

55th Meeting of the National Institutes of Health (NIH)
Advisory Committee on Research on Women's Health (ACRWH)
Office of Research on Women's Health (ORWH)
Bethesda, MD
October 21, 2021

Members Present

Roger B. Fillingim, Ph.D.
Stacie Geller, Ph.D.
Scott Hultgren, Ph.D.
Reshma Jagsi, M.D., D.Phil.
Sabra Klein, Ph.D.
Ana Langer, M.D.
Margaret M. McCarthy, Ph.D.
Judy Regensteiner, Ph.D.
Michelle Robinson, D.M.D.
Yoel Sadovsky, M.D.
Melissa Simon, M.D.
Kimberly J. Templeton, M.D.

Other Attendees

Garnet Anderson, Ph.D.
Irene Aninye, Ph.D.
Wendy R. Brewster, M.D., Ph.D.

Haywood Brown, M.D.
Amanda Bruegl, M.D.

ORWH Leadership Present

Janine Clayton, M.D., FARVO, Director
Samia Noursi, Ph.D., Associate Director for
Science Policy, Planning, and Analysis
Sarah Temkin, M.D., Associate Director, Clinical
Research

Other NIH Leadership Present

Norman E. Sharpless, M.D., Director,
National Cancer Institute (NCI)
Douglas R. Lowy, M.D., Principal Deputy
Director, NCI
Elise Kohn, M.D., Head Gynecologic Cancer
Therapeutics, NCI

Call to Order

Samia Noursi, Ph.D., ACRWH Executive Secretary and ORWH Associate Director, Science Policy, Planning and Analysis, called the online meeting to order at 9:30 a.m. She introduced new ACRWH member Melissa Simon, M.D., Feinberg School of Medicine, Northwestern University. Committee members introduced themselves and approved the minutes of the 53rd ACRWH meeting held on April 14, 2021.

ORWH Director's Report

Dr. Noursi introduced Janine A. Clayton, M.D., FARVO, Director, ORWH, who delivered the Director's Report:

COVID-19. The pandemic is exacerbating health disparities: A study from the NIH intramural research program (2021) found that non-COVID-19 excess deaths have disproportionately affected Black, American Indians/American Native (AI/AN), and Latino persons. These findings may portend a further widening in health disparities.

The U.S. Centers for Disease Control and Prevention (CDC) is urging pregnant people to get vaccinated, citing higher risks of hospitalization, death, and adverse pregnancy outcomes. Results from the Gestational Research Assessments for COVID-19 (GRAVID) study funded by NIH's *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) indicated that pregnant women who experienced severe symptoms of COVID-19 had a higher risk of complications during and after pregnancy.

ORWH has updated its [Women Science, and the Impact of COVID-19](#) webpage with new resources, including funding opportunities for the GRAVID study and Applications to Investigate COVID-19 Vaccination and Menstruation (NOT-HD-21-035) that ORWH has issued in partnership with NICHD.

NIH has launched a series of Research Opportunity Announcements to learn more about how SARS-CoV-2 may cause long-term effects and to develop ways to treat or prevent them. The Researching COVID to Enhance Recovery (RECOVER) Initiative is applying a meta-cohort study design to pool participants; each study contributes distinct types of knowledge to advance understanding of post-acute sequelae of SARS-CoV-2 (PASC).

Scientific Collaborations. New activities to support clinical trial diversity and equity include the NIH-supported National Academy of Science, Engineering and Medicine (NASEM)'s Overcoming Barriers to Diversifying Clinical Trials: Third Public Workshop held on September 13, 2021, that will inform a consensus study report on promoting clinical trial equity and diversity (expected May 2022). Francis Collins, M.D., Ph.D., NIH Director, has re-established the NIH Clinical Trial Stewardship Task Force. Finally, the Diversity, Equity, and Inclusion Working Group is reviewing implementation progress of prior NIH policies focused on enhancing diversity and inclusion in clinical research, assessing effectiveness in fulfilling stated policy goals, and identifying areas of opportunity for further improvement.

Sex and Gender. Two new funding opportunities at NIH--a 2021 Notice of Special Interest (NOSI) from the National Institute on Drugs (NIDA) titled Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (NOT-DA-21-012) and a 2022 reissuance of NOSI: Sex and Gender Differences in Alzheimer's Disease (AD) and AD-Related Dementias (NOT-AG-20-038) by the National Institute on Aging (NIA)--reflect a growing body of research reporting outcomes that vary by sex. The NIA FOA moves beyond Sex as a Biological Variable (SABV) policy by seeking applications that have statistical power to detect sex and/or gender differences in outcomes. ORWH is participating in both NOSIs.

Maternal Morbidity and Mortality (MMM). ORWH is working to shape the federal response to the MMM crisis through Dr. Clayton's participation on the White House Interagency Policy Committee; the Agency Priority Goal--Maternal Health Working Group; and the NIH Maternal Morbidity Task Force.

Implementing a Maternal Health and Pregnancy Outcomes Vision for Everyone (IMPROVE) is an NIH-wide program funding interdisciplinary research in foundational biology, behavioral, and sociocultural science. It seeks to reduce preventable causes of maternal deaths; improve health before, during, and after delivery; focus on cardiovascular disease (CVD), infection, immunity, and contributing health conditions; and investigate obesity and inflammation as drivers of maternal morbidity in COVID-19. It is also designed to promote health equity by evaluating structural and health care system issues affecting populations with high rates of maternal deaths and complications as well as developing community partnerships to assess vulnerabilities and implement interventions. In Fiscal Year 2021, 22 awards totaling \$10.4 million were made with participation from 11 Institutes/Centers/Offices (ICOs).

In 2021, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) issued an announcement for Small Business Initiatives for Innovative Diagnostic Technology for Improving Outcomes for Maternal Health (NOT-EB-21-001) with participation from ORWH and other ICOs. NIBIB will also publish a cash prize competition announcement to solicit entries for the [NIH Technology Accelerator Challenge \(NTAC\): Maternal Health](#) to spur development of low-cost, point-of-care molecular, cellular, and/or metabolic sensing and diagnostic technologies to guide rapid clinical decision-making and improve patient outcomes.

