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Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2017–2018

Office of Research on Women's Health and NIH Support for Research on Women's Health

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Letter from the ORWH Director

I am honored to share with you the accomplishments related to the health of women achieved by the National Institutes of Health (NIH) for fiscal years (FY) 2017 and 2018. This biennial report is issued by the NIH Advisory Committee on Research on Women's Health (ACRWH). It summarizes NIH research investments and scientific advances in women's health research and related programs during the reporting period. Within these pages, you will find updates on the programs, initiatives, and activities of the NIH Office of Research on Women's Health (ORWH), as well as research highlights on the health of women from each NIH Institute, Center, and Office (ICO). Additional reporting addresses adherence to NIH policies on the inclusion of women and minorities in clinical research and FY 2017–2018 NIH budgetary expenditures for research on women's health.

The 21st Century Cures Act (Public Law 114–255), signed into law on December 13, 2016, introduced significant changes that are facilitating the efforts of ORWH as a focal point to promote the health of women across NIH. Its provisions stand on the shoulders of the groundbreaking sex as a biological variable (SABV) policy by increasing trans-NIH collaboration, accelerating the promise of personalized medicine, and requiring that certain Phase III clinical trials report their results in ClinicalTrials.gov by sex and gender and by race and ethnicity. The 21st Century Cures Act requires that members of the advisory body known as the Coordinating Committee on Research on Women's Health (CCRWH), who serve as liaisons between ORWH and the ICOs, be either directors or their senior-level staff designees. The Institute and Center (IC) directors must consult annually with the ORWH Director about their objectives to ensure that they are taking women into account and are focused on reducing women's health disparities. The strategic plans issued by the individual ICs, required at least every 6 years, must document the same priorities.

The inclusion of women and minorities in NIH-supported clinical research has been law since the enactment of the NIH Revitalization Act of 1993. The Inclusion Across the Lifespan policy (related to section 2038 of the 21st Century Cures Act) builds on the 1993 legislation and subsequent NIH commitments to inclusion. It applies to grant applications and contract solicitations submitted after January 25, 2019, expanding current policies for the inclusion of women, minorities, and children in clinical research to include individuals of all ages. It clarifies that justifications for exclusion based on age must be because of valid ethical or scientific reasons and requires that participant age at enrollment be provided in progress reports. Implementation of these requirements will serve as a major milestone in achieving the goals of ORWH, as it will ensure that women, people of all ages, and racial and ethnic minorities are appropriately represented in clinical research and will shed light on whether the treatments studied would work for these populations. NIH has been preparing to implement this policy during the reporting period by revising policies and research guidelines and preparing to collect data on the age of participants.

The progress made by NIH in the past 2 fiscal years on behalf of women's health is impressive. However, we have more work to do as we continue to implement the SABV policy and the requirements of the 21st Century Cures Act. The NIH vision is that sex and gender influences are integrated throughout the biomedical research enterprise; that every woman receives evidence-based disease prevention and treatment tailored to her circumstances, needs, and goals; and that women in science careers reach their full potential. We are continuing to work toward these aims by building on our past successes and forging an increasingly transdisciplinary path for the next generation of women's health and sex/gender research.

Janine A. Clayton, M.D.
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health
October 23, 2019

Preface

This **Report of the Advisory Committee on Research on Women's Health (ACRWH) for Fiscal Years (FY) 2017 and 2018** describes the programs and initiatives undertaken across the National Institutes of Health (NIH) in service of the core mission of the NIH Office of Research on Women's Health (ORWH), which was established in 1990. The mission, outlined in the NIH Revitalization Act of 1993 (Public Law 103–43, Section 141), is:

- To advise the NIH Director on matters relating to research on women's health
- To strengthen and enhance research related to diseases, disorders, and conditions that affect women
- To ensure that research conducted and supported by NIH adequately addresses issues regarding women's health
- To ensure that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH
- To develop opportunities for and support recruitment, retention, reentry, and advancement of women in biomedical careers
- To support research on women's health issues.

