joint replacements.

OA can lead to chronic pain and difficulties with activities of daily living. Women are more likely to attribute self-reported limitations to having arthritis than men. Among those with self-reported arthritis, women are more likely to note limitations in activities of daily living and lost days from work than men. Significant interactions occur between OA and other health conditions. Individuals with obesity, diabetes, or heart disease are more likely to also have OA. Hypertension, depression, and COPD are among the most common comorbidities for women and men with OA. The prevalence of each of these conditions is greater among women than men with OA, and women have a higher number of comorbidities. OA comorbidities is a topic that requires more research. Important questions include these: Is there “crosstalk” among these conditions? Are there common etiologies such as hormonal changes or inflammation?

OA of the knee increases CVD-related and all-cause mortality in women. Increased mortality occurs primarily among women with knee pain and not just radiographic changes and is primarily due to increased CVD. This was not the case among individuals with hand OA. In studies looking at OA of the knee, only about 40 percent reported results based on sex—a figure that has remained constant over time (2002–2019).

Dr. Templeton identified future research directions. There is a need to understand the impact of sex and gender on OA in terms of (1) risk factors (ideally, leading to prevention); (2) treatment response; and (3) impacts on function, comorbidities, and mortality. This requires disaggregating data based on sex and gender to better inform clinical care, health communication, and future lines of research. The field also needs targeted research and funding for OA risk factors and response to treatments, especially among women given the differing etiology and outcomes and the relationships among OA, other health conditions, and mortality. Dr. Templeton stressed that researchers must consider women when designing studies, which means addressing disparities in care for women who are underrepresented minorities, those living in rural communities, and transgender populations. For all health conditions, clinicians and researchers need better education in sex and gender.

The Case of Fibroids as a Female-Specific Chronic Debilitating Condition

Dr. William Catherino, Professor of Obstetrics and Gynecology with tenure at the Uniformed Services University of the Health Sciences, stated that a chronic debilitating disease significantly affects a person’s QOL and ability to be a productive member of society. Dr. Catherino remarked that comparing the effect of diseases to the commitment to studying these diseases at NIH reveals a notable disparity: Every woman who goes through menarche and begins to have periods will ultimately also go through menopause. Of these women, 85 percent (approximately 140 million women in the U.S.) are significantly affected (e.g., experience significant symptoms). The percentage of NIH funding

in 2020 dedicated to studying menopause was less than 0.00001 percent. Similar disparities exist for menstrual disorders, fibroids, polycystic ovary syndrome (PCOS), premenstrual dysphoric disorder, pelvic inflammatory disease, and several other female-specific diseases. A number of highly prevalent female-specific diseases and conditions are not well-studied or understood, and therefore are difficult to treat. Dr. Catherino focused on fibroids (uterine leiomyomas), but pointed out that examination of most conditions specific, prevalent, poorly understood, or with high morbidity in women would generate the same conclusions.

Among women on active duty in the U.S. armed forces, those in every racial and ethnic group have significantly increasing prevalence of uterine fibroids with age. Black women have substantially greater risk of developing uterine fibroids and developing symptomatic fibroids with age than other groups. Women experience symptomatic uterine fibroids during prime reproductive and working/career years. Across the reproductive lifespan, by the end of the reproductive years (early 50s), 70 percent of White women and 80 percent of Black women will have identifiable uterine fibroids. The best-understood symptom of fibroids is heavy menstrual bleeding that interferes with physical, emotional, social, and material QOL. Heavy menstrual bleeding affects up to 30 percent of women in their lifetime, and uterine fibroids are one of the most common causes of heavy bleeding. Heavy bleeding accounts for 18 percent to 30 percent of gynecological visits, with estimated annual direct costs of \$1 billion. The estimated indirect costs over lifespan, including lost days of work and QOL, are \$12 billion.

Another significant issue caused by uterine fibroids is pain. As tumors grow, they can compress other tissue and affect other areas, causing menstrual, low-back, and abdominal pain, as well as pelvic pressure and pain during sex. A quarter of women find such symptoms extremely bothersome. In patients who try to get pregnant, fibroids increase risk of losing otherwise healthy pregnancies and increase the likelihood of a miscarriage. In women who carry a pregnancy to term, fibroids increase the risk of abnormal labor, cesarean section, preterm delivery, breech position, postpartum hemorrhage, premature rupture of membranes, placenta previa, and abruption.

Uterine fibroids are hormonally sensitive, benign tumors that produce an abundance of fibrosis. They are disordered bundles of cells with abundant scar tissue around them. The dense nature of fibroid tissue compresses other tissues and generates pain. This pain is not amenable to standard therapies because it is not an inflammatory process but a compression injury. Fibroids tend to grow in the presence of estrogen and progesterone (menarche through menopause), typically regress after menopause, and account for 50 percent of hysterectomies. Therapies that could specifically target fibroid cells and destroy them will be insufficient; there is also a need to address and break down scar tissue that surrounds and is caused by fibroids. In addition, fibroids can extend beyond the uterus.

About 150 years of research indicates potential points for intervention. Fibroids need blood, which has led to destructive interventions that obstruct blood (e.g., hysterectomy, myomectomy, and uterine artery embolization). Ovarian hormones stimulate fibroid growth, which has led to therapies to block estrogen and progesterone (e.g., gonadotropin-releasing hormone analogues and aromatase inhibitors). Treatment options for fibroids are unsatisfactory. Oral contraceptives and NSAIDs are ineffective. Hysterectomy, uterine artery embolization, and other destructive interventions, as well as hormonal treatments, risk damage to the uterus and/or infertility. Selective progesterone receptor modulators are not FDA-approved. Various forms of myomectomy are not effective for those who are not good surgical candidates, who have had multiple surgeries in the past, or who have other diseases associated with pelvic inflammation or scarring.

One might expect treatment options to be better after 150 years of study. Dr. Catherino commented that despite remarkable capabilities and function, the uterus is the most disrespected organ in the body. The assumption is that hysterectomy is appropriate unless an individual plans to become pregnant, because the only function of the uterus is to support a pregnancy. However, if the uterus is removed, this creates a hole in the pelvic floor and can cause prolapse, urinary incontinence and many other issues. Therefore, hysterectomy is a poor option. Another barrier to progress in the treatment of fibroids is the taboo of bleeding or any symptoms related to menstrual periods.

Women are expected to hide severe bleeding because of where blood extrudes from. Dr. Catherino emphasized the need to normalize the concept that menstrual bleeding is like any other bleeding.

Models of uterine fibroids are poor. They are based on the removal, sectioning, and comparison of fibroid tissue to other tissue, providing very limited information on how fibroids develop. However, there are now ways to grow human fibroid tumors in the laboratory and in vivo in a mouse uterus. Researchers need to use such models to understand fibroid growth and development, as well as the impacts of fibroids on pregnancy and menstruation. Dr. Catherino noted that to improve women's care, the field will need to address the following gaps in fibroid knowledge:

- Increased public awareness
- Diversified study populations
- Improved understanding of fibroid growth
- Improved understanding of fibroid impact on pregnancy
- Identification of novel therapies
- Improved fibroid classification
- Identification of environmental exposures
- Identification of different fibroid phenotypes
- Large-scale cohort studies
- Mechanism of hormonal and anti-hormonal regulation

Dr. Catherino identified challenges to research on fibroids, for which it is difficult to get consistent support. Between 2018 and 2021, 62 percent of Research, Condition, and Disease Categorization (RCDC) fibroid applications were awarded through *ad hoc* review (Special Emphasis Panel), awarding a single grant, rather than through a study section. This leads to a lack of consistent effort to understand uterine fibroids and develop novel insights that allow development of effective treatments for fibroids.

Dr. Catherino also highlighted the need for focused research in women's health, emphasizing that adding women to a study population is not the same as studying women. Intermittent research in women's health is insufficient. Additionally, diseases unique to women result in lifelong disability. Research on CDCW will lead to decreased death, disability, and suffering and improve QOL and productivity. Because women are the majority of primary caretakers, addressing chronic conditions will result in improved care of children and the elderly. Therefore, Dr. Catherino recommended the following: Develop a National Institute of Women's Health that specifically addresses diseases unique to or more common in women. Such an institute could collaborate with others regarding diseases that affect women and men, with a focus on designing trials directly related to how these diseases are experienced in women.

Fortifying Opportunities to Advance Female-Specific Chronic Disease Research

Dr. Stacey Missmer, Adjunct Professor of Epidemiology at the Harvard T.H. Chan School of Public Health, focused on endometriosis but noted that many of its characteristics, challenges, and research opportunities apply to all female-dominant and female-specific conditions. Endometriosis is a condition marked by growth of endometrial-like tissue (glands and stroma) outside of the uterus that responds to the cues of the menstrual cycle—building, sloughing, and resulting in scarring and adhesions. This condition affects 200 million women worldwide and is associated with

chronic pelvic pain (cyclic and acyclic), fatigue, infertility, depression, and anxiety. Although highly prevalent and life-impacting, the symptoms of endometriosis are nonspecific and associated with other disorders, as in many other female-specific conditions. This results in a circuitous path to diagnosis that involves many other organs, evaluations specific to medical discipline, and testing. Often, menstrual-related symptoms are dismissed as being “normal,” and embarrassment around discussing menstruation and pelvic pain occurs in both patients and health care providers. Because of this, there is an average of 6.7 years delay from symptom onset to diagnosis. Dr. Missmer emphasized that a delayed diagnosis is not unique to endometriosis and occurs in autoimmune and other chronic overlapping pain conditions. Notably, 65 percent of women with endometriosis report having been misdiagnosed, and they typically see five or more doctors before being correctly diagnosed.

