

51st 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 20, 2020

Members Present

Roger B. Fillingim, Ph.D.
Stacie Geller, Ph.D.
Scott Hultgren, Ph.D.
Sabra Klein, Ph.D.
Ana Langer, M.D.
Alyson McGregor, M.D.
Amy Paller, M.D.
Judith Regensteiner, Ph.D.
Elena Rios, M.D.
Michelle Robinson, D.M.D.
Neel Shah, M.D., M.P.P.
Marcia Stefanik, Ph.D.
Kimberly J. Templeton, M.D.

Other Attendees

Reshma Jagsi, M.D., D.Phil.
Carolyn Mazure, Ph.D.
Yoel Sadovsky, M.D.

ORWH Leadership Present

Janine Clayton, M.D., Director, Chairperson
Elizabeth Spencer, B.S.N., Deputy Director,
Executive Secretary
Samia Noursi, Ph.D., Associate Director for
Science Policy, Planning, and Analysis

IC Leadership Present

Monica Hooper, Ph.D., Deputy Director,
National Institute of Minority Health and Health
Disparities (NIMHD)
Helene Langevin, M.D., Director, National
Center for Complementary and Integrative
Health (NCCIH)
Bruce Tromberg, Ph.D., Director, National
Institute of Biomedical Imaging and
Bioengineering (NIBIB)

Call to Order, Introductions, and Approval of Minutes

Elizabeth Spencer, B.S.N., ACRWH Executive Secretary and ORWH Deputy Director, called the online meeting to order at 9:30 a.m. Ms. Spencer announced her new position as Senior Advisor for Workforce Development at the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), and the appointment of Samia Noursi, Ph.D., Associate Director for Science Policy, Planning, and Analysis, ORWH, as the new Executive Secretary of the Committee. She acknowledged Wendy Brewster, M.D., Ph.D., Louise McCullough, M.D., Ph.D., Amy Paller, M.D., and Susan Wood, Ph.D., who are retiring from the Committee. Committee members introduced themselves and, via an online vote, unanimously approved the minutes of the April 21, 2020 meeting.

ORWH Director's Report

Ms. Spencer introduced Janine Clayton, M.D., NIH Associate Director for Research on Women's Health and ORWH Director. In recognition of ORWH's 30th anniversary, Dr. Clayton shared photographs of and comments from women who were instrumental in the creation of ORWH-- first Acting Director, Ruth Kirschstein, M.D.; first Director, Vivian Pinn, M.D.; former U.S. Senator Barbara Mikulski and former Representatives Constance Morella, Patricia Schroeder, and Olympia Snowe--throughout her presentation. She also acknowledged the work of ACRWH members past and present who published "Sex and gender: modifiers of health, disease, and medicine" in *The Lancet* (August 22, 2020).

New in Science: As an illustration of sex as a biological variable (SABV) in action, Dr. Clayton cited a study in *Science* that found that sex differences in gene expression are ubiquitous. In a study of tissues taken from 44 areas in the body by NIH's Genotype-Tissue Expression (GTEx) Program, researchers found that 13,295 genes across these tissues had sex effects; 37 percent of those genes exhibited sex-biased regulation of gene expression in at least one tissue.

Dr. Clayton described coronavirus disease 2019's (COVID-19) impact on women in academia, especially women of color, who face more severe versions of long-standing gender gaps, e.g., there is an increased gender gap in publications since the pandemic began and a devastating impact on early-career investigators. These COVID-influenced factors will affect the direction of future biomedical research in fundamental ways.

New at NIH and ORWH: There are three new women NIH Institute/Center (IC) directors, bringing the total to 10 out of 27. They include Lindsey Criswell, M.D., M.P.H., D.Sc., National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); Rena D'Souza, D.D.S., M.S., Ph.D., National Institute of Dental and Craniofacial Research (NIDCR); and Shannon Zenk, Ph.D., M.P.H., R.N., FAAN, National Institute of Nursing Research (NINR).

As part of the NIH Anti-Harassment Program to end the culture of sexual harassment in science, the Office of the Director for Scientific Workforce Diversity surveyed NIH employees, contractors, fellows, and trainees. For the previous 12 months, one in five respondents reported experiencing sexual harassment; trainees were at higher risk.

Because women's career progression in academic science, technology, engineering, and mathematics (STEM) disciplines lags behind men's, ORWH has established new programs to support women during critical life events. These include Promoting Career Continuity for K Awardees ([NOT-OD-20-054](#)) and Promoting Career Continuity for RPG Awardees ([NOT-OD-20-055](#)) award.

The new NIH Challenge Prize for Enhancing Faculty Gender Diversity will recognize and disseminate transformative institutional approaches to enhancing gender diversity. Up to \$50,000 may be awarded to up to ten institutions. The application deadline is April 16, 2021.

ORWH, in partnership with the Food and Drug Administration (FDA)'s Office on Women's Health (OWH), has expanded its Bench to Bedside: Integrating Sex & Gender to Improve Human Health e-learning initiative with new courses. Coming soon will be a Sex as a Biological Variable Primer and an Introduction to the Scientific Basis of Sex- and Gender-Related Differences.

The Centers of Excellence in Pain Education program has a new website (<https://coepes.nih.gov/>). CoEPE, supported by ORWH, is an online resource for the development, evaluation, and distribution of pain management curriculum materials for medical, dental, nursing, pharmacy and other schools.