The members of the ACRWH are pleased to submit this report to the NIH Director through the Associate Director for Research on Women's Health. They have reviewed the report and find that it provides essential information about the research, programs, and other activities of ORWH and all NIH Institutes, Centers, and Offices (ICOs). It describes the breadth and depth of the work undertaken by NIH to achieve its mission in FY 2017 and 2018, including:

- NIH-supported research on women's health and the influence of sex and gender on health and disease. This research was supported by the Institutes and Centers (ICs) across NIH, as well as by program offices within the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) in the NIH Office of the Director (OD).
- NIH budget allocations for women's health research, submitted by the U.S. Department of Health and Human Services' Office of the Assistant Secretary for Financial Resources.
- Continuing implementation of the sex as a biological variable (SABV) policy, including revised business practices.
- The continued focus on increased inclusion of women, minorities, and children in NIH-funded clinical research and efforts to lay the groundwork for grants/contracts submitted on or after January 25, 2019, when new requirements became effective based on the Inclusion Across the Lifespan policy.
- Creation of the Specialized Centers of Research Excellence (SCORE) on Sex Differences cooperative agreement program, based on its predecessor, the Specialized Center of Research (SCOR) on Sex Differences.
- Addition of a new administrative supplement program for populations of women that are understudied, underreported, or underrepresented (U3) in biomedical research. The first 2 years of the program took place in FY 17 and FY 18.

Over the past 2 fiscal years, the Trans-NIH SABV Working Group has continued collaborative efforts across the ICOs to improve rigor and transparency in NIH-funded research. In April

2017, the Trans-NIH SABV Working Group was charged with implementing the SABV policy into NIH business practices. With ORWH support, tools and resources were developed. SABV-related information has been disseminated to the ICOs through road shows across NIH, website resources, and grant review guidance. New and updated FAQs were developed for NIH and grant applicants. ORWH is continuing to provide support for consideration of SABV across the research continuum.

ORWH has made significant progress in another key element of the mission: to promote career advancement for women in biomedical careers. ORWH provided resources on mentoring, retention, and career advancement; leadership development; and work–life integration. The ORWH Director co-chairs the NIH Working Group on Women in Biomedical Careers with the NIH Director. This working group led the request for applications (RFA) titled "Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering," with support from 11 institutes and centers and 4 OD offices.

ORWH has supported supplements to assist women and men as they reenter research careers after interruptions for family or other responsibilities with participating ICOs. Resources for women in biomedical careers are regularly made available on the ORWH website at nih.gov/women and womeninscience.nih.gov. ORWH also hosts the Women of Color Research Network (https://womeninscience.nih.gov/women-of-color), an online members forum that aims to facilitate the research careers of women of color.

ORWH sponsored a workshop titled "Raising the Bar," which shed light on important issues about the relative disadvantages concerning the health of women in the U.S. in comparison with women in 16 other economically advanced nations. The workshop identified key research areas for

decreasing mortality and morbidity, in both the short term and the long term. It also identified areas in which small, relatively inexpensive interventions could have large effects. In 2017, insights from a "Raising the Bar" data analysis were presented at the 44th meeting of the ACRWH. The challenge now is to communicate and educate the research community and the public, in part by disseminating information to journal editors and colleagues and getting the word out to additional women. The report based on this workshop has been downloaded more than 5,000 times. It is available at orwh.od.nih.gov/research/resources/raising-bar-improving-health-women-united-states.

Outreach

NIH is continuing integration of sex and gender considerations throughout the entire research continuum, from basic and preclinical studies to clinical trials and implementation science. ORWH created the Sex and Gender in Health and Disease (SGHD) Scientific Interest Group (SIG) to align with these efforts, exploring the influences of sex as a biological variable and gender as a social construct as they relate to health and disease. This SIG fosters interdisciplinary collaboration among NIH scientists who work on or are interested in sex differences research at various points in the research continuum. It also aims to leverage the scientific expertise of neighboring research institutions. During the reporting period, three SGHD meetings were held that featured presentations from representatives of various disciplines who had relevant information to add to the discussion of sex and gender in research.

Policy

The 21st Century Cures Act, signed into law in 2016, introduced several significant changes in the way ORWH operates and how research is conducted. It has increased interaction and collaboration between the ORWH Director and the directors of all the NIH Institutes and Centers (ICs). The 21st Century Cures Act ensures that the ICs' strategic plans have objectives that take women into account and focus on reducing women's health disparities. The act's Inclusion Across the Lifespan section applies to grant applications and contract solicitations submitted after January 25, 2019. It also ensures that women, racial/ethnic minorities, and people of all ages are appropriately represented in clinical research. Participant age at enrollment must now be provided in progress reports, and certain Phase III clinical trials must report their results in ClinicalTrials.gov by sex and gender and by race and ethnicity, which reinforces the SABV policy.