When endometriosis is considered across the life course, most symptoms emerge in adolescence and early adulthood—an important characteristic that clinicians and researchers must consider. Adolescence and early adulthood represent a critical window for research and potential intervention. Untreated symptomatic endometriosis has a cumulative impact. Dr. Missmer explained that as symptoms develop in adolescence, negative effects on health, wellness, and stability accumulate (e.g., school absences, development of maladaptive coping mechanisms, and alterations in career paths and job attainment). These also present many opportunities for study and the potential for great intervention and benefit.

Chronic, symptom-associated conditions such as endometriosis often result in long-term treatments with side effects. For example, hormone-dominant treatments result in vasovagal responses, bone mineral density alterations, and androgenizing symptoms. Long-term high-dose analgesics (e.g., NSAIDs, acetaminophen, and opioids) have multisystemic effects (e.g., kidney, liver, and stomach). The primary response of health care providers to gynecologic-associated conditions is often hysterectomy or similar, resulting in surgical menopause—which is associated with earlier onset and higher incidence of CVD, Alzheimer’s disease, and mental health issues.

Dr. Missmer stressed that as co-existing conditions and subsequent disorders accumulate, the siloed approach to women’s health funding and medical care is less and less appropriate. Endometriosis has co-existing interactions with virtually every organ system and area of medical care, including pain, gastroenterologic, genitourinary, and mental health. The field needs to facilitate a view of research and clinical care that considers the whole woman with gynecologic medicine as an integral part. For this research, investigators need data beyond the surgical and imaging phenotype of endometriosis itself (e.g., biomarker/genetic/omic evaluations, data on interactions with other conditions, and environmental and behavioral exposure information). Detailed clinical and phenotypic data—tied to critical life course windows—from a diverse population of women are needed. Such data rarely exist in biobanks or EMRs but do exist in longstanding prospective cohorts in the National Cancer Institute (NCI) Cohort Consortium. Dr. Missmer noted that generating detailed clinical and phenotypic datasets from the NCI Cohort Consortium is an important opportunity. More than 60 cohorts exist currently, and there is now a lot of funding and infrastructure around harmonizing and collaborating in a cohort consortium initiative. Most cohort studies do not collect information on endometriosis and gynecological conditions, and very few record pain measurement or reporting. Resources do exist but are failing female-specific and -dominant conditions.

Another major research opportunity resides in the data and information available from research across different biomolecular and genetic pathways (e.g., proteome, metabolome, and interaction of phenotypic expressions with the environment) as well as large, disease-specific databases. Currently, these largely do not include the tissues and data relevant to female-specific conditions, like the endometrium. The tissues that are included in these valuable data sources often ignore menstrual cyclicity and menopausal status. These are major gaps that impede progress in research on women’s health. Therefore, Dr. Missmer agreed with Dr. Catherino’s recommendation for the formation of a National Institute of Women’s Health. Such an Institute could collaborate with other ICs to build

female-specific foundational normative and chronic condition databases and to design trials directly related to the disease and symptom experience in women.

What We Do and Do Not Know About the Leading Killer of Women and What We Should Do About It!

Dr. C. Noel Bairey Merz—Professor of Medicine at Cedars-Sinai Medical Center, Director of the Barbra Streisand Women’s Heart Center, the Linda Joy Pollin Women’s Heart Health Program, the Erika J. Glazer Women’s Heart Research Initiative, and the Preventive Cardiac Center at the Smidt Cedars-Sinai Heart Institute—stated that CVD is the number one cause of death and a major source of morbidity. Looking at age-standardized CVD mortality in women in 2019 across the globe, more CVD-related deaths occurred in the United States than in peer countries. Dr. Bairey Merz stressed that many problems with stagnant or rising rates in morbidity and mortality for multiple conditions are a result of inadequate public health and access to health care. In the United States, both male and female CVD death rates declined between 1990 and 2010 but have been increasing since 2010. Mortality rates are likely to further increase, as a result of the COVID-19 pandemic and delayed or deferred care as well as a decline in the management of risk factors.

Trends in United States. CVD mortality among young women between 1990 and 2008 are alarming. CVD mortality is stagnant for young women overall and rising for young women of color, while CVD mortality is decreasing for young men, including men of color. Young women of color are experiencing greater CVD death rates than young men of color in the United States. When one looks holistically at the causes of morbidity among women, ischemic heart disease is the leading cause of disability-adjusted life years (DALYs). To maximize return on health care investments, CVD in women must be addressed.

Dr. Bairey Merz summarized the current state of knowledge on CVD in women. The life course perspective and multidimensional framework outlined in the Trans-NIH Strategic Plan for Women’s Health Research is helpful when considering opportunities to deliver comprehensive care and intervene in CVD. Socioeconomic risk factors (e.g., unhealthy diet, sedentary lifestyle, smoking, obesity, loneliness, and social isolation) offer many areas to intervene in CVD. Applying sex and gender lenses is important because only women develop gestational diabetes, which predicts premature CVD, yet the field has no systematic approach to studying this relationship. Similarly, only women develop peripartum cardiomyopathy. Research on peripartum cardiomyopathy has led to knowledge about other kinds of cardiomyopathies (e.g., Takotsubo syndrome).

Risk factors for CVD are well-known, and the field has developed prevention methods. The well-established risk factors for CVD in women (e.g., hypertension, dyslipidemia, and obesity) affect both sexes and have only minor differences between women and men. As the Framingham Heart Study investigated men and women separately, the importance of sex differences was known even in the 1950s. Sex-specific risk factors (e.g., PCOS and some pregnancy complications) offer opportunities to identify CVD risk in young women. There are good therapeutics for CVD, but they are only effective when people have access to and take them. Antiplatelet therapies, beta blockers, calcium channel blockers, fibrinolytics, streptokinase, thrombolytics, and ACE Inhibitors are all equally effective in women and men. However, public and clinician awareness that CVD is the top cause of death for women remains low. A significant issue is fat shaming, and some women assume CVD risk is solely linked to weight and delay visits to physicians until having lost weight. An additional challenge is that health care systems are not set up to support diagnoses and treatments that would have a better impact in women. Furthermore, physicians report feeling poorly equipped to diagnose and treat women’s heart disease and welcome better education on this issue. Additionally, delayed care during the pandemic is likely to lead to a new CVD epidemic.

Noting the need for researcher accountability regarding the inclusion of female animals in research on diseases that affect men and women, Dr. Bairey Merz commented on the need to “put more teeth” into policies requiring consideration of SABV. How to reduce avoidable morbidity and mortality and achieve equity in CVD and comorbidities in women, especially diverse women and women under 55, is a key knowledge gap. Dr. Bairey Merz

also discussed the importance of including female subjects in research supporting drug and device development. A problem is that journal editors continue to not require reporting of sex-stratified data in animal or human studies.

Sex-specific thresholds for CVD-related tests are needed. Despite widespread use, cardiac troponin assays lack sex-specific reference values, even commercial assays that indicate 99th-percentile cutoffs or ranges one- to twofold higher in men than women. Men and women have different troponin levels when there is damage to the heart, primarily due to the size of the heart muscle. At-risk women and women having heart attacks can be missed when using the standard, male sex-specific threshold. Women who meet standard (male) threshold have suffered a greater degree of myocardial damage. Application of an ultra-high sensitivity troponin test with sex-specific diagnostic thresholds increased diagnosis of heart attacks in women but not in men because male-standard threshold was already being applied. Stratified thresholds could also improve diagnoses for smaller men with smaller hearts.

Women are under-involved in FDA approval studies for therapies for the most lethal cardiac conditions (e.g., acute coronary syndrome [ACS], coronary artery syndrome, and heart failure). Higher ACS mortality in women persists; despite decreases in overall mortality, mortality rates in women continue to exceed those in men for all age groups. Guideline adherence and improvements in hospital care for women with ACS have not been optimized.

To improve the research and recognition and care for CVD in women, Dr. Bairey Merz recommended the following:

- Emphasize CVD in women as a social justice issue (as the Women's Heart Alliance does in its campaign to raise awareness, drive support for women-focused CVD research and treatment, empower women to take action to fight heart disease, engage doctors in improving diagnosis and treatment, and garner support for policy changes and women's heart disease funding).
- Address funding gaps and imbalances. Ten times more NIH and NGO funds are spent on breast cancer research despite the fact that CVD kills 10 times more women.