ORWH is working with the National Institute on General Medical Sciences (NIGMS) to expand research on women's health across the lifespan through the Centers of Biomedical Research Excellence (COBRE)

program that advances research capacity in Institutional Development Awards (IDeA) States, i.e., those states that have historically received low levels of NIH funding and where women and children often have less access to health care and suffer from poorer outcomes. Another development that is part of the NIH-wide initiative on MMM is a new Pathways to Prevention (P2P) project from the NIH Office of Disease Prevention with participation from ORWH and several ICs. ORWH has redesigned its [MMM web portal](#) that now also features information on how each IC is addressing maternal health within its mission.

Cervical Cancer. ORWH is partnering with the National Cancer Institute (NCI) on the Department of Health and Human Services (HHS) Interagency Cervical Cancer Collaborative and is supporting a series of roundtables in 2022 on improving cervical cancer prevention and care. This effort will culminate in the development of a provider-facing web-based toolkit to support adherence to American Society for Colposcopy and Cervical Pathology (ASCCP) Risk-Based Management Consensus Guidelines and will increase access to high-quality cervical health services in community health centers and other safety net settings of care.

Advancing NIH Research on the Health of Women: A 2021 Conference. On October 20, 2021, ORWH sponsored this conference at the request of Congress, focusing on MMM; chronic debilitating conditions in women (CDCW); and cervical cancer survival rates. The goal of today's ACRWH meeting is to identify research priorities in these three areas and to make recommendations for a report to Congress.

Farewell to Dr. Collins. Long-time NIH Director Dr. Collins has announced his resignation. There has been tremendous growth in women's health research under his leadership, as well as a dramatic increase in leadership by women leadership at NIH during his tenure. He will be sorely missed.

Dr. Clayton introduced Dr. Sarah Temkin, M.D., Associate Director, Clinical Research, ORWH and Co-Chair of the "Advancing NIH Research on the Health of Women" conference, who moderated the conference review and discussion.

Maternal Morbidity and Mortality: Conference Review

Dr. Temkin introduced ACRWH member Yoel Sadovsky, M.D., who summarized the presentations and discussions within the MMM session of the conference. Dr. Sadovsky reported that there was a great reduction in maternal deaths in the 20th century due to improvements in standards of living, environment, and healthcare; increased in-hospital deliveries and use of antibiotics; deployment of Medicaid; and advanced provider training. The increase in maternal mortality over the past 25 years reflects factors such as increasing maternal age, maternal comorbidities, health disparities, social inequities, and access to care. Substance use and increasing rates of pre-pregnancy chronic conditions that can lead to pregnancy complications and maternal death are other important factors.

While maternal mortality has increased in the United States over the past 25 years, it has decreased in other developed countries. In the U.S., Black women and women over 40 experience the highest rates of maternal mortality. Overall, cardiac disease is the leading cause of maternal morbidity; maternal mortality, however, is primarily caused by hemorrhage and hypertensive diseases of pregnancy. Examined in the broader context, the etiologies of MMM are inseparable from social determinants of health (SDoH) and racism. Causes must be placed where women are born, live, and work and the policies that shape whether those places are protective or harmful to health. Racism is also an important component, leading to lack of trust in doctors and hospitals; implicit and explicit bias; weathering from

toxic stress; and exposure to erosive social determinants. Stress was emphasized by several speakers as a confounding variable to the biological causes of MMM.

Important principles to guide MMM research funding include: Pregnancy research is critical for people who may become pregnant. Follow-up should continue after pregnancy. Research to address causes of pregnancy requires large sample sizes to address multiple components of diversity; funds are needed beyond the scope of traditional R01s and the duration of research needs to extend beyond five years. NIH's organization into 27 Institutes/Centers (ICs), each with a specific research agenda, may lead to research silos that miss important insights about women's health.

Three innovative approaches to addressing maternal health were described at the conference: 1) the National Birth Equity Collaborative (NBEC) that uses a health services approach to create global solutions that optimize Black maternal, infant, sexual, and reproductive well-being. It shifts systems and culture through training, research, technical system, policy, advocacy, and community-centered collaboration. 2) The California Maternal Quality Care Collaborative (CMQCC), founded in 2006 with multi-stakeholder input and launched with funding from the California Department of Public Health, has resulted in quality improvement (QI) toolkits, large-scale QI change collaboratives, widespread partnerships, and a Maternal Data Center. The Collaborative has focused on "pulling all the levers" -- adoption of evidence-based practices, implementation science, and quality improvement—to rapidly affect change. The results have been a striking decline in MMM in California between 1999-2016. 3) The Alliance for Innovation in Maternal Health (AIM) is a national, cross-sector commitment to improve safe care for every U.S. birth and lowering the U.S. rates of MMM. Funded by a cooperative agreement with the Health Resources and Services Administration's Maternal and Child Health Bureau (HRSA/MCB) and the American College of Obstetrics and Gynecology (ACOG), AIM supports 47 state teams and health systems, aligning national, state, and hospital quality improvement efforts to improve overall maternal health outcomes.

Recommendations. Dr. Sadovsky organized recommendations from the conference into these categories:

Science: 1) Stratify maternal mortality by etiology and pathogenesis. 2) Expand research on pregnant women's long-term health (pre- and post-pregnancy)—place pregnancy in the proper context. 3) Focus on implementation science, effectiveness, and health services research. 4) Enroll pregnant women in clinical trials: a) expand current networks and/or create new ones; and b) focus on non-obstetrical trials (e.g., COVID-19, chronic diseases), including testing non-obstetrical interventions in pregnancy to justify exclusion of pregnant women. 5) Broaden research on structural racism and root causes on inequity in women's health. 6) Expand biological and data sciences research, e.g., What are the causes of preeclampsia? Why does cardiomyopathy develop in pregnancy or post-partum? Is pregnancy uncovering a preexisting cardiometabolic dysfunction?