Dr. Clayton also highlighted Department of Health and Human Services (HHS) initiatives that target hypertension and maternal health, including National Women's Blood Pressure Awareness Week (October 11-17), the Million Hearts Challenge, and the new Implementation Plan (August 2020) from the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC).

COVID 19 Update: There is a new NIH-wide Strategic Plan for COVID-19 Research (July 2020). It identifies five priority areas, including: 1) Improve Fundamental Knowledge; 2) Advance Research to Improve Detection; 3) Support Research to Advance Treatment; 4) Accelerate Research to Improve Prevention; and 5) Prevent and Redress Poor COVID-19 Outcomes in health disparity and vulnerable populations, including pregnant and lactating women. Several cross-cutting strategies specifically address the health of women. This document will guide ORWH COVID-19 initiatives.

ORWH is leveraging the collective strength of NIH Institutes, Centers, and Offices (ICOs) to accelerate sex and gender research on COVID-19's impacts on women's health by developing and prioritizing initiatives for future research; providing strategies for incorporating SABV and NIH inclusion policy into COVID-19; developing COVID-19 women's health research priorities; systematically collecting and curating relevant information on the current COVID-19 landscape; and promoting collaboration to accelerate the impacts of research. To date, ORWH has participated in developing 15 Funding Opportunity Announcements (FOAs), e.g., by including language specific to the health of women or the consideration of sex and gender; ORWH team members have participated in over 20 reviews of proposals. In addition, ORWH has recently established a COVID-19 Working Group under the NIH Coordinating Committee for Research on Women's Health (CCRWH) to perform a portfolio analysis to accelerate research. ORWH has also developed a guiding principles document on sex and gender influences in COVID-19 and the health of women and, in collaboration with NIMHD and the Sexual & Gender Minority Research Office (SMGRO), an annotated bibliography on issues germane to sex and gender and COVID. ORWH is leveraging its own signature programs to expand the scope to meet the COVID-19 challenge. Specifically, the Sex and Gender R01 has been expanded to address COVID-19 as part of its scope, as has the Notice of Special Interest (NOSI) for the Understudied, Underrepresented, and Underreported (U3) Populations program.

NIH is moving at an unprecedented rate to develop testing, serology, and technology to combat COVID-19. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) is a public-private collaboration to pursue four fast-track areas: preclinical treatments; testing of the most promising vaccines and treatments; clinical trial capacity and effectiveness; and evaluation of vaccines. The Rapid Acceleration of Diagnostics (RADx) Program seeks to improve COVID-19 testing through four initiatives: 1) Tech: Speed development of point-of-care tests; improve laboratory tests; 2) UP: Identify disparities in Underserved Populations and mitigate factors associated with poor outcomes; 3) Radical: Support nontraditional approaches to testing and nontraditional applications of current methods and 4) ATP: Scale up existing Advanced Technology Platforms to increase testing capacity with rapid turnaround.

Men have poorer outcomes with COVID than women. The article, "Sex differences in immune responses explain disease outcomes," by Takahashi et al. in *Nature* (2020) reported that distinct immune responses predict symptom severity in men and women. Males and females with moderate COVID-19 symptoms have different immune profiles, i.e., males have higher plasma levels of innate immune cytokines IL-8 and IL-18, and robust induction of non-classical monocytes, while for females, robust T cell activation is sustained in old age. Case deterioration is associated with distinct immune processes between the sexes. This article highlights the importance of including SABV in research and disaggregating data by sex and age.

Scientific Collaborations: NIH has mounted a vigorous effort in **maternal health**. Dr. Clayton is co-chair of the NIH Maternal Mortality Task Force, which has launched a new \$7 million Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) initiative focused on maternal health with three foci: cardiovascular disease, infection/immunity, and mental health. ORWH created a new research program on women's health covering all of the IDeA states with an emphasis on

maternal health. ORWH partners with the National Institute of General Medical Sciences (NIGMS) on the Institutional Development Award States program that provides administrative supplements to expand research and research capability on maternal health and with NIHMD which has issued an R01 on Addressing Racial Disparities in Maternal Mortality and Morbidity (MMM). ORWH's U3 program has supported over 50 awards, including biological and social determinants of severe maternal morbidity. ORWH's MMM response focuses on education and resources. Two workshops—NICHD/ORWH Pregnancy and Maternal Conditions That Increase Risk of Morbidity and Mortality Workshop on May 19 and National Institute of Nursing Research (NINR)– Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)– National Institute on Minority Health and Health Disparities (NIMHD)– Office of Research on Women's Health (ORWH)– Tribal Health Research Office (THRO) Workshop on Models of Care for Reducing Disparities in Maternal Health on September 29—were convened. In addition, ORWH's MMM web portal provides “one-stop shopping” across NIH and HHS, and the MMM brochure has been updated in 2020.

Inclusion: Recent inclusion initiatives include the Community Engagement Alliance (CEAL) Against COVID-19 Disparities; an interview on Research!America about Inclusion and SABV; the NIH Inclusion Across the Lifespan-II Workshop (September 2); the 2020-21 NIH Introduction to the Principles and Practice of Clinical Research (IPPCR), a free course that includes presentations by Drs. Clayton and Noursi on NIH inclusion policy; the NIH Inclusion Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research; and Diverse Women in Clinical Trials in collaboration with the FDA/OWH.