Chronic Debilitating Conditions—The Heart of the Matter

Dr. Judith G. Regensteiner, Director of the Ludeman Family Center for Women's Health Research and Professor of Medicine in the Divisions of Internal Medicine and Cardiology at the University of Colorado Anschutz Medical Campus, noted that the list of chronic conditions that cause significant morbidity in women is long (e.g., heart disease, cancer, diabetes, depressive disorders, autoimmune diseases, headache, musculoskeletal disorders, and Alzheimer's disease). Women's health is still understudied and undervalued, as therapeutics are still largely based on men and there are few sex-specific treatment guidelines. In some cases, progress is slowing or being reversed. For example, rates of chronic debilitating conditions (as measured in DALYs) are rising across all ages and causes in women. The impact of chronic debilitating conditions on quality of life is profound, as shown by lower exercise tolerance among women than men with type 2 diabetes.

Many considerations affect chronic debilitating conditions, including intersectionality. Less is known about CDCW of color despite their higher rates. Health disparity-focused studies relevant to diverse populations of women across the life course are needed. Multimorbidity is another important consideration, as having one chronic condition increases the likelihood of others. Environmental, biological, physiological, behavioral, nutritional, social, and aging factors as well as prevention strategies affect multimorbid conditions. Interactions between multimorbid conditions influence symptoms, treatment, and universal outcomes of functional status, quality of life, and death.

CDCW present a complex picture and much remains unknown. More information is needed to provide evidence-based prevention, treatment, and cures. Compelling clinical questions still need to be answered. Dr. Regensteiner identified the following possible solutions and pathways forward:

- Create an infrastructure for research on health of women at NIH. This could take the form of a Common Fund program for women's health or another NIH-wide women's health initiative. In addition, ORWH should become a center (or even an institute) with grant-making authority and work with the National Academy of Sciences to define chronic diseases in women.
- Partner with the national professional and lay communities to promote interprofessional and lay community-facing education on women's health and to raise funds.
- Continue and accelerate building the workforce of women and men M.D. and Ph.D. scientists who will do the critical research.

Dr. Regensteiner commented that NIH provides hope and promise for biomedical progress for the health of women through funding for women's health research. However, the workforce in this area needs to increase across the organization. NIH also has the power to mobilize research efforts on behalf of the health of women and effect change. Scientists need to work within NIH and across the country to perform the research, however complex, that will lead to preventions, treatments, cures, and sex-specific guidelines where needed.

Integrating Biopsychosocial Determinants of Health to Develop and Implement Culturally Sensitive Care for Women

Dr. Cheryl Giscombe, Associate Dean of the PhD Division and Program and the Levine Family Distinguished Scholar in Quality of Life, Health Promotion, and Wellness at the University of North Carolina School of Nursing, opened her presentation with two quotations:

"Of all the forms of inequality, injustice in health is the most shocking and inhumane."

—Dr. Martin Luther King Jr., 1966

"Without mental health there can be no true physical health."

—Dr. Brock Chisholm, first Director-General of the World Health Organization (WHO, 1954)

She remarked that the second quotation is true not only for physical health but also for mental health, emphasizing the role of mental health in health inequities and in women's health as part of a larger system. The Bioecological Systems Theory can inform ways to make women's health research a greater priority. It acknowledges that health is informed by individual factors (e.g., sex and age) and components at the microsystem (e.g., family, school, and peers), exosystem (e.g., neighbors, mass media, and social welfare services), and macrosystem levels (e.g., attitudes and ideologies of the culture). All these are part of the chronosystem, or patterning of individual events and transitions over the life course plus sociohistorical conditions. When planning studies, researchers must consider social and historical factors as well as influences on the current health care situations (i.e., time, condition, and context).

SDOH are crucial, and researchers cannot look at physical health solely through a biological and genetic lens but must also consider psychosocial factors. One of the major SDOH is psychological stress, which affects health behaviors and physiological responses to stress. Both place women at higher risk of chronic debilitating conditions, depending on coping mechanisms and the ways that stress chronically and acutely affects health status. According to HHS, women of color—and African American women in particular—experience disproportionately high rates of morbidity and mortality related to various chronic health conditions. Dr. Giscombe stressed that numerous chronic conditions (e.g., CVD, obesity, lupus, and diabetes) can be prevented, and QOL can be improved through research into their causes and potential interventions. She highlighted several models that inform the prevention of chronic conditions, particularly women of color—such as the Bioecological Model (Bronfenbrenner), Weathering Hypothesis (Geronimus), Allostatic Load (McEwen), and Environmental Affordances Model (Mezuk/Jackson).

Significant mental health disparities exist in the United States, and the current mental health crisis was worsened by the COVID-19 pandemic. Annually, approximately 18 percent of U.S. adults have a diagnosable mental disorder (4% having a serious mental illness). Mental illness is a leading cause of disability in the United States, and these and behavioral disorders account for 13.6 percent of all years of life lost to disability and premature death. Although rates of depression are lower among Black (24.6%) and Hispanic (19.6%) than White (34.7%) individuals, minority groups are more likely to experience risk factors that can cause mental health disorders and persistent illness. Members of these groups are less likely to receive mental health care because of a number of social mechanisms (e.g., stigma about mental health issues, lack of insurance, financial and logistical barriers, and racism or provider bias/cultural microaggressions).

Inaccessibility of high-quality mental health services and disparities in access are critical issues to address when researching and treating chronic health conditions in women. Although effective treatments for mental disorders are available, workforce shortages are a significant barrier to care. Increased collaboration is needed to provide culturally and linguistically appropriate services, and the American Psychological Association has noted the critical role of the federal government in addressing racial and ethnic disparities in mental health status and mental health care. In addition to chronic shortages, the mental health workforce also lacks diversity and the ability to address cultural and gender-relevant factors that will lead people to make healthy choices, engage in the health care system, and have a higher QOL.

Dr. Giscombe remarked that the Environmental Affordances Model illuminates the link between mental health and chronic health conditions. The model suggests that stigma and what is available in the environment are related to healthy coping and behavioral lifestyle engagement. Mental health conditions (including chronic stress) may appear to be medical or chronic physical health conditions when healthy coping strategies and lifestyle behaviors are not available, and stigma impedes seeking care. Research indicates an intersection between race, gender, and SES, and that all three have an influence on how people experience and cope with stress, which can lead to disparities in chronic illnesses. Among African American women, 80 percent are overweight, 50 percent are obese, and 25 percent older than age 55 have diabetes. The field has not yet developed sustainable interventions in these areas, so rates of chronic conditions remain disproportionately high in this population.

Dr. Giscombe reviewed the effects of stress to influence chronic illness on multiple body systems. For example, stress causes increased heart rate and muscle tension along with a release of cortisol into the body to fight the perceived threat in the short term. Long-term stress response involves retention of sodium and water by the kidneys, increased blood volume and blood pressure, protein and fat conversion to glucose/breakdown for energy, increased blood sugar, and suppression of the immune system. To effectively study and understand the influence of stress on the health of women, researchers must use culturally and gender-relevant definitions and operationalizations of stress. Measures should be comprehensive but minimize participant burden.

The influence of stress on chronic health conditions in women is also affected by schemas (mental processes and structures for perceiving and understanding the world), as they can shape coping mechanisms. The Superwoman Schema (SWS) is a sociocultural and historical phenomenon characterized by the perceived obligation to project strength, suppress emotion, resist support or the appearance of vulnerability, the motivation to succeed despite limited resources, and disproportionate caregiving. Although women who hold the SWS have strong survival skills, they also tend to neglect self-care, and this schema may exacerbate stress and stress-related disparities. A related concept is network stress (the stressful experiences of those around an individual), which is often not included in research but is equally as important as individual stress.

After reviewing the stages of the stress response, Dr. Giscombe mentioned the concept of “skin-deep resilience,” apparent coping with underlying physiological effects that may not appear as symptoms until they have become chronic conditions. This phenomenon may apply to the SWS. Research suggests that some aspects of this schema

(e.g., strength) are protective but emotional suppression and prioritization of caregiving are consistently associated with outcomes—such as allostatic load, shorter telomere length, and other outcomes—that are related to adverse chronic illness. The ongoing HARMONY RCT is applying a race and gender lens and an understanding of the importance of social relationships in how women respond to stress to reduce cardiometabolic risk in African American women. Dr. Giscombe recommended that ORWH be made an NIH Institute to support research (such as HARMONY) that will improve chronic health conditions in women.

Beyond Sex as a Biological Variable: Addressing Chronic Debilitating Conditions Among All Women

Dr. Melissa Simon, Vice Chair for Research in the Department of Obstetrics and Gynecology at Northwestern University's Feinberg School of Medicine, pointed out that to ensure that research results are representative of the issue in need of improvement, investigators need to ask the right questions and involve the appropriate people in the relevant underlying structures. This is especially critical when studying chronic health conditions. As noted previously, sex and gender and their intersections with race/ethnicity, SES, stress, and SDOH profoundly influence biology—including cell physiology, metabolism, biological function, symptoms, manifestations of disease, and responses to treatment. SDOH advantage some populations and disadvantage others, including women overall and especially women of color. Disparities are not due solely to SES, as women of color suffer economic and political inequities, with systemic racism as a driving cause.