The 21st Century Cures Act also calls for the NIH Director to encourage efforts to: (1) improve research related to the health of sexual and gender minority populations through increased participation in NIH clinical research and reporting, (2) develop valid and reliable methods for research relevant to sexual and gender minority populations, and (3) address methodological challenges.

Research

During 2018, the SCORE on Sex Differences cooperative agreement program was created. It was based on its predecessor, SCOR. SCORE investigators must develop a translational research program in an area that considers sex differences underlying women's health issues. A new requirement for SCORE investigators was the addition of a Career Enhancement Core (CEC). The goals of this CEC are to make funds available for junior faculty or established investigators who wish to enhance or refocus their careers on translational research in the area of sex differences and to facilitate educational opportunities for participants.

During the reporting period, ORWH also began to provide administrative supplements to support interdisciplinary, transdisciplinary, and multidisciplinary research focused on the effects of sex and gender influences at the

intersection of many social determinants. These social factors include, but are not limited to, race/ethnicity, socioeconomic status, education, and health literacy. Funds are awarded for one year to supplement NIH parent grants for preclinical, clinical, and behavioral studies related to U3 populations of women.

In Summary

The ACRWH would like to express gratitude for the focused attention of NIH leadership and scientific leaders in the ICOs. These leaders have conducted praiseworthy work on behalf of women's health and sex/gender issues over the past 2 years. Their successful strategies have included ICO-sponsored workshops, specific sex- and gender-related funding opportunity announcements, and working groups focused on women's health research. They have regularly initiated symposia, travel awards, scientific presentations, and journal publications. Science, technology, engineering, and mathematics (STEM) efforts by the ICOs have been attracting more women investigators to the field. Collectively, these accomplishments have demonstrated the importance of conducting research specific to women, taking a sex/gender-based research approach, analyzing data separately for males and females, and promoting the advancement of women in biomedical careers.

The ACRWH also acknowledges the accomplishments of the Coordinating Committee on Research on Women's Health, the Trans-NIH SABV Working Group, the Raising the Bar Working Group, the NIH Working Group on Women in Biomedical Careers (including the Women of Color Committee, the NIH Intramural Research Program, and the Committee on Advancing Women in Independent Positions), and the Sex and Gender in Health and Disease SIG. Their members are dedicated professionals from a range of backgrounds and scientific disciplines who are committed to achievements in women's health and the advancement of women in the sciences. Finally, the many accomplishments of NIH and the broader research community on behalf of women over the past 2 years would not have been possible without the exemplary work of all ORWH staff members.

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Organization of the Fiscal Years 2017–2018 Report of the Advisory Committee on Research on Women's Health

The fiscal years (FY) 2017–2018 report of the Advisory Committee on Research on Women's Health (ACRWH) illustrates how NIH has put science to work for the health of women during the reporting period. The sections that follow describe specific ORWH programs, initiatives, and activities; continuing implementation of the sex as a biological variable (SABV) policy across NIH, including updated business practices; research initiatives on the health of women conducted by the NIH Institutes, Centers, and Offices (ICOs); programs that promote the professional development of women in biomedical careers; and recent information on the inclusion of women and minorities as subjects in clinical research. Although this report highlights specific NIH research efforts on women's health, it is not exhaustive. Rather, the projects described convey the breadth and depth of the work undertaken by NIH during the reporting period to improve the health of women.

This report is divided into two major parts. The first describes ORWH activities and programs. The second describes the research and other activities of the individual NIH ICOs.

ORWH Activities and Programs

I. ORWH Background

II. ORWH Research

III. ORWH Biomedical Career Development Activities

IV. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

V. NIH Budget for Women's Health Research

Section I: ORWH Background describes the historical events leading to the establishment of ORWH and the mission assigned by congressional mandate. Current information is provided on NIH policies that support the ORWH mission, including ongoing SABV implementation, the requirements of the 21st Century Cures Act, and updates to NIH inclusion polices.

Section II: ORWH Research provides an overview of the research investments and co-funding dollars used by ORWH to further knowledge on diseases, disorders, and conditions that affect the health of women. It describes the work of specific ORWH programs designed to advance women's health research and increase understanding of the influence of sex and gender on health and disease.

Section III: ORWH Biomedical Career Development Activities highlights programs designed to increase the number of women in biomedical careers and the number of researchers focused on women's health concerns. It describes training and mentoring programs and initiatives that facilitate reentry of women into the biomedical workforce after extended absences.