Research Investments: ORWH's Fiscal Year 2020 budget is \$45,458,253. Extramural funds across ORWH's signature programs are distributed as follows: SCORE, 35 percent; Building Interdisciplinary Research Careers in Women's Health (BIRCWH), 29 percent; Sex and Gender Administrative Supplements, 7 percent; Career Concepts, 5 percent; U3 Administrative Supplement, 5 percent; and R01, including a new R01 on Sex and Gender, 3 percent.

Outreach: Recent ORWH presentations include “ORWH Interprofessional Education: Courses and Resources on Sex and Gender and Women's Health” at the Sex and Gender Health Education 2020 Summit (Chyren Hunter, Ph.D.), and “Advancing Sex and Gender-Based Research: Transitions over the Life Course for Understanding Young Women's Risk for Affective Psychopathology” at the 2020 American Academy of Child and Adolescent Psychiatry 2020 Annual Meeting (Rebecca DelCarmen-Wiggins, Ph.D.). Drs. Noursi and Clayton published an article on “The Intersection of Maternal Morbidity and Mortality and Intimate Partner Violence in the United States” in *Current Women's Health Reviews* (2020) and Lisa Begg, Ph.D., M. Ghim and Dr. Clayton co-authored an article with ACRWH member Judith Regensteiner, Ph.D., on “Sex As a Biological Variable: The Importance of Curriculum Development in the 21st Century” in the *Journal of Women's Health* (2020).

ORWH's message on managing stress and building resilience during the pandemic was published in *NIH News in Health*, reaching 300,000. In addition, ORWH reached over 30,000 people through four Facebook Live broadcasts on careers among women in science, technology, engineering, mathematics, and medicine (STEMM) fields. To celebrate its 30th Anniversary, each issue of *Women's Health in Focus at NIH* this year focused on a theme, including ORWH history, careers, SABV, and inclusion. The monthly email *The Pulse* will highlight upcoming 30th Anniversary events, including the ORWH 30th Anniversary Virtual Meeting Series: Advancing the Health of Women through Science on December 14-16, 2020.

Whole Person Health

Elena Gorodetsky, M.D., Ph.D., ORWH, introduced Helene Langevin, M.D., Director, NCCIH, who presented NCCIH's journey to place whole person health at the center of its work.

As part of its recent strategic planning process, NCCIH examined definitions of "Complementary" in the Center's title, identifying dietary, psychological and physical as primary domains. Interventions in each domain are not isolated from one another, e.g., cardiac rehabilitation may include better eating, mindfulness-based stress reduction (MBSR), and exercise. NCCIH adopted the following explanation of the term "complementary:" Includes complementary therapies, practices and systems that use dietary, physical, and/or psychological approaches and may have originated outside of conventional medicine.

The planning process also addressed the "I" in NCCIH. Integrative health is considered a combination of conventional and complementary approaches. There are cross-currents of analysis (e.g. breaking the study of the body into separate systems), and synthesis or integration. Research focused on the breakdown of diseases into molecular parts has led to the biochemical treatment of diseases. Treating an individual's health conditions separately with a fragmented, disease-specific focus leads to drug-induced pathology over time. The alternative is to adopt the whole person perspective. Despite discussion about personalized medicine and precision medicine and some movement toward examining the interaction among different systems, e.g., systems biology and genome-wide association studies (GWAS), most research on the physical body remains in separate silos; the psychosocial aspects of functioning are usually not incorporated.

A related concept of interest to NCCIH is called inter-reception, i.e., how the nervous system receives, interprets, and integrates signals from within itself. This is basic research that the Center is promoting. However, a brain-centric approach may not provide the only perspective; a gut-centric or musculoskeletal-centric perspective may ultimately be more valuable because the microbes, inflammatory response, etc. that occur elsewhere in the body could influence the brain. Thus, the issue of integration is very multi-faceted, and may map out differently in terms of potential dietary, psychological, and physical interventions. NCCIH has adopted the following goal of integration, i.e., the "I" in the Institute's acronym: To advance research on the whole person and on the integration of complementary and conventional care.

In considering the "H" in NCCIH's acronym, Dr. Langevin noted that people tend to think about two extremes: health or disease. She posited that there is a state that falls between them, i.e., "unhealth." It is more difficult to reverse course from disease to unhealth than it is to move from unhealth to health, e.g., diabetes is reversible when it is still in the predisease phase, and impacted by obesity, a sedentary lifestyle, insomnia, and stress. These comorbid conditions do not happen independently, yet healthcare providers treat them as if they are independent with separate medications. If providers consider how to prevent these contributing factors at the predisease stage, there is the potential to reverse the condition through self-care, dietary, psychological, and physical interventions. Behavioral interventions can play an important role in helping a person move from "unhealth" back to "health."

Thus, whole person health can be summarized as supporting a person's health in multiple domains along the continuum between health and unhealth. Medicine today fails to pay attention to the process of a person becoming healthier. From a research perspective, there is a need to develop robust measures of well-being and resilience. More research is needed to understand basic physiological and psychological responses when people change, including mechanisms of repair, recovery, and regeneration and how these happen at the whole person level. This issue is particularly acute with

COVID. Thus, the “H” in NCCIH addresses health promotion and restoration, resilience, disease prevention and symptom management.