Dr. Simon remarked that NIH research should represent the U.S. population, 50.6 percent of which is currently female. In addition, approximately 40 percent of the female population is non-White. Another important factor is the aging U.S. population, and the related likelihood that chronic debilitating conditions will become even more prominent in the future. Yet only about 11 percent of the NIH research budget is spent on research focusing on women, and the annual budget of ORWH has remained flat (\$41 to \$45 million) since the office's inception.

In addition to the previously mentioned disparities in chronic debilitating conditions (e.g., mental health), Black women experience more symptoms of menopause than White women despite being substantially underrepresented in clinical trials. Although Black and Latina women bear a disproportionate burden of chronic debilitating conditions (e.g., CVD, diabetes, obesity, osteoarthritis, and PCOS), they are underrepresented in almost every study. There are significant research gaps on preventive services for chronic debilitating conditions and this limits the applicability of guidelines and recommendations. Services for conditions that influence chronic illness, such as violence against women, are underfunded and understudied, as is trauma-informed care.

Dr. Simon commented that the current NIH structure advantages some populations and types of research and actively disadvantages others, such as women's health research. A research- and health-justice framework can help determine the causes of the imbalance. In one approach to rebalancing the research portfolio, NIH examines its structure and considers ways to improve pathways that enhance women's health research. NIH research should aim to protect all populations, including women, by involving them in research and studying topics such as sex and gender differences and intersectionality. Dr. Giscombe discussed the potential inequities in the structure and design of the research pipeline, which can depend on the priorities of the director's office, funding allocations, the scientific workforce, and the staff members developing funding opportunities. Most women's health research at NIH is supported through RFAs. These are "temporary" proposals with specific deadlines and advantage individuals in institutions with many resources and the ability to focus on quickly submitting a large grant proposal and quickly completing the work. In addition, the siloed nature of NIH funding inhibits transdisciplinary and life course research approaches required to advance women's health. The design of current research funding created by the structure of NIH does not align with its Mission to "turn discovery into health." The structure of NIH does not readily allow scientists to comprehensively and adequately address the transdisciplinary and nuanced sex- and gender-specific research needed to address the whole woman (especially women of color) and does not meet the true women's health clinical care needs.

To advance research on the health of women and meet their clinical needs in an equitable way, Dr. Giscombe recommended establishing the following foundational components:

- A definition of chronic debilitating conditions
- RCDC codes that accurately capture women's health conditions (e.g., menopause, menstrual disorders, and PCOS)
- An enhanced workforce dedicated to women's health research at NIH and across the country (which will be challenging when emerging from COVID-19's impact)
- Standing study sections that comprise women's health research experts (including obstetrics/gynecology)
- Standing parent announcements (and other funding opportunities) that receive higher proportions of cutting-edge research that ultimately improves detection, diagnosis, and treatments

In conclusion, Dr. Simon argued that if the field lacks women's health research, then it cannot adequately meet the health care needs of half the population. Therefore, NIH needs to be intentional when addressing research on the health of women. She recommended that NIH increase research funding not just to focus on women but to ensure diversity in the populations of women included (e.g., race/ethnicity and SES). The current NIH structure does not meet the needs of women. Creating a center or an institute that focuses on advancing sex and gender research or women's health research at NIH is a pressing need. Such a structure would confer grant-making authority, augment and enhance and promulgate increased women's health research, especially on the three focal areas discussed at the conference. A center or institute devoted to research on the health of women would encourage the development of the scientific workforce to ensure a steady stream of diverse investigators.

Questions and Answers

Do you see broad application of the models you presented across many diseases, the lifespan, sexes and genders? Dr. Nelson responded that the effects of prevention are immense, but many unanswered questions remain. Research on mechanisms and epidemiology is important, especially for conditions for which we do not have preventive services. The pathway she presented can be used as a framework to focus research and may help to identify methods for applying findings. Perhaps other conditions will be added to the well-woman chart to advance our understanding about how to intervene and at what point in the life cycle interventions can make a difference.

How much can research improve screening without addressing the wide economic and resource gaps for health services? Dr. Nelson responded that the framework she presented is very simplistic. However, researchers can view the whole continuum as having multiple interconnected levels of influence, with some that are better enacted at a population or societal level and others that can be influenced at a health system level. It is difficult to draw a line between them and how they influence prevention. The inclusion of preventive services under the ACA was a good first step but is not enough. To address disparities, funders should provide dedicated resources for research that goes beyond typical research questions (e.g., improving existing tests).

In response to a comment on the importance of autoimmune diseases (75% to 80% of people who have the conditions are women), Dr. Catherino remarked on the need to focus on the big picture. There are many different disease processes that are understudied and require significant research. A National Institute of Women's Health would help set priorities and facilitate collaboration, which is essential. Dr. Regensteiner emphasized the role of advocacy in this process. Dr. Missmer highlighted the importance of breaking down silos in the health care system and funding structures. Although there is a growing body of literature related to the health of women, it is very difficult to fund, report, and translate into clinical care multisystem and multidisciplinary science. Dr. Simon noted

that the National Institute on Minority Health and Health Disparities could provide a model for a potential National Institute of Women's Health, as it has not taken away the importance of disparities research across ICs. In fact, it has helped to promulgate the director's fund and many important RFAs and Pas for advancing more health equity work.

Regarding the absence of standardized data collection or the siloing of data that is collected, Dr. Missmer remarked on the key problem, which is that most studies do not collect data on gynecologic characteristics and menstrual health. Her team created an endometriosis- and uterine fibroid-specific data collection tool that has now been disseminated. The National Cancer Institute Cohort Consortium has a standardized, recommended set of data collection tools, but the field needs one that is inclusive for female-specific and female-dominant traits, disorders, and symptoms. The tools are available but need to be brought together.

A participant commented on the need to get PCOS to be a recognized factor for CVD. Dr. Regensteiner remarked that Dr. Melody Cree-Green has a multidisciplinary clinic for girls with PCOS because mental health and metabolic disorder aspects have been underrecognized. This complex condition needs to be studied holistically or key parts of the problem will go untreated. Dr. Bailey Merz noted that an upcoming National Heart, Lung, and Blood Institute consensus conference will identify knowledge gaps on PCOS. This condition is well-studied among a relatively small number of strong phenotypes that receive clinical care from obstetricians/gynecologists and reproductive endocrinologists. However, longer-term studies of PCOS are poorly phenotyped and lack sufficient rigor. PCOS is not implicated as a potential cause of CVD—which is the knowledge gap. A PCOS-Framingham study is needed.

Dr. Nelson encouraged researchers to go beyond identifying disease risk factors to developing and testing predictive models. Much of clinical risk assessment is based on collections of associations, but the field needs predictive models that are clinically useful. Regarding health equity research, Dr. Giscombe commented on the growing attention to this area. A body of small studies have facilitated the proposal of theoretical frameworks to help generate research questions, but studies with large samples are needed to test subjective and objective outcomes. Such large studies are now possible, and they will allow researchers to test known associations and lay the groundwork for developing models. Future cohort studies should include measurements of race-related and race-specific trauma.

Stagnant Cervical Cancer Mortality

Moderated by Wendy Brewster, M.D., Ph.D., Director of the Center for Women's Health Research, University of North Carolina School of Medicine

During this session, participants explored research gaps and blind spots regarding stagnant cervical cancer survival rates. How can we use the well-established data on the stagnant rates to do something about the problem and use opportunities to realize deliberate, measurable, and impactful change? What are the next steps?

The Future of Cervical Cancer Prevention in the United States: The Realities of Evidence Beyond Innovation

Dr. Cosette Wheeler, Regents' Professor at the University of New Mexico Health Sciences Center and Director of the New Mexico HPV Pap Registry, mentioned that New Mexico has many health disparities, including those related to cervical cancer. HPV causes virtually all cervical cancers. Effective vaccines and screens exist to prevent cervical cancer. WHO has promulgated accelerating the elimination of cervical cancer as a global public health goal. WHO strategies involve a threshold of four cervical cancer cases per 100,000 women-years, and set the following 2030 targets: 90 percent of girls fully vaccinated with the HPV vaccine by the age of 15, 70 percent of women screened using a high-performance test by the age of 35 and again by the age of 45, 90 percent of women with precancer treated, and 90 percent of women with invasive cancer managed. Cervical cancer screening and HPV vaccination represent huge health care investments (i.e., estimates of \$7–8 billion annually for HPV prevention). In the United States, cervical cancer results from a failure to screen women and, to a lesser extent, to follow up with women who

have abnormal results. Inequities associated with poverty, race, ethnicity, education, geographic location (rural or urban), English fluency/acclimation, insurance coverage, and age exist.

The focus of the past decades has been innovating to improve prevention and determining appropriate vaccination dose regimens (e.g., one-, two-, or three-dose regimens). Substantial funds have been dedicated to improving vaccine uptake, but we may have reached a plateau of vaccination coverage in the United States. HPV vaccination uptake correlates with later-life cervical screenings in individual patients. Ultimately, cervical cancer may become a disease of those who are unvaccinated and unscreened. Vaccination coverage varies by state, and coverage correlates with racial, ethnic, socioeconomic, and other demographic factors.