Science to Community: 1) People live in the community, not in hospitals. Health begins and ends in the community in which women live. Emphasize prevention and wellness. 2) Integrate research into community practice, e.g., meet pregnant women in their community/environment; offer training, mentorship, and access; lead to more diverse representation; and include midwives, nurses, and doulas on the research team. 3) Community-Based Participatory Research (CBPR) component—build trust and alliance. Affect at least two levels of influence, patient and provider, and mobilize a broad range of public, private, and community partners.

Education: 1) More funding for trainees. 2) Establish the importance of reproductive sciences and specifically, pregnancy, to young trainees. 3) Train a new, diverse, and most capable workforce at all levels: Physician assistants, midwives, and doulas; community healthcare practitioners; data scientists; and physicians from other disciplines.

Government, Policy, Funding: 1) Expand Medicaid (>60 days). Establish a taskforce to address MMM. Develop better statistics, national surveillance, and quality care protocols. 2) Create trans-NIH Obstetric Research Consortium to direct/lead agenda. Consider an Institute for Women's Health. 3) Create a standing study section specific to women's health, which includes OB/GYN, internal medicine, adolescent medicine, epidemiology, health equity, implementation science expertise and related fields. 3) Grants: Increased funding for maternal mortality at multiple levels (include T0 to T4 translation). Create funding pathways for long-term follow-up, including pregnancy research links into ongoing pediatric cohorts. Include "Patient Voice Core" grant component, incorporating patient-reported outcomes and life quality measures.

Diversity, Equity, Inclusion: 1) Need to understand how generational racism impacts trust and engagement with the healthcare system. 2) From the pre-pregnancy period to post-partum, enhance communication, community engagement, and reduce bias. 3) Identify and address barriers to research in underrepresented groups. 4) Include more diverse scientists in the research pipeline. 4) Collect data on underrepresented groups and those less likely to be involved in clinical trials. 5) Focus on changing policies, systems, and environment, as opposed to changing people.

Implementation, Clinical Service: 1) Quality improvement (QI) measures, CMQCC-style: Create a system of rapid-style maternal-infant data to support QI projects; address equity QI along with clinical QI; and implement a series of data-driven, large-scale QI projects to change culture. 2) Promote carefully-tailored interventions. 3) Build electronic health record (EHR) analytics for research and learning pathways. 4) Create minority midwifery care groups that address the needs of minority women, including a culturally-adapted, patient-centered program and diversification of the workforce, empowering minority participants. 5) Pull all change levers at once, in hospitals, communities, and broader spheres.

Dr. Sadovsky concluded by stating that a healthy pregnancy is a human right. Approximately 1 percent of the U.S. population is pregnant at any given time, yet they carry 100 percent of the future of humankind. Therefore, healthy pregnancies are essential for everyone's health.

Discussion. Key points raised during the ACRWH discussion of MMM included:

- Infection is the second leading cause of maternal mortality. It includes urinary tract infections and sepsis.
- There is a strong desire among participants of the conference to continue the conversation about MMM that began there.
- State-level data regarding the causes of maternal mortality should be examined; there may be important differences by state.
- COVID has contributed to maternal mortality and to related racial/ethnic disparities, with the greatest impact on the mother and more limited impact on the fetus. Unfortunately, the latest available data is for 2019 so the full picture is not yet available.
- Given mistrust of the medical community among many racial/ethnic groups, it is possible that non-medical interventions could have an impact on MMM, e.g., providing racially/ethnically concordant

care, provider training in implicit bias/racism, and integrating racially/ethnically concordant doulas and telehealth into maternal care.

- Implementation science studies examining routine perinatal care are needed to help improve outcomes.

Chronic Debilitating Conditions: Conference Review

Dr. Temkin introduced ACRWH member Judy Regensteiner, Ph.D., who summarized the presentations and discussions in the Chronic Debilitating Conditions in Women (CDCW) session. CDCW are a diverse set of conditions; presentations at the conference focused on specific diseases, including cardiovascular disease, osteoarthritis, fibroids, endometriosis, mental health and stress in women of color, as well as prevention pathways. Existing definitions of chronic conditions are not specific to the clinical and/or research frameworks relevant to the health of women. For example, HHS (2010) defines chronic illnesses as “conditions lasting a year or more and requiring medical attention and/or limit activities of daily living.” The Centers for Medicare and Medicaid Services (CMS) provides data on prevalence, utilization, and Medicare spending for specific chronic conditions and multiple chronic conditions; again, this data is not specific to women.

Women have more multi-morbidities than men. Across diagnoses, comorbidities are more common in women, especially those from communities that are underserved based on race or ethnicity. Women experience not just more symptoms, but more “atypical” symptoms and poorer responses to first-line treatments. “Comorbidity” in women is likely a proxy for poorly understood (and inadequately treated) complex morbidity.

Dr. Regensteiner presented a conceptual model for studying multi-morbidity from the NIH Office of Prevention. It is very complex and suggests that women’s health cannot be studied in a simple way. Among challenges cited by Conference speakers were these: Women’s symptoms in female-specific diseases are often non-specific or associated with other disorders, making the path to diagnosis circuitous. Clinically meaningful knowledge on sex and gender is lacking, due to policies from NIH and the U.S. Food and Drug Administration (FDA) that suggest sex and gender considerations may be optional. Treatments are sometimes unsatisfactory, e.g., there are multiple treatments for uterine fibroids, but these treatments may have adverse consequences. There is a need to address health disparities in women’s research, e.g., the influence of stress is high and may be more profound in women of color. Women are family caregivers more often than men and often feel shame at having a disease themselves. As a result, they may ignore symptoms. At the same time, misperceptions by physicians may lead to failures in diagnosis, e.g., some fail to diagnose heart disease in women based on their belief that women don’t get heart disease, despite the fact that it is the number one killer of women. The NIH budget for women’s health research (\$4,466 million) is exceedingly small, and the ORWH budget has been flat in recent years. More money is needed to study CDCW and to fund ORWH.