Section IV: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research describes programs that monitor and foster the inclusion of women and minorities in NIH-funded clinical research. It includes aggregate data on the numbers of women and minorities who participated in this research.

Section V: NIH Budget for Women's Health Research summarizes NIH funding of women's health research for FY 2017–2018 by disease, condition, or initiative and by sex.

Activities of the NIH Institutes, Centers, and Offices

This section contains reports from the ICOs on the research, publications, and other activities conducted during the reporting period to advance the health of women.

Appendices

The biennial report appendices, starting on page 400 of this report, include:

- **Appendix A.** Coordinating Committee on Research on Women's Health (CCRWH) Roster
- **Appendix B.** ORWH-Co-funded Research Summaries
- **Appendix C.** Members of the NIH Working Group on Women in Biomedical Careers
- **Appendix D.** Aggregate Enrollment Data and Tables
- **Appendix E.** 2019 Biennial Advisory Council Reports Certifying Compliance With NIH Policy on Inclusion Guidelines

I. ORWH Background

The History of the NIH Office of Research on Women's Health

The NIH Office of Research on Women's Health (ORWH) has a long history of highlighting and promoting efforts to improve knowledge about the health of women at NIH through research on women's health, inclusion of women in clinical research, and support for the professional development of women in biomedical careers. The ORWH path began in 1983, when the U.S. Public Health Service Task Force on Women's Health Issues was established by the Assistant Secretary for Health, Dr. Edward N. Brandt Jr., and co-chaired by Dr. Ruth Kirschstein in response to the lack of research on diseases, conditions, and disorders that affect women. Two years later, the task force published a report, "Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume I," recommending an expansion of women's health research (U.S. Public Health Service, 1985). The next year, NIH incorporated a policy in line with these recommendations, urging greater inclusion of women in its clinical research (NIH, 1986a; NIH, 1986b). The following year, an additional policy recommended similar efforts to increase the inclusion of minority populations in clinical research (NIH, 1987).

In 1990, in response to a request from the Congressional Caucus for Women's Issues, the General Accounting Office (now known as the Government Accountability Office) investigated the implementation of these policies and found several issues hindering their uptake. Barriers included poor communication of the new standards, delays in implementation, and a lack of routine analysis by sex or gender in clinical studies (NIH, 1990). The analysis also found that implementation of these policies had little effect overall in increasing the inclusion of women in clinical research.

These findings prompted the establishment of ORWH that year within the NIH Office of the Director (OD). In 1993, the NIH Revitalization Act established ORWH in statute. The ORWH Director is mandated by this act to advise the NIH Director and staff on issues related to women's health research, strengthen research on health issues that affect women, ensure that NIH research addresses women's health and includes appropriate representation of women, and develop increased opportunities for women in biomedical careers.

Additionally, the act created two committees that advise the ORWH Director on issues related to women's health research. The Advisory Committee on Research on Women's Health (ACRWH) comprises leading non-Federal experts in many fields and provides the ORWH Director with recommendations from an external perspective. The Coordinating Committee on Research on Women's Health (CCRWH) is a trans-NIH group of Institute, Center, and Office (ICO) directors or their designees who can offer suggestions based on internal knowledge of NIH and its processes.

In 2006, the NIH Reform Act led to a reorganization of the NIH OD. ORWH was placed within the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), which focuses on trans-NIH concerns. The ORWH statutory responsibilities were unchanged, but its placement in DPCPSI emphasized its role as the focal point for NIH research on the health of women across the ICOs. This interconnection allows ORWH to fully engage with the ICOs and ensure that all science at NIH properly incorporates issues related to women's health. The current ORWH mission statement emphasizes the importance of biomedical research that appropriately includes women, considers sex and gender, and highlights

the ORWH role in facilitating this research. Additional efforts shepherded by ORWH include understanding and decreasing disparities among populations of women with various demographic characteristics—including age, socioeconomic status, and racial and ethnic group membership—and supporting research and training in interdisciplinary areas.