Herd immunity matters. Despite lower than targeted HPV vaccine coverage in the United States, major reductions have been observed in HPV infection. While there was virtually a 100 percent risk for HPV infection among women at age 18 in 1989, by 1996, the risk had dropped for the common cancer-associated forms of HPV to below 20 percent—a spectacular outcome. Likewise, there was a relative reduction in the percentage of HSIL (high-grade Pap test) and CIN2+ (high-grade precancers). Also, among women ages 21 to 25, where vaccine impact is observable, disease declined by year of cervical screening across time (per New Mexico data).

Medical management of cervical cancer is based on three pillars: HPV vaccination (before exposure/infection), screening, and cancer treatment. There is a long sojourn time between HPV infection and development of cervical cancer. Peaks of infection follow onset of sexual initiation (around mean age 18 with some cultural variance), but peaks of cervical cancer occur approximately 25 years later. Because of this long period, we will not have complete data on the efficacy of HPV vaccination for some time.

For several decades, U.S. research and health care resources have focused on efficiencies in screening and triage tests/methods (e.g., co-testing for HPV and with Pap, HPV testing with genotyping, self-sampling, improving colposcopy), but not on population screening coverage. Screening and follow-up management algorithms are complex for clinicians and are different for women by age and risk profiles. Many failures are associated with screening, but the main failures include underscreening, non-participation, and screening less often than recommended. Older women are not followed as often for abnormal cytology. We need major interventions to these problems, including television PSAs, social media, no-cost screening, and electronic surveillance.

Data from New Mexico (which are comparable to national data) show that 64 percent of women with invasive cervical cancer were not screened or had only inadequate screening tests; older women (aged 45–64 years) and women with more advanced cancers were less likely to have been screened, and if screened, were more likely to have a false-negative screening test; women with adenocarcinomas vs. squamous cell cervical cancers were more likely to have had a negative screening test (72% versus 45%); only 32 percent of all cervical cancers were screen-detected; and 9 percent of cancers were diagnosed in women who did not get follow-up with biopsy or treatment recommended after positive screening tests.

Dr. Wheeler's recommendations were (1) to scale up interventions to population- and community- levels (e.g., mass media campaigns to screen, diagnose, and treat cervical cancer); (2) to implement bold interventions to screen and follow-up underserved groups by overcoming the barriers of race, language, poverty, and geography; (3) to embrace innovative models of service delivery (e.g., nontraditional provider delivery, self-sampling at community venues like Costco, Walmart, Target, or community pop-ups); and (4) to invest in building information systems (statewide, regional, national) that transcend health care systems, clinics, providers, and patient locations to support call/recall for screening, diagnosis, and cervical precancer treatment.

Dr. Wheeler concluded by commenting that the United States does not have a health care delivery system. There is no order, integration, or accountability, which creates a barrier to equitable health care. Incremental benefits from our current investments will not likely address inequity. We need to do more.

A Path Forward Toward Accelerating Cervical Cancer Eradication

Dr. Diana S.M. Buist, Senior Investigator and Director of Research and Strategic Partnerships at the Kaiser Permanente Washington Health Research Institute and Professor at the Kaiser Permanente Bernard J. Tyson School of Medicine, outlined her view that it is possible to meet the WHO goals of eliminating cervical cancer deaths in the next century (i.e., 90% of girls fully vaccinated with the HPV vaccine by the age of 15; 70% of women screened using a high-performance test by the age of 35, and again by the age of 45; 90% of women with precancer treated; and 90% of women with invasive cancer managed).

The field can improve important prevention efforts. There is a threefold difference in HPV vaccination rates between high- and low-income nations. Within nations, there are similar disparities dependent on income and location. There is a need to increase vaccination and screening uptake to realize the greatest impact on cervical cancer mortality. A one-size-fits-all approach will not work for all contexts and locations. The global focus must take local contexts into account, and NIH must allocate cervical cancer research funding domestically and internationally. Mandating vaccines is difficult and requires clear public health benefits, a process that is further complicated by the long sojourn time between vaccination/HPV exposure and the development of cervical cancer. The field must re-evaluate vaccine mandates and weigh the expenditures for additional research against the cost of getting shots in arms.

Among 73.2 million U.S. women ages 30–64, 18.3 million are under-screened. There are 14,000 cervical cancers diagnosed annually in the United States, 50 percent of which are in under-screened females. There is a need to increase screening uptake. Patient barriers to screening include knowledge, fear, body image, access, sexual trauma, time, transportation, and others. Our disjointed health care system creates a barrier. Although the ACA helped remove some of those barriers, screening rates have not changed (and may have decreased). Some barriers can be overcome with HPV self-screening/self-collection, the accuracy of which is comparable to that of clinician-performed screenings. According to one study, self-screening increased screening uptake by 50 percent; however, HPV home testing does not allow for cytology from the same sample. Further complications may arise when follow-up colposcopy is needed. Patients responded well and liked the home test, but information and outreach are still needed to convey additional complex messages in an age- and culturally appropriate manners. Dr. Buist noted that she and colleagues are currently testing different outreach strategies and assessing impacts of age-tailored informational materials. Fractured systems of care, in the United States and abroad, present challenges for effective screening and vaccination instructions and follow up.

Dr. Buist recommended (1) learning from COVID-19 (e.g., addressing vaccine hesitancy, considering how complex scientific concepts can be delivered to the public, using self-collection strategies, working at fast speeds); (2) using multilevel, multisite, multimodality, multilingual, and multicultural techniques; (3) investing in training for researchers to communicate to various stakeholders; and (4) reforming the NIH funding paradigm to move faster and use innovative funding mechanisms (e.g., UG3-UH3; NIDDK PAR-20-160).

Improving Treatment for Cervical Cancer: What Can Tumor Biology Tell Us?

Dr. Julie Schwarz, Director of the Cancer Biology Division and Vice Chair for Research in the Department of Radiation Oncology at the Washington University School of Medicine in St. Louis, reviewed NIH research funding on cervical cancer research and how it is underrepresented in the budgets of NCI and other Institutes, Centers, and Offices. Projects involving biology and treatment were particularly underrepresented compared with studies of etiology, prevention, and early detection. The standard of cervical cancer care has not changed much in 30 years: pelvic irradiation and concurrently administered cisplatin chemotherapy. However, radiation therapy techniques have

improved and can deliver high-dose precision radiation (external radiotherapy and internal brachytherapy), but there is still about a 33 percent failure rate in some patients.

As a physician-scientist, Dr. Schwarz uses patient data (tumor and blood samples), functional imaging, tumor biology, model systems (computer models), and new therapies. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) and computed tomography (CT) scans enable clinicians to assess glucose uptake by cervical cancer tumors. FDG is a labeled glucose analog. These scans help clinicians design radiation fields (i.e., targets for radiation therapy) and provide information about the type of tumor by the amount of glucose the tumor takes in (e.g., standard uptake value or SUV = tissue radioactivity concentration/injected dose/patient weight). Some tumors take up a lot of FDG, and some do not, with little relation to tumor volume. Tumors that take up a lot of FDG are correlated with inferior outcomes. How can we use that information to improve outcomes?

About 70 percent of patients have a complete metabolic response to radiation + cisplatin treatment with no cancer at 3 months after treatment and good survival outcomes; 30 percent of patients receiving the same treatment have a partial metabolic response with small residual tumors and intermediate survival outcomes. The biology of tumors should inform personalized treatment. We should not treat all patients the same, which is the current clinical standard.

Dr. Schwarz summarized her history of winning NIH funding over 13 years, beginning with her work as a BIRCWH Scholar and continuing into R01 grants. Part of her team's ongoing work involves radio-resistant cervical cancers that respond to metabolic drugs. The hypothesis is that an oral pill glutaminase inhibitor may help to treat high-energy tumors. Also, she would like to investigate whether genomic biomarkers can inform personalized treatment. Data from The Cancer Genome Atlas (TCGA) could enable more effective personalized treatments. Further, differences in HPV genotypes and gene expression likely have prognostic value for cervical and other types of cancer. New drugs on the market (e.g., senolytics, DNA damage response inhibitors) may help treat certain HPV types. Imaging biomarkers are another area for investigation. Macrophage involvement with tumors with high glucose uptake can lead to treatment resistance.