Because women use many complementary interventions, NCCIH funds a variety of research on women’s health. Common themes across this research includes pain, symptoms, stress, yoga, botanical, and inflammation, integrated into the whole person. NCCIH incorporates SABV into multiple processes, including review, clarification of expectations, recruitment tracking, addressing recruitment challenges, and data analysis. All of NCCIH’s large clinical trials are addressing sex differences in their analyses. Forty-three (43) percent of NCCIH’s grantees are female, compare to 29 percent across all of NIH.

Discussion: Committee discussion centered on how to promote the whole person concept in biomedical education, clinical practice, and research, including lobbying journal editors about its value and including it in public health messaging; how NCCIH leverages its relationships with other ICOs to achieve a bigger impact than its small budget would otherwise allow; and the important role of family and community in supporting people’s health journeys.

Sex Differences in COVID-19 Immunity

Rebecca DelCarmen-Wiggins, Ph.D., ORWH, introduced ACRWH member Sabra Klein, Ph.D. Dr. Klein explained that sex is a biological variable that affects people’s immune responses. Current research is demonstrating that hormone-dependent signaling affects immune cells to alter innate and adaptive immunity, development of inflammation, and development of autoimmune diseases. X-linked genes play a still-unknown role in these processes. There are a number of differences between males and females in genes that are encoded within the autosome. All of these factors combined account for how male and female immune responses differ in response to a virus such as SARS-CoV-2.

Immune function changes over the life course. During the reproductive years, females tend to mount more robust immune responses to various stimuli than do men. In older age, there is generally a reduction in some of those sex differences or even a reversal of them.

Sex and gender intersect to alter the outcome of infectious diseases like COVID. While SABV may influence the disease, pathophysiology, manifestation symptoms, and response to treatment, gender constructs such as lifestyle, nutrition, exercise, perceived stress and smoking influence outcomes such as disease perceptions, health-seeking behaviors, use of the health care system, decision-making, and the therapeutic response. Sex and gender influence the behavior of both providers and patients.

Females are more likely than males to survive a SARS-CoV-2 infection. Countries around the world are inconsistent in the degree to which they report sex-disaggregated data. What is striking is the extremely high death rate (87 percent) among men in the 34 percent of nations that report data with a male bias. In a *Science* article based on data from France, men with COVID-19 were consistently more likely to be hospitalized, admitted to an Intensive Care Unit (ICU), and to die. Severity of the disease increases among both older men and women, but men suffer more severe outcomes. Researchers at Johns Hopkins University are also identifying differences in COVID-related hospitalizations and deaths across racial/ethnic lines, with Latinx men being affected at younger age groups (40s and 50s), African American men most affected at age 60-75, and white men at 75 and older. These are important disparities to track over time.

Some hypothesized ways that sex could impact men's and women's responses to the virus include viral entry, viral sensing/early antiviral response, innate immune response, and adaptive immune response. The coronavirus uses a receptor called ACE2 to enter the body, particularly through respiratory epithelial cells. ACE2 is a sex-linked receptor that is regulated by oestrogens. TEMPRSS2 is a co-receptor the virus uses to attach itself to the cell. Androgens help to regulate this process. One Italian study observed that men treated for prostate cancer with anti-androgen therapy were less likely to become infected with COVID, suggesting that testosterone may play a role in men's greater susceptibility.

Once the virus has entered the cells, the body uses different receptors, e.g., pattern recognition receptors such as TLR7, an X-linked gene. Women have greater expression of TLR7 than do men. A recent study suggested that men with a mutation in TLR7 experience greater severity of COVID. Because it is a sex-linked gene, these mutations will occur in men but not women.

The issue of the cytokine storm among those already infected with the coronavirus has generated a great deal of scientific interest and there is some evidence to support it. The cytokine storm means a greater amount of inflammation occurring at the site of infection, i.e., the respiratory tract in the case of COVID-19. Men, older adults, and patients with severe COVID have a greater number of cytokines. In a recent study, there did not appear to be racial/ethnic differences in the amounts of these cytokines, nor differences based on Body Mass Index (BMI). Males, however, had greater concentrations of the pro-inflammatory cytokine interleukin 6 (IL-6) than females, as did older individuals. Those individuals with the highest concentrations of IL-6 had the lowest probability of survival.

Women have greater CD8+ T cell activity than men during COVID. CD8 refers to receptors on the T cells that kill virally-infected cells. It is not so much the number of T cells that differ between men and women, but their activity; there appears to be something transcriptionally different about these cells in women and men. In one study, the activity of these T cells remained fairly constant for women as they aged, but men experienced a statistically significant decline in T cell activity as age increased. The factors that account for this pattern are still unknown.

Antibodies are the gold standard for measuring efficacy of a vaccine. In a study at Johns Hopkins, Dr. Klein and her colleagues measured the immune response of 126 patients by examining convalescent plasma across multiple assays. Males, older adults, and hospitalized patients who had recovered had greater antibody responses than others. The researchers placed all study subjects into quartiles to look at the adjusted coefficients. Just being male could increase a patient's score by 1.5 points out of 12. Being older was not as significant (< 1 point increase). Being hospitalized could increase the score by 5.2 points. These factors could be investigated to better understand the progression of the disease.

Despite having more antibodies, males shed more virus and for a longer duration of time than females, according to Chinese studies that reported sex-disaggregated data.