The impact of CDCW on women’s quality of life (QOL) is profound. For example, osteoarthritis has a severe impact on QOL that remains understudied. Another example from Dr. Regensteiner’s research is that exercise tolerance is drastically less (20 to 30 percent) in women than in men with recently-diagnosed, uncomplicated Type 2 diabetes. While this detriment may not greatly affect women in their younger years, the impact is likely to increase as they age and could affect their ability to live independently. Thus, QOL is an important area to evaluate when considering the impact of CDCW.

Dr. Regensteiner displayed the ORWH infographic on sex and gender across the lifespan, adding pregnancy and menopause under the heading “Adulthood.” She reiterated that it is important to consider sex and gender across the entire lifespan, deliberately and prospectively across all clinical trials.

Common Themes. The common themes that emerged from the CDCW presentations and discussions at the conference included: lack of scientific knowledge; lack of public awareness; complexity, such as the presence of comorbidities; need to consider race and ethnicity; need to consider sex and gender; current diagnoses and treatments are unsatisfactory, and effects on QOL are not considered; lower priority is put on the health of women/research on the health of women; and the need for NIH to more highly fund research on the health of women.

Possible Pathways/Solutions: The following recommendations were made: 1) Create infrastructure for research on the health of women at NIH, such as creating a Common Fund for Women’s Health; establishing other NIH-wide Women’s Health Initiatives; transforming ORWH into an Institute with grant-making authority and a strong budget; and ORWH partnering with the National Academy of Sciences (NAS) to define chronic diseases in women. 2) Partner with the national professional and lay communities to promote interprofessional and lay community-facing education on women’s health, fundraise with the community, and work with a celebrity to lead national and local campaigns to increase awareness and education about women’s heart health, among other issues. 3) Continue and accelerate building the workforce of male and female M.D. and Ph.D. scientists who will do the critical research.

Discussion. Key discussion points about CDCW included:

- Infection is a huge contributor to CDCW and is disease-agnostic. Thus, studying the pathogenesis of inflammation can contribute to developing useful medications that would reduce the incidence of CDCW.
- Pain reported by minority populations is often ignored by providers. Put health disparities at the forefront of considerations of CDCW along with comorbidities.
- Sex and gender, as well as intersectionality, should also be addressed in every study design.
- An NIH Institute on Women’s Health or on Sex and Gender Differences would facilitate cross-disciplinary research on CDCW, help set policy regarding SABV, and encourage collaboration with stakeholders to promote reporting of sex and gender differences in biomedical research.
- Improve data used by providers in diagnosing diseases so that it is more applicable to minority populations by including more women of color in clinical trials.
- Emphasize the need for the healthcare workforce to apply for funding to address clinical care needs for CDCW.
- Ground discussions of CDCW on the patient’s voice and issues, such as QOL. To do so, patient-reported experience measures should be integrated into studies of diseases affecting women.
- Recognize the need for research that addresses the health of women specifically and educate study sections about justifications for single sex studies.

Cervical Cancer: Conference Review

Dr. Temkin introduced former ACRWH member Wendy R. Brewster, M.D., Ph.D., who reported on the cervical cancer session at the conference. Over the past four decades, improvements in cervical cancer rates have occurred but the picture has been stagnant for the past twenty years. Between 2016-2020, NIH funding for cervical cancer has been largely devoted to prevention and early detection rather than biology and treatment.

The rate of new cases of cervical cancer is disproportionately higher among Black women, Asian women, and Native American women. Cervical cancer mortality also disproportionately affects these same racial and ethnic groups. In the United States, cervical cancer remains a failure to screen and a failure to follow up with women who have abnormal results. Both of these failures have been associated with inequalities among racial and ethnic groups; groups with lower educational attainment and health literacy; groups with higher poverty; groups who live in rural vs urban settings; groups with lower levels of acculturation, including language; and being uninsured or covered by public vs private or military insurance.

HPV vaccination is the key to making cervical cancer even rarer than it is today. However, it will take a generation before the impact of vaccination on cervical cancer incidence will be seen. Impacting stagnant cervical cancer rates requires bold action to modify the focus of prevention efforts and research directions beyond HPV-based innovations and majority populations.

Prevention Focus: New study designs are needed, including 1) Scaling up interventions to population and community levels (e.g., mass media campaigns to screen, diagnose, and treat cervical cancer). 2) Implementing bold interventions to screen and follow up underserved groups by overcoming the barriers of race, language, poverty, and geography. 3) Embracing innovative models of service delivery (e.g., non-traditional provider delivery, self-sampling at community venues, such as Wal-Mart, Costco, mobile units, community pop-ups). 4) Investing in building information systems (state-wide, regional, national) that transcend health systems, clinics, providers, and patient locations; these are needed to support call/recall for screening, diagnosis, and treatment.

Invasive Cervical Cancer: Invasive Cervical Cancer (ICC) is a disease of the unscreened, under-screened, and failures to follow up abnormalities. Sixty-four percent of the women with ICC were unscreened or had only inadequate screening tests. There is an opportunity for the EHR to more efficiently track a patient's history of cervical cancer across different delivery systems. There is a need to think about having more equity and more inclusion so the healthcare system can meet patients where they are. Cervical cancer prevention research based in HPV innovation will not address equality and empower patients to reduce disparities. Larger, novel, extramural funding programs developed in collaborative investigator-initiated programs are needed.

Genomic Biomarkers: There was information presented at the conference about genomic biomarkers to treat cervical cancer. Breast cancer diagnosis, a heavily-researched area, is no longer about stage but about molecular characterization. That transition has not yet occurred in cervical cancer. There are opportunities to more richly define cervical cancer, e.g., not all HPVs are created equal. There are opportunities to distill the molecular characterization of cervical cancer and affect outcomes, learning from proteomics and genomic predictors of radiation therapy response. There is a need to focus on tissue specificity in the cancer. There are plentiful opportunities in cervical cancer research to look at new targets, to look at better model systems, and to personalize treatments in a way that's already been exploited for breast, ovarian, and endometrial cancers.