In conclusion, future directions for research include new treatment targets (e.g., DNA damage response inhibitors, metabolic targets, inflammatory pathways), better model systems (e.g., 2D co-cultures, 3D cultures, patient-derived xenografts, and genetically engineered mouse models), and personalized medicine approaches involving genomics and imaging. The timeline for bringing new approaches to patients could be accelerated with additional funding, a faster path to establish safety for new drug and radiation combinations, and a team science approach involving collaborations across centers domestically and globally. Funding opportunities should include training grants to support research workforce development in gynecologic oncology and radiation oncology (e.g., NIH K12 BIRCWH), group grants to improve innovation in treatment approaches for cervical cancer (e.g., Specialized Programs of Research Excellence [SPORE] and P- and U-level grants), and increased R01-level funding for investigators working on tumor biology and treatment. A gynecologic-oncology-specific study section could prioritize needs for cervical cancer treatment innovation. Her suggestions for RFAs included the following:

1. Improving preclinical models for treatment assessment in HPV-associated cancers
2. Novel imaging and genomic biomarkers for outcome prediction in cervical cancer
3. Optimizing technology to improve outcomes in resource poor settings
4. Novel targeted therapy approaches with and without radiation in cervical cancer (e.g., DNA damage response inhibitors, metabolic therapy [drugs and diet], immunotherapy)

5. Personalized treatment to improve outcomes in cervical cancer

Translating Science into Improved Patient Care for Women with Cervical Cancer

Dr. Janet Rader, Jack A. and Elaine D. Klieger Professor and Chair of the Department of Obstetrics and Gynecology at the Medical College of Wisconsin, observed that invasive surgical cancer can be prevented by vaccine, but judging by COVID-19's example, we can predict that vaccination and prevention will not eliminate cervical cancer entirely. Opportunities to improve treatment of cervical cancer include better adherence to established treatment standards, effective chemotherapy, use of biomarkers to guide therapy, and a diverse workforce. The potential years of life lost because of cervical cancers equals 20.7–23.7 years per patient. Less than 50 percent of women with cervical cancer in the National Comprehensive Cancer Network (NCCN) receive guideline treatment due to misalignment of money to quality treatment, fragmented care, inadequate treatment leading to stagnant survival rates, and a lack of skilled brachytherapists. The guideline treatment—external beam radiation, brachytherapy, and chemotherapy—is effective.

Dr. Rader called for expanding the science to study advanced and recurrent cervical cancer and highlighted two studies involving patients with cervical cancer with a mean age of 50. Most women in the study were dead within 5 years. Response rates to current chemotherapy treatments are low. Identification of different cancer driver genes is important, as there are different growth-regulating pathways. Not all cervical cancers are the same; differences related to different driver genes and different HPV types exist.

Funding has been dedicated to prevention and vaccine development/administration. Less funding has been dedicated to cervical cancer itself. NIH work has expanded the cervical cancer dataset and shared it through TCGA and the HIV+ Tumor Molecular Characterization Project (HTMCP). Hundreds of articles were published based on the data emerging from these studies.

Following the science means following the virus. HPV integration affects the human genome. Better elucidation of these mechanisms and interactions could inform disease treatment and identify novel cervical cancer target genes for treatment. Researchers understand the expression of some of these genes, but we need to learn about other genes. The field also must diversify our workforce. The roles of clinical research professionals (CRPs) have expanded over recent years. CRPs now work more directly with PIs. We need to recruit and train ethnically, racially, and linguistically diverse CRPs to represent the communities they serve. In conclusion, the field can improve cervical cancer survival rates by expanding the science, encouraging adherence to treatment guidelines, mobilizing resources, expanding trial access, and developing a diverse, well-trained workforce.

The Future of Clinical Research in Cervical Cancer Treatment

Dr. Charles Kunos, Medical Director of the University of Kentucky Markey Cancer Center's Clinical Research Office, a radiation oncologist, stressed the following topics related to the national priority of uterine cervix cancer treatment in his presentation:

1. The advanced-stage uterine cervix cancer survival rate has not risen in two decades.
2. Radiotherapy use drives survival for advanced-stage disease.
3. Intensifying regional treatment improves survival.
4. Identifying women at risk for distant disease relapse impacts survival outcome.

Radiation therapy is effective, improves survival, and provides palliation. Advances in radiotherapy have placed this treatment on the leading edge of personalized medical oncology. However, because, clinically, genetically, and molecularly, cervical cancer is heterogeneous, personalized medical therapies are difficult to develop. Survival rates

have remained consistent over two decades, but research and clinical opportunities exist for improvement. Upon disease presentation, 52 percent of cervical cancer has spread to lymph nodes or distantly metastasized to other organs. When localized, patients have a 92 percent 5-year survival rate; regional spread cancer has a 58 percent 5-year survival rate; and distantly spread cancer has an 18 percent 5-year survival rate.

Dr. Kunos reviewed the geographic distribution of cervical cancer incidence, which is higher in southern/Appalachian states and Nevada. About 4 in 11 women residing in Appalachian counties diagnosed with cervical cancer die within 1 year of diagnosis. Research spending is generally lower in states with high incidences of cervical cancer. Kentucky has the highest cervical cancer mortality rates in the contiguous United States, upwards of three times national averages in some counties (i.e., Appalachian counties). HPV31 linked to adenocarcinomas of the cervix drives mortality in this geographic region.

Standard of care now involves daily weekday teletherapy of radiation treatment for 5 weeks. With further study and innovation, we may be able to reduce the number of treatments required. Brachytherapy, which many consider to be the most important component of cervical cancer radiation treatment, involves five treatments commonly. Once-weekly cisplatin chemotherapy is critical to treatment of cervical cancer. However, whether cisplatin is the best agent is in question, and new agents are being tested with and without cisplatin. Monthly radiopharmaceutical therapy is currently being tested; this involves radioactive drugs with cell-targeting capacity to destroy tumors while leaving other tissues intact and could be used in concurrent and adjuvant settings.

Intensifying treatment at the region of the cancer could improve survival rates with surgery, radiotherapy (e.g., external radiation, brachytherapy, radiopharmaceuticals), and antibody-drug conjugate therapies. NCI-based research has and will continue to study antibody-drug conjugate therapies for many types of cancer and has resulted in three FDA-approved drugs. Such a drug for cervical cancer may be forthcoming. Also, future studies may explore personalized dose intensification and personalized schedule intensification. Strategies involving more intense frontline therapies could be used for low-resource settings and patients. Laboratory assays of shed peripheral blood may also provide information from deoxyribonucleotides from HPV DNA and dead circulating tumor cells. Such assays could provide information about therapeutic success and risk of relapse. Pre- and posttherapy FDG-PET/CT scans (as discussed by Dr. Schwarz) may be useful as well. Circulating blood may provide other clues about metastasis and other complications. Dr. Kunos commented that socioeconomic factors affect clinical trial participation and cervical cancer outcomes. These factors should inform future clinical trial designs and other public health initiatives.

NCI Clinical Trials in Gynecologic Cancer: A Changing Landscape

Dr. Robert Mannel, Director of the Stephenson Cancer Center at the University of Oklahoma College of Medicine, reviewed the history of the NCI National Clinical Trials Network (NCTN) to provide some context to efforts related to cervical cancer. In 1971, the Gynecology Oncology Group (GOG) was founded with support from NCI with 11 member institutions. Over its first 40 years, GOG expanded to include 300 member institutions; gynecologic, radiation, and medical oncology; and almost 92,000 patient participants, including almost 41,000 participants in phase III clinical trials. There were 128 trials (including 26 gynecologic trials), which overall showed survival favoring the experimental arm and great cost-effectiveness.

In 2010, the IOM analyzed the National Cancer Clinical Trials System and made several recommendations. One recommendation resulted in consolidating the system's nine adult cooperative groups into four groups. As a result, GOG joined with the Radiation Therapy Oncology Group and the NSABP (National Surgical Adjuvant Breast and Bowel Project) Foundation to form NRG Oncology. This reorganization resulted in less funding and decreases in participation in gynecologic cancer clinical trials (until 2016). The GOG Foundation introduced a new concept to partner with industry partners. The resulting revitalization and new collaborations pushed the science forward, increased clinical trial participation (though not yet to 2011 levels), and mentored young investigators.

Dr. Mannel concluded by listing some opportunities for additional NCI involvement in gynecologic cancer clinical trials:

- Prioritize clinical research in gynecologic cancers on par with other disease sites.
- Facilitate international collaboration—especially with new drugs and in rare diseases.
- Facilitate real-time data sharing.
- Simplify layers of review to allow streamlined timelines.
- Emphasize feasible research on interventions likely to be practice-changing.
- Support critical surgical, imaging, and radiation therapy studies—trials that will not be funded by industry.
- Restructure funding to support trial costs adequately (current funding structure covers only about 50 percent of costs).

The Urgent Need for Crosscutting Anti-Racist Approaches to Cancer Disparities Research

Dr. Kemi Doll, Associate Professor in the Department of Obstetrics and Gynecology at the University of Washington and Adjunct Associate Professor in the Department of Health Systems and Population Health at the University of Washington School of Public Health, asked the audience to question and reframe health and cancer to address minoritized women's outcomes. Racial and ethnic disparities in cervical cancer mortality in the United States are large and unacceptable. Similar disparities exist for endometrial cancer, which is four times more common than cervical cancer and is the only cancer in the United States that is increasing in incidence. Black women with endometrial cancer have 90 percent higher 5-year mortality rates than White and other groups of women with endometrial cancer.

Racial disparities in cancer outcomes are not a surprise. They are the default outcome of current biomedical research and care delivery systems. The fundamental cause theory states that race and socioeconomic status are linked to health outcomes in general and cancer-related mortality specifically. The disparities exist because of limited access to five key societal resources: knowledge, money, power, prestige, and social connections. In sum, social position largely determines the treatability of a condition.