Discussion: Questions posed to Dr. Klein included if there are sex differences in Multisystem Inflammatory Syndrome in Children (MIS-C) response. Unfortunately, one of the largest pediatric studies, Biospecimens from Respiratory Virus-Exposed Kids (BRAVE Kids), did not disaggregate their data for girls and boys, so the answer remains unknown. Regarding "long haulers," Dr. Klein noted that they tend to be women. Biology may play a role: In mice and humans, women have robust inflammatory response but run into problems later in turning that inflammation off.

The meeting broke for a virtual group photo and lunch at 12:07 p.m. and reconvened at 1:01 pm.

Bioengineering for COVID-19: The RADx Tech program at NIBIB

Rajeev K. Agarwal, Ph.D., ORWH, introduced Bruce Tromberg, Ph.D., Director, NIBIB, whose presentation addressed Rapid Acceleration of Diagnostics: RADx (Tech + ATP). On April 24, 2020, NIH received \$1.5 billion in COVID-related federal stimulus funding to support the RADx program. Of that funding, NIBIB received \$500 million to launch RADx Tech, a highly competitive challenge to identify the best candidates for at-home or point-of-care tests for COVID-19, and RADx Advanced Technology Platforms (RADx-ATP) that supports rapid scale-up of advanced technologies. Remarkably, the two initiatives launched on April 29, 2020.

The objectives of RADx Tech and RADx ATP are to 1) Expand COVID-19 testing technologies, including their number, type, and access; and 2) Optimize performance, both technologically and operationally, and by matching community needs. These objectives were accomplished via an “innovation funnel” that fast-tracked development: A National Call for Innovative Technologies on April 29 yielded 3,000 applications, of which 707 promising candidates were selected. In Phase 0, in a “Shark Tank”-like rapid selection process, those 707 candidates were reduced to 136. In Phase 1, Validation and Risk Review, 46 applications advanced to Phase 2, clinical test, regulatory approval, and scaling. By the end of the summer, 22 technologies advanced to manufacturing and distribution. More than 6 million tests per day are expected to be deployed by the end of 2020 through this process.

RADx Tech and ATP leverages NIBIB’s Point-of-Care Technologies Research Network (POCTRN) to drive implementation of the innovation funnel. The POCTRN has a RADx Validation Core; a RADx Clinical Studies Core; and a RADx Deployment Core. NIBIB is also working closely with the National Cancer Institute (NCI) to support digital health platforms in the form of apps to bring COVID tests into people’s homes and with Google and Apple to conduct digital contact tracing.

The biggest implementation challenge to RADx Tech and ATP was the need to deliver millions of tests per day to rapidly assess and track COVID-19 in a large and often asymptomatic population. This required a shift from standard medical diagnostic procedures, and the barriers to accomplish that have been both cultural and economic. RADx partnerships have been invaluable to developing guidelines for matching and deploying technologies and test protocols for a range of use cases, as well as to evaluate performance, impact, efficiency, and validation of models, and to inspire testing and digital health platforms for widespread screening and surveillance.

Discussion: ACRWH discussion about RADx centered on the opportunities for addressing sex differences in testing preferences and on the importance of messaging to the public about these technologies. NIBIB teams are beginning to address how to match technologies and messaging to the needs of communities, so this is a timely opportunity for such input.

Panel: COVID-19 and the Health of Women

Damiya Whitaker, Psy.D., M.A., ORWH, introduced the panel discussion about COVID-19 and women’s health, comprised of presentations by ACRWH members Alyson McGregor, M.D., and Neel Shah, M.D., as well as by panel moderator Monica Hooper, Ph.D., Deputy Director, NIMHD.

Not Just a Women’s Health Problem

Dr. Whitaker introduced Dr. McGregor who provided an overview of the coronavirus pandemic through a sex and gender lens, noting that COVID impacts men, women, and society. The World Health

Organization (WHO) found early on that men and women were getting infected at the same rate. However, sex-disaggregated data is not consistently reported. A COVID tracker at Global Health 5050 of 179 governments found that while 125 reported sex-disaggregated data on cases, only 8 reported such data on testing and on health care workers, only 18 on hospital admissions, and only 11 on intensive care unit (ICU) admissions. Eighty-eight reported sex differences on COVID-related deaths. Data on ICU admissions across nations indicated that men were consistently more likely to be admitted to the ICU. An analysis of COVID-related deaths from the United States established that men were more likely than women to die of the disease across all age groups.

Hormones: There are some gender differences that appear to emerge with men as more likely to have negative outcomes for COVID-19; one factor that may account for this gender difference is the presence of ACE2 receptors in the nasal passages to which the SARS-CoV-2 spike protein attaches are higher in men than in women. Hormones also play a role. The male hormone androgen upregulates TMPRSS2, the protein that helps the spike protein fuse to the cell surface, thus creating a more receptive environment for men.

Symptoms: Men are more likely to present with “hard signs” (e.g., cough, fever) of COVID, whereas women are more likely to present with “soft signs” (e.g., anosmia, dysgeusia, fatigue, headache); women’s symptoms are often not considered objective and hence may be difficult to measure.