Research Opportunities: It's important to support research workforce development training grants in gynecology oncology and radiation oncology. Cluster grant applications to improve innovation in treatment for cervical cancer; increase R01 level investment for researchers working in this field; and include a gynecological oncology study section that prioritizes needs in cervical cancer treatment and innovation. Sample RFAs might include: Improving preclinical models for treatment assessment in HPV associated cancers; novel imaging and genomic biomarkers for outcome prediction in cervical cancer;

optimizing technology to improve outcomes in resource poor settings; novel targeted therapy approaches +/- radiation therapy (RT) in cervical cancer, e.g., DNA Damage Response Inhibitors (DDRIs), metabolic therapy (drugs and diet), and immunotherapy; and personalized treatment to improve outcomes in cervical cancer.

Translating Science to Improve Stagnant Cervical Cancer Survival Rates. Recommendations here included 1) Expand Science: Until primary and secondary preventive measures have eliminated cervical cancer, increase basic and translational cancer research, clinical trials, in-vivo models, biobanking, and data sharing for stage 0-4 cervical cancer. 2) Encourage Adherence: Align cancer care payments to high quality, evidence-based care models. 3) Mobilize Resources: Improve access to high quality care for all patients through supporting travel, housing, and provide infrastructure for collaboration with regional hospitals. 4) Expand Trial Access: Step up clinical trial enrollment for novel agents through investment and international collaborations. 5) Develop the Workforce: Increase diversity and investment in workforce training to deliver complex, multidisciplinary care and increase clinical trial participation.

NCI Gynecologic Cancer Clinical Trials. Recommendations included: 1) Prioritize clinical research in gynecological cancers on par with other disease sites; 2) Facilitate international collaboration, especially with new drugs and in rare disease. 3) Facilitate real time data sharing. 4) Simplify layers of review to allow streamlined timelines. 5) Emphasize feasible research on interventions likely to be practice-changing. 6) Support critical surgical, imaging, and radiation therapy questions, which are the hallmark of cervical cancer care—trials which will not be funded by industry. 7) Restructure investments to adequately support trial costs.

Redefine the Approach to Women's Care Research. Recommendations for redefining the approach to women's care research included: 1) Recognize that the default structure of cancer research creates and exacerbates inequities for marginalized women. 2) Embrace cross-cutting approaches that acknowledge the power and complexities of how structural racism influences health. 3) Align investments to incentivize the study of unjust creation, dissemination, and delivery of cancer research knowledge. 4) Prioritize equity research grounded in theories that undergird race, gender, and health. 5) Embrace a goal of NIH-funded research as a tool to disrupt the default outcome of marginalized women as the secondary priority.

Suggested Funding Solicitations for Gynecologic Cancer Equity. Recommended topics included: 1) Quantitative and qualitative evaluation of bias and exclusion in biomedical cancer research. 2) Development of multi-level approaches to equitable representation of marginalized populations in cancer clinical trials. 3) Impact of structural and personal racism on outcomes in the cancer care continuum. 4) Life course approaches to evaluate cervical cancer disparities among Black and Native American women. 5) Interdisciplinary structural interventions to overcome expected inequity in clinical trial participation.

NIH/NCI has invested in cervical cancer treatment. However, the challenge has been adherence to science. Cervical cancer is largely a disease of surgery or radiation. Less than 50 percent of women receive National Comprehensive Cancer Network (NCCN) guideline-concordant treatment. The women who are less likely to receive this treatment are older, have public insurance, and are Black. They have lower rates of brachytherapy. There has been a decline in the rate of brachytherapy because cervical cancer has gone from a very common to a rare cancer, which has impacted brachytherapy training and development of a skilled workforce. Alternative radiation therapies are less effective. Thus, there is a misalignment of dollars to quality treatment; it's not in the financial interest to deliver brachytherapy.

Care is fragmented. These factors lead to inadequate treatment and stagnant cervical cancer survival rates.

In conclusion, Dr. Brewster noted that the field has known for decades that cervical cancer survival rates are stagnant. The historical and traditional disease-specific model that is largely designed to meet the needs of White women is not addressing the larger scale public health needs. The field must be able to measure and be accountable to these goals: Deliberate realignment of priorities, addressing equity AND therapy. The inclusion of women in clinical trials needs to be proportionate to the representation of these women in the target population. The speakers at the conference all emphasized that the field needs to think big; otherwise, cervical cancer rates will continue to remain stagnant.

Discussion: Key discussion points included:

- Prevention for cervical cancer needs to be re-thought, e.g., self-swabbing for HPV has been successfully demonstrated in other countries. The FDA has not yet approved self-swabbing.
- Large-scale community-engaged trials, such as those needed to address cervical cancer prevention, screening, and follow-up/treatment, require larger budgets than the current \$500,000 per year R01 permits.
- Interdisciplinary research between basic and translational scientists is needed to address health disparities in cervical cancer.
- It is important to meet women where they are in order to address their cervical cancer needs. Education and follow-up are important components in that effort.
- Philanthropy has funded some clinical trial recruitment strategies for minority populations and supported patient navigators and social support for minority women in cancer centers.
- Lessons from the COVID vaccination experience may help increase HPV vaccination rates.
- Access to care remains an issue. Existing resources should be deployed more broadly, e.g., midwives and other non-M.D. providers can do Pap smears.

Women-Centered Health Care is Trauma- and Resilience-Informed

Dr. Noursi introduced Brigid McCaw, M.D., FACP, Senior Clinical Advisor, California Quality Improvement Learning Collaborative (CALQIC), University of California San Francisco (UCSF) Center to Advance Trauma-Informed Health Care. Dr. McCaw began her presentation by saying that she hoped to stimulate ACRWH members to think beyond health disparities, noting that inclusion of information about trauma and resilience-informed care might be included in the upcoming Trans-NIH Strategic Plan for Women's Health Research. Trauma is a root cause of poor health for women, affecting risk for illness; development of disease; access to and engagement in care; diagnosis, intervention and treatment; and well-being. This is true for all health issues, not just for injury-related disease. Understanding the role of trauma in women's lives will help design a healthcare system that meets women's needs.