Dr. Doll presented a four-phase model showing how social position affects treatability of a given condition. Phase 1 involves natural inequalities resulting from limited knowledge about risks and effective treatments. In phase 1, mortality rates tend to be stable. Phase 2 sees increasing inequalities resulting from an unequal diffusion of innovations, risk reduction, and improved treatment strategies. In phase 2, mortality rates decrease, but disparities increase. Phase 3 involves reducing inequalities with greater access to new knowledge and innovation. In phase 3, both mortality rates and disparities decrease. Phase 4 sees reduced mortality with widely available prevention and treatment. In phase 4, mortality and disparities are minimal or absent.

Treatability increases because of federally funded biomedical research, which helps us move from phase 1 to phase 2. However, seldom do equity concerns inform this stage of biomedical research. We often have largely White clinical trial cohorts. Equity science expertise does not routinely inform trial design or new biomedical interventions. Disparities persist into phase 3 because of the disproportionate lack of federally funded equity research. Equity work can disrupt these racist trends by providing the five key resources to minoritized groups. The default approach does not work and results in the underfunding of women's health research, the underfunding and exclusion of

researchers who are members of underrepresented racial and ethnic groups (data support this conclusion), misaligned incentives, exclusion of community input, and exclusion of research on racism and societal structures.

Dr. Doll suggested several anti-racist approaches to disrupt this system and improve equity in biomedical research on diseases like gynecological cancers. First, we need to recognize that the default structure of cancer research creates and exacerbates cancer inequities for marginalized women. Second, we need to embrace cross-cutting approaches that acknowledge how the power and complexities of racism influence health (e.g., early detection, clinical trial design, funding practices, treatment environment, treatment completion, Black workforce). Third, we need to align funding to incentivize the study of unjust creation, dissemination, and delivery of cancer research knowledge. Fourth, we must prioritize equity research grounded in theories and frameworks on how race, gender, and health operate in our society. Fifth, we should embrace a goal of NIH-funded research as a tool to disrupt the default outcome of marginalized women as the secondary priority.

Dr. Doll proposed a race-conscious approach to women's cancer research as one that (1) recognizes that the default structure of cancer research creates and exacerbates cancer inequities for marginalized women; (2) embraces cross-cutting approaches that acknowledge the power and complexities of how racism influences health; (3) aligns funding to incentivize the study of the unjust creation, dissemination, and delivery of cancer research knowledge; (4) prioritizes equity research grounded in theories on how race, gender, and health operate in our society; and (5) embraces a goal of NIH-funded research as a tool to disrupt the default outcome of marginalized women as the secondary priority.

Dr. Doll concluded by suggesting some RFAs for gynecologic cancer equity, including these:

- Quantitative and qualitative evaluation of bias and exclusion in biomedical cancer research
- Development of multilevel approaches to equitable representation of marginalized populations in cancer clinical trials
- Impact of structural and interpersonal racism on outcomes in the cancer care continuum
- Life course approaches to evaluate gynecologic cancer disparities among Black and Native women
- Interdisciplinary structural interventions to overcome expected inequity in clinical trial participation

Clinical Trials in Cervical Cancer: Can They Be All That We Want Them to Be?

Dr. Charles "Trey" A. Leath III, Director of the Division of Gynecologic Oncology at the University of Alabama at Birmingham, noted that cervical cancer is a global problem representing over 3 percent of cancer deaths in women. It is the leading cancer in women in sub-Saharan Africa and other areas. While there is a decreased incidence of cervical cancer in the United States and HPV vaccines have been introduced, African American women have a higher baseline risk of this disease, and mortality rates have remained constant. Cervical cancer is more common among URM and is clustered in areas of the United States. NCI-designated comprehensive centers and NCCN are in most, but not all, states with higher rates of cervical cancer and are active participants in cervical cancer research.

For locally advanced cervical cancer (LACC), whole pelvic radiation and brachytherapy was the standard of care until 1999, at which time five practice-changing publications urged practitioners to combine chemotherapy with both forms of radiation therapy. This revolutionary work was NCI-funded and resulted in new, lifesaving guidelines. Such guidelines are important, but they must be implemented in the clinic. Currently, only about half of women with cervical cancer receive the standard of care for LACC. Many groups of women (e.g., older women, women with public insurance, Black women) do not routinely receive the standard of care treatment, and these demographics

are predictive of negative outcomes. Dr. Leath explained that data from Alabama indicate that patient distance from a comprehensive cancer center (CCC) affects cervical cancer outcomes, with lower overall survival for women living more than 100 miles from a CCC. Other outcome predictors include race, ethnicity, geography (e.g., rural, urban, Alabama's "Black belt"), distance to an ACOG provider, and insurance status.

Dr. Leath concluded by making the following points. Two recent FDA approvals for cervical cancer treatment (tisotumab vedotin-tftv and pembrolizumab combination) were developed outside of NCI mechanisms. NCI-sponsored research has had a substantial impact on women with cervical cancer. Novel approaches may be needed in different geographical regions. More recent paradigm-shifting trials have been performed outside of the NCI. While therapeutic advances remain important, novel approaches to improve primary vaccination and screening should not be forgotten. Clinical trials can be improved by enrolling representative populations, pursuing research on enrolling people who are in underserved racial and ethnic groups, and using "real-world" designs.

Questions and Answers

Dr. Brewster posed questions from the audience and from the conference chat room, and later asked panelists to name one top priority for NIH relevant to cervical cancer. In response to a question about the funds needed to "meet patients where they are" instead of waiting for them to show up in our clinics and laboratories, Dr. Wheeler answered that it would take a huge change for a population-level study that cannot be accomplished with R, U, or P awards. Investigators must reinvent what it would take to do mass interventions and to have surveillance systems that could enable evaluation of intervention on a broad scale. Dr. Buist added that time is of the essence. Education around vaccines is needed. Issues around HPV, a virus that causes cancer, are not well understood. There is a lack of public understanding that HPV vaccines can prevent cervical cancer.

Regarding cervical cancer screening, Dr. Buist emphasized that education is key, particularly for high-risk groups. The field needs to educate and encourage regular screening. Self-testing is another important avenue to pursue. Providing options for screening is the best strategy for screening uptake. Dr. Brewster commented that increased use of telehealth appointments for contraception and treatment of menopausal symptoms may result in decreased Pap testing. She asked what type of RFA could stimulate research into diagnosis and treatment of subtypes of cervical cancer. Dr. Schwarz replied that the interest is already there and that many people would apply. Cervical cancer could serve as a model system for HPV-associated cancers. Microtumor environments have subtle differences. Some cervical cancers respond well to treatment, while others do not. More research is needed, and access to good samples is crucial to such work. Deep genomic sequencing is costly, and because this is sometimes considered "discovery" rather than hypothesis-driven research, it can be difficult to secure funding. Dr. Rader agreed with Dr. Schwarz. Cervical cancer is different from other forms of cancer. We need to treat it like a cancer, but there have been few opportunities to study it as a cancer.

Dr. Brewster asked about equity and inclusion in training scientists. Dr. Rader mentioned the SPARK program. The workforce for CRPs has expanded. Being a CRP can be a great, well-paying job for students as they transition to graduate school. Early grad students could be an untapped workforce to help enroll patients in clinical trials. Dr. Brewster asked about patients who do not receive appropriate brachytherapy and other challenges of care. How do we incentivize creation of different models of care that "meet patients where they are?" Dr. Kunos remarked that doing so remains challenging. Incentives can be offered to institutions or patients. In some areas like Kentucky, it is difficult to overcome local attitudes, choices, deep-rooted trust issues, faith issues, and faith in local practitioners (i.e., some patients trust their GP over an unfamiliar, centralized treatment center). Dr. Brewster noted that the field does not know how to meet them where they are. What are the models that work? Dr. Doll cited decades of work on enrolling URMs in trials (by Lisa Cooper, Jonathan Jackson, and others). These studies show that engagement with intervention improves when design and execution are done in partnership with community. Researchers should not think of recruitment at the end of developing a clinical trial. Recruitment needs to be part of study design

and development. Development must be done in partnership with the community. Evidence-based recruitment strategies exist. Researchers need funding to pay community advisers and other outreach/retention personnel to achieve diversity and inclusion in clinical trials. Adding gynecologic cancers on top of the challenge of recruiting people from underrepresented racial and ethnic groups adds complication, and the study of this complication is nascent.

Dr. Brewster asked what is needed from NCI to add equity science expertise to clinical trials and to the development of treatment models practical for some of the women dying from the disease. Dr. Mannel responded that researchers should study the problem through multiple lenses. From a clinical trial perspective, we should follow Dr. Doll's recommendations. Dr. Mannel's organization in Oklahoma has managed to get good participation in clinical trials from members of poor, minoritized, Native, and rural communities. They have done so with community advisory boards, outreach programs, financial and patient care navigators, social workers, and cultural sensitivity training for research staff. These things require funding, which Dr. Mannel raised through philanthropy, but Federal/NCI funds could advance these efforts further and help improve partnerships with underserved communities. Dr. Temkin added that the cancer center in Oklahoma has been exceptional in terms of its recruitment efforts and outcomes. Dr. Brewster conveyed an audience question about how the United States compares to other nations in terms of cervical cancer outcomes. Dr. Doll did not have that information.