Response to Therapeutics: Sex-specific data about responses to therapeutics is frequently missing. None have been reported for the effectiveness of remdesivir or dexamethasone; women are at greater risk from hydroxychloroquine because it prolongs the QT interval in women, which can lead to fatal arrhythmia. For convalescent plasma donation, a small study in China suggested that females mount a higher IgG antigen response compared to men, but then the pattern evens out over time. This study also found that when the disease is mild or general, men and women have about the same concentrations of IgG, but females mount a higher immune response (higher levels of IgG) when the symptoms are severe. This may help explain why the severity of illness is worse in men.

Vaccines: Based on experience with influenza vaccinations, scientists know that women mount a higher magnitude immune response, experience lower hospitalization rates and mortality, and have more severe adverse events from vaccines. Thus, women’s response to a COVID vaccine may be different than men’s, e.g., perhaps women will not require a booster shot. Understanding such differences may allow a more efficient public health vaccination effort.

COVID Treatment Considerations: If the patient is lying on her back in a supine position in the hospital, liquid can settle into alveoli in the lungs and cause acute respiratory distress syndrome (ARDS). Women are more likely than men to experience ARDS from a critical injury. Prone positioning allows for better aeration in the lungs and has been adopted for COVID treatment. Pregnant women in particular benefit greatly from a prone position. However, most work on prone positioning has been done on men and women’s different facial structures and body compositions are not currently being taken into account. Women are also less likely to be on protective ventilation and require different ventilator regulation because of their differences in body weight and composition. Highlighting these factors could improve providers’ understanding of sex-based differences in the treatment of COVID.

Sociocultural Behaviors: Men and women behave differently in their use of COVID preventive practices. For example, only 7 percent of women but up to 70 percent of men do not wash their hands

after visiting the rest room. Men are also less likely than women to not wear a face mask. Due to such behaviors, men are more likely to be super-spreaders of the virus than are women.

Healthcare Workers: Personal protective equipment (PPE) does not fit female healthcare workers as well as their male counterparts. On the website of the U.S. Centers for Disease Control and Prevention (CDC), the infographics illustrating proper use of PPE present only male models, suggesting a need for different messaging that is more inclusive of women and other racial/ethnic groups.

Psychological Stress: Women are more likely to undergo psychological stress due to stay-at-home orders, potentially suffering from worsening mental health and intimate partner violence (IPV).

Long-Haulers: A significant issue for women is their becoming “long haulers” who experience COVID symptoms well past the initial period of illness. CDC reports that one-third of non-hospitalized COVID patients are still symptomatic after two weeks; they are more likely to be women and to have fatigue.

Clinical Trials: There is a lack of consideration of sex and gender in clinical trials for COVID-19. Of 2,484 registered trials, only 16.7 percent mention sex and gender as a recorded variable and only 4.1 percent allude to it in the analysis plan.

System Disruptions to Childbirth During COVID-19

Dr. Whittaker introduced Dr. Shah who organized his presentation to address several overarching questions:

Are pregnant people more likely to be severely infected by COVID 19? Unclear. While the possibility of severe infection is similar to others, case reports suggest that pregnant people are more likely to be hospitalized. There is also some emerging evidence that pregnant people are more likely to become long haulers. Large cohort studies are currently underway to answer this question more definitively. Placental infection is possible but rare, as is vertical transmission. Doctors are currently seeing an increase in stillbirths and prematurity, but it is not yet clear if this is a true trend. Finally, maternal-infant transmission is possible but rare, and there are few cases of severe neonatal infections. Transmission via breastmilk appears unlikely. Thus, the pattern for infants is relatively reassuring.

Are pregnant people more likely to be severely affected by COVID-19? Definitely, based on peer-reviewed health services research. During prenatal care, pregnant people are experiencing fewer/disrupted visits compared to usual care. There are also reports of more IPV. During labor and delivery, pregnant people may experience less agency about the birth due to protocols of the pandemic (e.g., masks, less labor support, visitors). Hospitals have been discharging moms and babies more quickly without education to ease the transition to home.

Are SOME pregnant people more likely to be severely impacted by COVID-19? Definitely. In a recent CDC cohort study of COVID, nearly one-half of the pregnant participants were Hispanic. Native, Black, and LatinX people make up a disproportionate number of infections, severe cases, and deaths in the general population. Unfortunately, the field does not yet have robust data to address this pattern.

Is a higher performing system possible? Definitely. Maternal health is a leading indicator that racism is a clear and present danger. There is momentum to move the field to be more responsive to the needs of pregnant women. The National Institute of Child Health and Human Development (NICHD) issued a

birth settings report that noted that the pandemic has expanded access to a wider array of birth settings and provider types (e.g., midwives, doulas) and increased targeted use of telehealth and group visits. Investments in building community trust can lead to better maternal health outcomes.

NIH Scientific Initiatives: Women’s Health and Intersections with Underserved Populations

Dr. Whittaker introduced Dr. Hooper, who began her presentation by reviewing the mission of NIMHD: To lead scientific research to improve minority health and reduce health disparities. NIMHD raises awareness about health disparities and disseminates interventions to help achieve health equity. Dr. Hooper noted that the United States is currently in the midst of two pandemics, one of COVID-19 and the other of long-standing health disparities. Social determinants of health influence the existence and outcomes of both pandemics. The health of underserved women is of particular concern.