Dr. McCaw distinguished between abuse, cruel or violent treatment of a person that can be physical, emotional or sexual; trauma, an event, series of events, set of circumstances experienced by an individual as physically or emotionally harmful or threatening and has lasting adverse effects on individual's function and well-being; and violence, the intentional use of physical force or power, threatened or actual, that results in injury, death, psychological harm, or deprivation. She used trauma in her presentation as the overarching term, focusing on interpersonal abuse and trauma.

Current and past trauma is common among women. For example, 37 percent have experienced sexual violence, physical violence or stalking by an intimate partner during their lifetime, and 23 percent have experienced severe physical violence by an intimate partner. Among sex/gender minorities, 40-60 percent have experienced sexual violence, physical violence, or stalking by an intimate partner during

their lifetimes. One in five women have experienced completed or attempted rape during their lifetime, and just over one-quarter (26 percent) have experienced three or more adverse childhood experiences (ACEs), which are associated with increased health risks.

Trauma contributes to illness as sequelae of injuries, through the development of coping behaviors that are unhealthy (e.g., smoking, substance misuse), and via acute and chronic stress-related activation of neuro-endocrine immune system pathways, i.e., toxic stress response which may manifest years after exposure to the trauma. Multiple systems are disrupted by toxic stress, including neurologic, immunologic, endocrine, and epigenetic ones.

Dr. McCaw said that it is imperative to recognize the intersectionality of trauma that many women experience, including the additional impact of systemic racism and historical trauma; sexism, gender identity, and sexual orientation discrimination; poverty; and war, global pandemics, and climate change.

To highlight the importance of trauma, Dr. McCaw displayed an updated version of ORWH's Health of Women Across the Lifespan graphic in which she had placed "trauma" in the "Women in Context - External Factors" section, so that it read: "... such as gender, trauma, social determinants of health, behavior, environment, & policies." She pointed out that incorporating trauma/abuse/violence as a root cause of illness and disability in the new Trans-NIH Strategic Plan for Women's Health Research will improve the science of women's health and inform the re-design of health care services that are woman-centered, effective, and improve outcomes. The current healthcare system does not support women, i.e., it does not support women's multiple roles; care is fragmented and difficult to coordinate; services are not easy to access nor convenient nor inclusive; care is not tailored to meet needs that change over the life course; the cost of care is often prohibitive; and the system emphasizes disease and pathology, as well as body/mind separation. In short, care is not trauma- and resilience-informed.

In contrast, women-centered systems of care, as outlined in the Institute of Medicine's 2001 report *Crossing the Quality Chasm: A New Health System for the 21st Century*, are characterized by care based on healing relationships; cooperation among clinicians; customization based on patient needs and values; the patient as source of control whose needs are anticipated; shared knowledge; evidence-based decision making; decreased waste; and care that is trauma- and resilience-informed.

Trauma- and resilience-informed care shifts the focus to a whole person approach, understanding that trauma is just one aspect of the individual's experience and engaging the patient's strengths, competencies, protective factors and supports, and neuroplasticity.

The next steps are to acknowledge that current and past trauma is a root cause of disease, morbidity, and mortality in women, and to incorporate this acknowledgment into research, delivery of healthcare, and policy. In terms of research, this means including trauma, violence, and abuse in the NIH-Wide Strategic Plan for Women's Health Research; considering current and past trauma as risk factors in all diseases/conditions; funding research in biomedical science and health services research; and emphasizing cross-disciplinary efforts. Healthcare systems and delivery of care should be redesigned to improve patient access and engagement in care; services should be connected, coordinated, and affordable; healthcare providers should be trained in trauma- and resilience-informed care; and evidence-informed practices should be adopted. Policies that emphasize collaboration across agencies to address trauma- and resilience-informed care should be promoted.

Discussion. Dr. Noursi moderated an ACRWH discussion of Dr. McCaw's presentation that included the following key points:

- The issues highlighted by Dr. McCaw are critical; there is a need to generate research on these topics so that women’s healthcare can be informed based on data-driven outcomes. Every MMM committee in the country funded by CDC should hear Dr. McCaw’s presentation.
- Acute and chronic stress from living with racism and childhood mistreatment are causes of MMM and CDCW, as well as suicide, homicide, and drug overdoses.
- Abusive treatment of women during pregnancy impacts women’s desire for care; this could be addressed from a trauma or mental health perspective.
- Women make up the majority of the healthcare workforce and many may have experienced trauma. They, and all providers, need trauma-informed training that includes how to be present, to listen, and to connect with patients.

Open Discussion

Drs. Noursi and Temkin moderated an open discussion among ACRWH members. Dr. Temkin began by reviewing ACRWH member comments on gaps and opportunities in MMM, CDCW, cervical cancer, and women’s health in general based on a survey prior to the meeting. She encouraged ACRWH members to focus on opportunities in their discussion. Key points included:

- A write-in suggestion was to partner with the National Academy of Sciences (NAS) to develop a framework for chronic debilitating condition research that is specific to women. Several members expressed interest in exploring this possibility with NAS; it could become a topic for discussion at the next ACRWH meeting.
- There is an opportunity to improve women’s health via bioinformatics data, possibly drawn from EHRs, which has not yet played a significant role in women’s health research. Oncology is a field that may offer lessons learned in the use of bioinformatics.
- Pregnancy is one area that lends itself to “Big Data” approaches, as all healthcare settings collect standard physiological measures and outcomes are easy to quantify. Women are more engaged in their health during this period in their lives and thus likely to be willing to engage in research.
- There are many gaps and opportunities in provider training around trauma-informed care, training specific to the health of women with CDCW, and training about older women for residents who typically only see younger women.
- Engage patients in identifying appropriate outcome measures in CDCW, e.g., focusing on function.
- Focus on increased professional education on sex and gender for providers, starting early in medical school or even undergraduate education.
- Focus on structural racism, as well as sex and gender. Multiple interventions of new ways to deliver care are needed; implementation science plays an important role in developing these. Drs. Clayton described ORWH’s and NIH’s funding opportunities in transformative health disparities interventions.
- Conduct a granular and comprehensive review of the NIH portfolio to identify pathways that advance the science of women’s health.
- In response to a request from Dr. Noursi to comment on implementation science, Dr. McCaw said that data is needed to identify new risk factors, such as trauma. No breakthroughs in women’s health research will occur if trauma and racism is not included. Once the data is available, then provider education on how to look at patient access and engagement with a new lens, e.g., how to measure patient engagement, can be developed.
- Diversity provides an opportunity to test new ideas and interventions within a non-randomized framework. Some interventions identified in this way could be promoted as promising practices.
- Implementation research that embraces heterogeneity and diversity is more costly than the typical R01 grant covers.
- Government agencies need to rethink what they want to fund. Adequate funding makes a huge difference. Some organizations and agencies have sought funding from philanthropy or industry.