In response to Dr. Brewster's request to panelists to share their No. 1 request from NIH, Dr. Leath responded that the field has large pieces of the solution already: screening, vaccination, and ensuring brachytherapy when needed. We need to get out to where the patients are. Rather than more research, we need more outreach to ensure that standard of care is delivered to all. Lay navigators are an effective approach. Dr. Leath also recommended standardizing HPV vaccination and hepatitis B vaccination at birth. Dr. Schwarz recommended pursuing personalized medicine, clinical assays of biopsies, and genomics data sharing. Dr. Rader suggested expanding research on invasive cervical cancer with new technologies and new models similar to other cancers.

Closing Session

Innovation Through the Lens of Women's Health Research: A Rising Tide Lifts All Boats

Dr. Linda Griffith, Professor of Biological and Mechanical Engineering and MacVicar Fellow at the Massachusetts Institute of Technology (MIT), stated that technology innovation is an exciting area that influences health. Dr. Griffith focused on innovation in how problems are defined. Great engineers decide what should be built and the design principles involved in using new areas of science to solve societal problems. She framed this innovation analysis around endometriosis—a chronic inflammatory disease that often begins during adolescence and affects about 10 percent of women. Endometriosis often requires years to be diagnosed accurately, causes debilitating pain, and can be associated with fertility problems. Current treatments manipulate hormones, and many patients do not respond to these therapies so must have multiple surgeries. Women with endometriosis who do not have access to high-quality care suffer.

Reviewing a quotation from a 30-year-old endocrinology textbook that described a “typical” endometriosis patient as “intelligent, egocentric, overanxious, and a perfectionist,” Dr. Griffith noted the bias in the diagnosis. Such a bias possibly exists today. She shared her own experiences of being a patient (diagnosed in 1988) as well as that of her niece, who sought care for symptoms at age 15 in 2006 and was told that she was making up problems to avoid school. Problems with accurate endometriosis diagnosis have persisted, even among patients with resources and access who seek care. In addition, the prevalence of endometriosis is greatly underestimated, and morbidity is poorly understood—therefore, the DALY cannot yet be determined.

In Dr. Griffith's view, such issues with diagnosis are related to gaps in funding on women's health research—specifically that typical menstruation and uterine function are still not well understood. In the United States, there

are more than 500,000 hysterectomies annually, and one-third of women have had one by age 60. Yet all side effects of hysterectomy and its impact on health in later life are not known. For example, hysterectomy is associated with increases in the risk for CVD and other illnesses, which may be related to poor management of diseases that lead to this procedure.

A major undiscussed question is the effect of the excess morbidity due to gynecological and female-skewed diseases on the “women’s pay gap.” Data indicate that women miss more work because they are sick (and not only because a family member is ill). Although more research is needed, a [recent analysis](#) suggests an underfunding of gynecologic conditions research at NIH. Dr. Griffith remarked that research on infertility and pregnancy, which are funded relatively well, is not the same as gynecology. She noted that there are many prevalent gynecologic conditions (e.g., adenomyosis) with very little research. In addition, the funding for research on women’s health is relatively unstable, with an unusually high reliance on special programs for major grants. This area of research also relies heavily on special programs (e.g., FOAs) that do not provide much time for response and cannot be resubmitted or renewed. Unsolicited, investigator-initiated proposals are preferable (from an investigator’s viewpoint and for establishing a robust research community) because there is more time to prepare an application, obtain feedback from a program officer, and resubmit. Other problems faced by gynecologic research include the lack of experienced reviewers on standing review panels and a paucity of collaborative funding models (which are needed because the relevant conditions are often comorbid).

Dr. Griffith argued that an outside analysis is essential for this multifaceted problem. Acknowledging Pierre Azoulay (MIT) and Rem Koning (Harvard Business School), she mentioned a number of confidential outside analyses performed for high-profile Government agencies (e.g., the U.S. Census Bureau and Internal Revenue Service) through the creation of secure data enclaves. Such an analysis might be performed at no cost by the National Science Foundation or similar organization. A key factor in data-sharing agreements is that data are shared, not only outcomes. This means that an analysis could provide valuable information—such as who applied, the content of the application, confidential reviewers’ score data, and cases of significantly discordant scores. It is important to consider how expertise and bias influence proposal review (Dr. Griffith cited the work of Danielle Li at MIT) and how new modes of funding research might shift new investigators into gynecology or women’s health (see work by Kyle Myers at the Harvard Business School). Dr. Griffith remarked that medicine embraces innovations, such as artificial intelligence (AI) and machine learning, and gynecology and women’s health should do the same (as in the prediction of breast cancer from mammograms). Similarly, AI may help spur advances in image-guided diagnosis and prognosis of adenomyosis, and there is currently no funding for infrastructure (e.g., relevant data sets) to support such work. Genomic insights should drive a mechanistic understanding of dynamic signaling networks as well as targeted drug discovery, and it is important to note that many gynecological diseases are related to multiple genes.

Dr. Griffith proposed the hypothesis that different molecular mechanisms of disease can classify endometriosis and adenomyosis patients and guide treatment accordingly (as in cancer). She highlighted that inflammation and invasion pathways are linked to highly complex molecular networks of cell-to-cell immune-signaling proteins (e.g., cytokines, chemokines, and growth factors) and enzymes. Studying these networks has led to the discovery of a non-hormonal target, c-Jun N-terminal kinase (JNK), and inhibition of this signaling pathway has reversed endometriosis in animal models without successful translation to humans. Dr. Griffith argued that better human models are needed for endometriosis lesions, and her team is modeling the birth of lesions and building microvascular networks with tissue engineering and organ-on-chips approaches. She stressed that the field must move beyond animal models—especially for chronic inflammatory diseases—and cited the human on a chip with protocols for sex dimorphism analysis as an example of women’s health research driving innovation for all.

The emergence of biological engineering, a new discipline, offers a model for NIH-wide collaboration. Dr. Griffith described how this discipline emerged over 10 years and noted that she hoped this example would spur discussion.

She remarked that research—which involves learning a way of thinking—and teaching are intimately linked. In her view, education must drive changes in research. Dr. Griffith commented on the urgent need for workforce development in gynecology. The current lack of a robust clinician-scientist research culture in gynecology affects the difficulty of creating evidence-based practice guidelines. In her experience, young women in STEMM have a strong interest in gynecology research, yet funding uncertainties in this field give one pause. Commenting that gynecology is an example of women's health research that needs a significant change in inter-IC collaboration, which will require structural changes. There is a need for extensive collaboration across ICs to address systemic and comorbid conditions in women—from childhood through menopause—with far more resources than are now available. Biological engineering concepts should be disseminated more broadly across NIH, with gynecology as a new collaborative model. However, it may be challenging to build collaborative projects across ICs, as each has its own budget and agenda. Dr. Griffith suggested that NIH pilot a new mode of collaboration with an NICHD Gynecology Center (or other means of dedicated funding for gynecology). An NIH institute should take the lead rather than the Office of the Director or ORWH.

Questions and Answers

In response to a question about attracting more people to research on women's health, Dr. Griffith remarked that there is a great deal of interest among young women engineers, but a translation of scientific language for individuals outside health fields is needed. A lack of funding is a significant barrier. Dr. Carnes and Dr. Bird both remarked that advances cannot be made until topics such as menstruation can be discussed freely. Dr. Jenkins mentioned the problem that keyword searches of research and publication databases are not really accurate when it comes to sex and gender. This problem goes beyond conflating those terms to a lack of tools and infrastructure. She added that when making changes in a field, people need to be intentional, establish and monitor tangible metrics, and create a plan. Dr. Carnes noted the need to be mindful that gender and status are conflated and to address root causes. Dr. Bird commented that stakeholders must be engaged in generating better science. It is important to distinguish between lack of gender differences in an outcome and a lack of research on gender differences in that area.

Closing Remarks

Many speakers thanked ORWH for the opportunity to present and provide feedback at the conference. Dr. Temkin thanked attendees, speakers, and staff members. Since the congressional request was issued, many people—including representatives from ICs, Federal partners, the advisory committees, Dr. Clayton and other ORWH staff members—have contributed to the development of the conference agenda and supporting NIH portfolio analyses to determine how to address public health needs in the three focus areas. Dr. Temkin also acknowledged the 248 members of the public who commented thoughtfully on the Request for Information and offered their personal experiences. The conference aligns with the Trans-NIH Strategic Plan for Women's Health Research.

Dr. Noursi thanked Dr. Regensteiner and Dr. Temkin, who served as co-chairs for the conference, speakers, staff, members of the working groups and planning committee, and all attendees. Dr. Clayton also expressed gratitude to the amazing team that organized the conference, as well as stakeholders at NIH, HHS, and the public. The day was special, with fantastic and thought-provoking discussions. She adjourned the conference.

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