One important health outcome is life expectancy; African American women’s life expectancy in 2017 was 78.1 years, compared to 81.1 for White women and 84 for Latinas. In general, African American women have poorer health outcomes from breast cancer, heart disease, diabetes, maternal and reproductive health, and HIV/AIDS. The research literature tends to treat women as a monolithic group with an emphasis on gender and miss the importance of other factors. Thus, it is important to look at SABV through a health equity lens.

In general, income is independently and inversely related to mortality. Among major racial/ethnic groups, only Latinos have a lower income than African Americans. Yet, as noted above, Latino women have a higher life expectancy than African American women. This is known as the Hispanic mortality paradox, and may be explained by the “healthy migrant” effect or the average younger age of Latinos.

There is consistent evidence of a disproportionate impact of COVID-19 on minorities. This pattern may be explained by systematic inequities in society, including factors such as population density, occupational exposure, testing deserts, access to health care, and health care system implicit bias. Minorities often work in essential jobs where they are exposed to the virus. Women of color encounter specific issues, e.g., they are responsible for primary caregiving roles, which impacts their careers and employment, as well as their mental health and allostatic load and weathering. They have higher levels of obesity, a biological factor that results from multiple social determinants. A recent Pew survey revealed that women were less likely to say they would take a COVID vaccine today than were men; African Americans were the least likely to say they would accept a vaccine, a reflection of institutional distrust.

The scientific response to the two pandemics is critical. NIH has several initiatives, including Rapid Acceleration of Diagnostics-Underserved Population (RADx-UP) and Community Engagement Alliance (CEAL) Against COVID-19 Disparities. RADx-UP is a consortium of community-engaged research projects with the overarching goal of reducing COVID-19 associated morbidity and mortality disparities. It is conducting research on how to increase COVID-19 testing among underserved and/or vulnerable populations across the United States, including the best methods to increase reach, access, uptake, and impact, as well as the social, ethical, and behavioral implications. CEAL’s objectives are to conduct community-engaged research and outreach focused on COVID-19 awareness and education to address misinformation and distrust, and to promote and facilitate inclusion of diverse racial and ethnic populations in clinical trials (prevention, vaccine, therapeutics), reflective of the populations disproportionately affected by the pandemic. It achieves these objectives by establishing

communication networks across multiple channels and through engagement with trusted organizations and trusted messengers in the communities.

Discussion: Discussion addressed the need for more studies on the intersection of health disparities and women's health; whether there were exemplar communities with better maternal outcomes and the need for more consistent reporting of data by sex to identify such communities; the impact of COVID on access to other reproductive health services, such as contraception; increases in IPV and mental health problems during the pandemic; the controversial role of ACE2 in the placenta and its potential impact on the infection in pregnant women; conflicting research about patterns of stillbirth during the pandemic; and the need for better programs to support long haulers.

Preliminary Report on the BIRCWH Program Evaluation

Dr. Noursi introduced Dr. Begg, Senior Research Program Officer, ORWH, who shared a preliminary report on the recently-completed BIRCWH program evaluation. Established in 2000, BIRCWH is a mentored career development institutional grant program (K12) that connects junior faculty (i.e., BIRCWH Scholars) with senior faculty who have a shared interest in advancing research on the health of women and the consideration of sex and gender influences. Interdisciplinary mentoring teams are an essential component of the program.

Methods: The evaluation covered the period from 2000-2018. It began with a focus group with nine K12 experts to discuss potential evaluation metrics that could be used to measure program success. Telephone interviews were conducted with six Principal Investigators (PIs). Internet-based surveys were then conducted with all living PIs (N=88), a sample of 391 out of 687 scholars representing all BIRCWH institutions, and 80 mentors. Additional data sources that informed the study included Scholar curricula vitae (CVs), the NIH RePORTER database and NIH data files, and a list of BIRCWH scholar publications.

Evaluation Questions: 1) What are the career trajectories of the BIRCWH Scholars after their period of training? 2) What are the career trajectories of the Principal Investigators (PIs) and the Mentors involved in the program? 3) To what extent have Under-Represented Minorities (URMs) been recruited as BIRCWH Scholars? 4) What is the career advancement of the URMs trained within the program? and 5) How have institutions of the awarded BIRCWH Scholars leveraged BIRCWH programs?

Findings about BIRCWH Scholars: Approximately 75 percent of the BIRCWH Scholars were between 30-39 years old at the time they entered training, and about 80 percent were female. Fifty-four percent had a Ph.D. degree, and 42 percent held an M.D. Thirteen percent of BIRCWH Scholars can be considered under-represented minorities (URM), as defined by NIH; the percentage of URM Scholars increased from 3 percent in the early years to 21 percent in 2015-2018. Thirty-four percent of URM Scholars achieved tenure post-BIRCWH; 54 percent achieved leadership positions; and 23 percent, both.

Just under one-third (30 percent) of Scholars were awarded a K-series grant post-BIRCWH. Three-quarters (77 percent), both women and men, received one or more foundation, institution, or other type of grants post-BIRCWH. All of the more recent BIRCWH programs provided seed money or small institutional grants to support the Scholars.

Seventy percent of all Scholars reported receiving at least one R level grant. The Scholars were well-published with a median of 33 publications per Scholar. ORWH will work with the National Library of Medicine to ascertain the impact of these publications.

Most Scholars continued to work in academia, but an intriguing 15 percent moved to industry and one percent to government.