- Basic science research is needed in women’s health, e.g., breast cancer issues beyond the BRCA gene to identify women’s risks for disease.
- There is much that could be learned from the response to the COVID pandemic, such as rapid vaccine development and high levels of community engagement, that could be applied to women’s health issues rather than continuing to conduct business as usual.

NCI’s Role in Promoting Research in Women’s Health

Dr. Clayton introduced Norman E. Sharpless, M.D., Director, NCI, who had pre-recorded a presentation about NCI’s role in promoting research in women’s health, especially highlighting research specific to cervical cancer. He noted that this is the “Golden Age” of cancer research. Cancer mortality in general is declining. Between 2018-2020, record numbers of new cancer drugs were approved by the FDA. The pandemic has impacted this pattern of declining mortality, however, because it has disrupted cancer care and screening.

Cervical Cancer. The HPV vaccine has had a huge impact on the incidence of cervical cancer. There has been a striking decline in cervical cancer rates with an impressive narrowing of the gap between Black and White patients. In the 1950s prior to widespread screening using the Pap test, the incidence of invasive cervical cancer in the U.S. was between 35 and 40 cases per 100,000 women annually. By 1990, the incidence of invasive cervical cancer had been reduced to about 10 cases per 100,000 women. Health disparities in mortality remain, however, with Black women at 3.5 times and White women at 2.2 times the annual standardized rate (2012-2016).

Recent advances in cervical cancer treatment included newly-approved drugs and immunotherapy. The best news about cervical cancer, however, is effective HPV prevention and screening. Chronic infection by about 15 HPV types is a primary cause of cervical cancer in the United States. HPV vaccination directly reduces risk of infection and disease in those vaccinated, but also indirectly reduces risk by reducing prevalence of “HPV vaccine types” in the general population. Worldwide control of cervical cancer requires worldwide female vaccination. However, fewer than 10 percent of young women in low- and middle-income countries receive the vaccine. One option being studied in a clinical trial in Costa Rica funded by the Bill and Melinda Gates Foundation and NCI is to reduce dosage to a single shot of an FDA-approved vaccine, instead of two or three. Initial results of the one vaccine dose are promising.

But increasing vaccination rates alone should not be the only approach to eradicating cervical cancer. An analysis from the Harvard School of Public Health showed that cervical cancer incidence in the U.S. will decline faster by increasing screening (i.e., elimination by 2028) than by increasing HPV vaccination (elimination by 2038). New tools to improve cervical cancer screening include artificial intelligence. NCI reported in 2020 on a dual stain automated cytology test that surpassed the performance of the current standard, Pap cytology. It reduced the number of false positive results and substantially reduced referral to unnecessary colposcopy procedures.

Discussion. Following Dr. Sharpless’ recorded presentation, Dr. Clayton introduced Douglas R. Lowy, M.D., Principal Deputy Director, NCI, and Elise Kohn, M.D., Head, Gynecologic Cancer Therapeutics, NCI, who responded to ACRWH questions. Key discussion points included:

- Lessons from COVID might be applied to international collaboration on cervical cancer, e.g. empowering patients to be their own advocates by self-sampling to continue care with limited resources.

- Another important aspect of international collaboration is helping low- and middle-income countries to develop expertise in addressing cervical cancer, e.g., via the provision of technical assistance related to clinical trials and healthcare improvement in general.
- Regulatory issues, particularly in the European Union, permit NCI to do international trials only for investigational drugs. There are fewer barriers for prevention and screening; thus, NCI is involved in studies such as the Costa Rica trial.
- Implementation science requires higher budgets than traditional R01 grants allow. NCI would like to think that the sizes of its awards are commensurate with what is needed.
- There have been sustained, multipronged efforts with different stakeholders over the past decade to increase HPV vaccine uptake which is now at 75 percent among boys and girls ages 13-17 with one dose and 60 percent with two doses. ORWH was an early supporter of the vaccine.
- NCI has a strong history of data sharing, e.g., the National Cancer Clinical Archives, and would be happy to share what it's learned about data archiving and sharing with ORWH.
- NCI has a strong history of including patient advocate consumers at all levels of planning, include development of protocols. It also uses patient-reported outcomes on QOL and other outcomes.
- To reach rural and frontier women, NCI partners with the National Community Oncology Program which funds sites for clinical trials focusing on rural and underserved women. The Institute also provides guidance and training to investigators to help broaden local advisory groups.
- About 60 percent of participants in NCI clinical trials have been women and 25 percent of participants over the past three years have been underrepresented minorities.

Concept Clearance: ORWH Research on the Health of Women of Understudied, Underrepresented, and Underreported (U3) Populations Administrative Supplement Program

Dr. Clayton introduced Miya Whitaker, Psy.D., Health Scientist Administrator/Program Officer, ORWH, who presented a concept clearance for the ORWH U3 administrative supplement program.

Brief Overview of U3 Administrative Supplement Program. The purpose of the U3 administrative supplement program is to provide one-year supplemental funding to active NIH parent grants to address health disparities among populations of women in the U.S. who are underrepresented, understudied, and underreported (U3) in biomedical research. ORWH created the U3 Administrative Supplement Program in 2016 and reissued it in 2017-2019.

The design of the Program reflects the Guiding Principles of the Trans-NIH Plan for Women's Health, i.e., "to advance science for the health of women, ... Interdisciplinary research initiatives integrating perspectives from multiple disciplines are crucial to capturing the complex interplay of multiple factors affecting the health of all women...." It applies these principles to the Health Disparities Populations designated by NIH, including racial and ethnic minority populations, sexual/gender minorities, women of low socio-economic status, as well as rural/urban populations.

Program Data. Between 2017-2021, ORWH received 120 applications to the U3 Program. Between FY2017-2020, ORWH made 59 awards to 99 applicants (a 59.6 percent success rate) for a total investment of \$10.75 million across 15 ICs. IC participation varied by year. U3 Principal Investigators (PIs) during FY2017-2020 were primarily female, white, non-Hispanic, and non-disabled. They were more likely to hold Ph.D. degrees than an M.D. Unfunded PIs were quite similar in demographic characteristics to funded ones. In terms of productivity, U3 PIs generally published between 40 to 70 publications annually during 2017-2020. The topics of focus in their U3 research varied by year. ORWH is currently working on a five-year evaluation of the program.

Programmatic Next Steps. ORWH has analyzed the gaps and opportunities in the U3 Administrative Supplements Programs and identified the following potential research opportunities:

Topics: PASC/COVID-19; autoimmunity/autoimmune conditions; multimorbidity/chronic disease disparities; comprehensive care models (preconception, postpartum, and antenatal care); multilevel/-sectorial health equity solutions; intimate partner/gender-based violence; addiction-related treatment services; structural racism/discrimination; and environmental exposures.

Geography: Workforce development/competency; expand capacity of institutions in IDeA states to conduct disparities research using a SDoH Lens.

Populations: American Indians/Alaska Natives; Asian Americans; Native Hawaiians/Other Pacific Islanders; Sexual and Gender Minorities; Elderly; Persons with Physical, Intellectual/other Functional Disabilities; Unstably housed/formerly incarcerated populations; and Immigrants.

ORWH plans to reissue the U3 Administrative Supplement Program for FY2022 with expanded areas of interest based on IC input and continuance of the Virtual Women's Health Lecture Series to amplify lessons learned from U3-supported research.

Discussion. ACRWH discussion of the U3 Administrative Supplements Program concept clearance included praise for the Program, as well as a suggestion to expand funding eligibility beyond those who hold a parent NIH grant, e.g., to those who hold other federal research grants, as a supplement to a K award in its 4th or 5th year, or to issue the program as an R01, possibly limited to those already funded under the Program as it is difficult to transition to an R01 with only one year of research. The goal should be to encourage more young investigators. Another suggestion was to require a partnership with a minority-serving institution, who may be more experienced in community engagement, as part of the Supplement.

Vote. The U3 Administrative Supplement Program concept clearance was approved with 12 ACRWH votes in favor.

Concept Clearance: Specialized Centers of Research Excellence (SCORE) on Sex Differences

Dr. Noursi introduced Rajeev Kumar Agarwal, Ph.D., Senior Research Program Officer, ORWH, and Rebecca DelCarmen-Wiggins, Ph.D., Health Science Administrator/Research Program Officer, ORWH, who presented a concept clearance for reissuance of the SCORE program.

Rationale & Objectives of the SCORE program. Dr. DelCarmen-Wiggins explained that SCORE, a signature program of ORWH, is the only NIH Centers program that supports disease-agnostic research on sex differences to improve the health of women. The program was first issued in 2002 as Specialized Centers of Research (SCOR), a P50 program on Sex Differences. In 2018, the program was expanded to a SCORE (Specialized Centers of Research Excellence) U54 program. That year, six SCORE awards were made. The RFA was reissued in 2019; five awards were funded in FY2020. The funded programs address a range of health conditions, such as addiction, aging, and mental health.

SCORE Program Highlights. The current SCORE U54 program includes three or more synergistic research projects and a Career Enhancement Core (CEC) to support pilot research and to train next generation of scientists in the study of sex differences. The NIH investment in the SCORE Program is \$17,758,398 to date.

The U54 Cooperative Agreement mechanism promotes collaborations among the SCORE programs. Dr. Agarwal explained that collaboration across SCORE centers is promoted through monthly conference calls and an annual SCORE meeting that supports collaboration and scientific sharing.

SCORE Program Achievements. The U54 SCOREs apply SABV to a diverse set of topics. The CECs have developed a variety of resources to promote women’s health research. Collaborative SCORE networks have also been created.

Future Directions. ORWH proposes to maintain the key features of the SCORE program, i.e. advance disease agnostic translational research on sex differences; support three interactive research projects and an administrative core; support the career enhancement core (CEC); and promote and support the building of collaborative networks. It also plans to expand ICO partnerships to advance the women’s health research portfolio at NIH.

Discussion. Dr. Noursi moderated ACRWH discussion of the SCORE U54 reissuance:

- Several ACRWH members praised the program as innovative and a key motivator for students and young investigators to pursue research on sex differences and to promote institution-wide interest in applying SABV to research studies.
- A lack of racial and ethnic diversity among SCORE investigators was noted. Suggestions to address this issue included promoting the reissued RFA to minority-serving institutions; creating partnerships between majority and minority-serving institutions; and including more community-based translational research.
- Requests for more funding for the CEC component and clarification of its role were made.

Vote. A motion to approve reissuance of the SCORE U54 program was made and accepted with 12 ACRWH votes in favor.

In Memoriam

Prior to closing, the ACRWH remembered the late Robert "Bob" J. Handa (1954-2021) who was a leader in both the previous P50 SCOR program and the current U54 SCORE program of ORWH for 8 years.

Closing Statement

Dr. Clayton thanked ACRWH members, staff, and contractors for their contributions. She adjourned the meeting at 4:26 p.m.

Certification

We certify that the contents above are accurate and complete.

Janine A. Clayton
Janine Austin Clayton, M.D., Director
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Samia D. Noursi
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Advisory Committee on Research on Women’s Health

Date 12/15/2021

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