Findings about Institutional Impact: The PI survey revealed that their Scholars all had a primary mentor. Of these, about 98 percent indicated their scholars also had a secondary mentor; 86 percent indicated their scholars had a career mentor; and 86 percent indicated their scholars had a scientific content mentor. Almost all (96 percent) of the PIs reported their institution had other K12, KL2, and P30 programs and that these programs interacted with their BIRCWH program. PIs indicated that their institutions have benefited through increased interdisciplinary research, mentorship opportunities, and a greater focus on women's health and sex differences research. Almost one-third (31%) of the PIs indicated their BIRCWH program collaborates with one or more historically black colleges and universities (HBCUs).

Mentor Survey: Approximately 68 percent of responding mentors indicated that their institution's BIRCWH program did not require mentor training. Nonetheless, the mentors self-reported that they generally felt equipped for the task. More than 80 percent of the mentors thought the mentor/mentee roles were formally established, but only about 47 percent of the Scholars responded similarly. Most mentors—90% of those responding to the survey— indicated that they encouraged or facilitated networking activities for their Scholars. Approximately 75 percent of mentors indicated that their participation as a BIRCWH mentor expanded their own research portfolios, and almost 70 percent indicated that their participation has led them to conduct more interdisciplinary research.

Institutional Survey Data: Almost all PIs (96 percent) indicated that the BIRCWH program resulted in an increased focus on women's health, while 94 percent of PI respondents indicated that participation in the BIRCWH program had resulted in more interdisciplinary research. Most PIs (89 percent) indicated that the BIRCWH program had resulted in more mentoring or training, and almost 70 percent of respondents indicated this had resulted in a different style of mentoring at their institutions. Approximately 86 percent indicated that the BIRCWH program resulted in an increased focus on sex differences research; almost 60 percent of PIs stated that the BIRCWH program resulted in the creation of new centers or programs focused on women's health or sex differences. Just over half (52 percent) of PI survey respondents indicated that the BIRCWH program resulted in new courses or new content offerings focused on women's health or sex differences research at their institutions, and about 40 percent of PIs responded that participation in BIRCWH resulted in new scientific committees at their institutions to address women's health and sex difference research.

Preliminary Conclusions: The BIRCWH evaluation revealed that BIRCWH scholars have shown high levels of success as recipients of various funding sources for health research projects, and most have published in multiple medical or health-related journals. The data suggest that the BIRCWH program has been instrumental in providing mutually beneficial mentor–mentee relationships. PIs indicated that their institutions have benefited through increased interdisciplinary research, increased mentorship opportunities, and a greater focus on women's health and sex differences research.

Preliminary Recommendations for Further Analysis: Next steps include working with the National Library of Medicine to study the impact of the publications and journals in which Scholars published; analyze career advancement for all Scholars, especially URM; analyze careers in industry in more depth; analyze ways to increase participation of HBCUs, Hispanic-serving institutions, and/or

other minority-serving institutions; and analyze data further on the 71 percent of the BIRCWH scholars who self-reported that they have pursued women's health-related research post-BIRCWH.

Discussion: Discussion addressed the feasibility of comparing BIRCWH to other NIH K12 programs; potential assessment of the career trajectories of PIs and mentors, given the challenges facing mid-career women; and the feasibility of addressing the impact of COVID-19 on BIRCWH participants.

Open Discussion

The open discussion focused on recommendations for future directions for ORWH, descriptions of what ACRWH members' institutions are doing to support women in biomedicine during the pandemic, and recommendations for supporting women researchers in mid-career.

Recommendations for Future ORWH Directions: Recommendations included creating a program that focuses on racial minorities/health disparities from an intersectional perspective beyond career issues, while also keeping the women's health emphasis; planning ahead for the next health pandemic, e.g., antibiotic resistance, and how it affects women; and vaccine uptake among women.

How Institutions are Supporting Women in Biomedicine During the Pandemic: Programs identified by ACRWH members included mentoring junior faculty; holding retreats on health disparities; working with high schools to open the pipeline in the community for URM and women; starting a program for women post-docs, particularly those who are underserved; scheduling weekly meetings of post docs and early stage investigators to encourage productivity and maintain connections during the pandemic; planning a summit to encourage STEM careers; creating a major Center of Health Equity; launching a series of mental health initiatives focusing on women, people of color, and those most negatively impacted by the isolation resulting from the pandemic; inviting a speaker on civility at a faculty retreat to discuss how to engage appropriately; changing the promotions processes to more highly value the contributions women tend to make, e.g., service; and adding a year to the promotion process across the board.

Supporting Women in Mid-Career in Biomedicine: Dr. Clayton invited Committee members to identify potential targeted interventions that ORWH and/or NIH might consider. Discussion centered on continuing to address the underlying mechanisms identified in *Promising Practices for Addressing the Underrepresentation of Women in Science, Engineering, and Medicine: Opening Doors* from the National Academies of Sciences, Engineering, and Medicine (NASEM) while recognizing that they may take new forms, e.g., comments that undermine female speakers via the chat function during meetings on digital platforms; ORWH taking the lead in determining how best to document the impact of COVID-19 in both CVs and biosketches, and ways that institutions are handling the tenure clock.

Closing Remarks

Dr. Clayton adjourned the meeting at 4:01 pm.

Certification

We certify that the contents above are accurate and complete.

Janine A. Clayton

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Date 2/5/2021

Date 1/25/2021