In 2016, the 21st Century Cures Act (Public Law 114–255) introduced significant changes affecting the conduct of NIH research and communication between ORWH and the NIH Institutes and Centers (ICs). It requires that CCRWH members be either directors or senior-level staff appointed by the directors. Also, the IC directors must consult annually with the ORWH Director about their ICs' objectives and portfolios to ensure that they are taking into account the health of women and that they address reducing women's health disparities. The strategic plans issued by the individual ICs, required at least every 6 years, also must address women's health and the reduction of women's health disparities. Although the inclusion of women and minorities in NIH-funded or -supported clinical research was enacted into law in 1993, the 21st Century Cures Act set forth the Inclusion Across the Lifespan policy,[1] which applies to all grant applications and contract solicitations submitted on or after January 25, 2019. It has expanded policies for the inclusion of women, minorities, and children in clinical research to include individuals of all ages; states that justifications for exclusion criteria based on age must have valid ethical or scientific reasons; and requires that participant ages at enrollment be provided in progress reports. The 21st Century Cures Act also requires that applicable[2] Phase III clinical trials report their results in ClinicalTrials.gov by sex and gender and by race and ethnicity. NIH prepared for implementation of this policy during the reporting period by revising policies on the inclusion of children, revising guidelines on age, and preparing to collect data on the ages of participants in clinical research.

Trans-NIH Strategic Plan for Women's Health Research and Emerging Strategic Priorities

Guiding Tomorrow's Research on Women's Health

In September 2010, ORWH released the Trans-NIH Strategic Plan for Research on Women's Health, titled *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research* (ORWH, NIH, HHS, 2010a; ORWH, NIH, HHS, 2010b; ORWH, NIH, HHS, 2010c). This research agenda was informed by input from the scientific community and public partnerships, including patient and advocacy groups. Three volumes—including an executive summary, reports from regional scientific workshops, and public testimony—summarize the Trans-NIH Strategic Plan for Research on Women's Health for 2010–2020. These documents served as a framework for research investigations galvanized by cutting-edge technologies and emerging scientific concepts to advance women's health research through collaborations among disciplines and across the research spectrum, from basic to clinical and translational (Pinn, Clayton, Begg, & Sass, 2010). In addition to providing a framework for research on the health of women across the NIH ICOs, it guided all ORWH activities, ensuring that resources capitalized on opportunities for advancing scientific research and career objectives for women in biomedical professions.

The research agenda comprised the following cross-cutting goals, each containing several objectives:

- Increase the study of sex differences in basic biomedical and behavioral research

1 NOT-OD-18-116: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html

2 This requirement does not apply to NIH-defined Phase III trials not considered "applicable" clinical trials under 42 CFR Part 11.

- Incorporate findings of sex differences in the design of new technologies, medical devices, and therapeutic drugs
- Actualize personalized prevention, diagnostics, and therapeutics for women and girls
- Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research
- Achieve a clearer understanding of women's health issues through strategic communication of research findings to diverse audiences
- Employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce.

Read the entire strategic plan at https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_StrategicPlan2020_Vol1.pdf.

Increasing Consideration of Sex as a Biological Variable in Preclinical Research

Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research outlined areas in which ORWH could improve the foundation of knowledge about women's health, evaluating and highlighting areas in which women's health knowledge was particularly lacking. The most critical gap noted was the dearth of preclinical research data related to female biology, physiology, and pathology. This gap is attributed to the historical tendency of research studies to include primarily male animals, ignore the sex of cell study donors, and overlook potential differences in study effects between males and females.

Closing this gap in animal and cell model research knowledge is critical, because these models provide foundational knowledge about basic biological processes and pathways to the treatment of both male and female humans. The ORWH mission requires NIH-wide efforts to ensure that studies appropriately address sex as a biological variable (SABV). These efforts aim to increase rigor, reproducibility, and transparency[3] in NIH-funded research.

ORWH led the charge and has urged greater consideration of SABV in animal and cell studies, i.e., ensuring that NIH-funded research purposefully addresses the biology of females and males. Starting in January 2016, NIH investigators were required to account for SABV in studies of vertebrate animals and humans.[4] Grant applicants are now required to define how they plan to address SABV, and study sections must assess these plans. ORWH has developed several resources that specifically address the importance of the consideration of sex as a biological variable to enhance rigor and reproducibility and of the NIH policy notice NOT-OD-15-102, "Consideration of Sex as a Biological Variable in NIH-funded Research." ORWH announced the continuation of the Administrative Supplement for Research on Sex/Gender Influences. This program, established in FY 2013, provides funding to investigators who are seeking to add a sex/gender component to an existing research project. ORWH and the NIH Common Fund sponsored a workshop titled "Sex as a Biological Variable" on October 26–27, 2017, on the NIH main campus. This workshop brought together NIH grantees who had received funding from the administrative supplement program to present their SABV findings, share lessons learned, and help chart the way forward in supporting other researchers incorporating sex as a biological variable into their research. ORWH also relaunched the ORWH Women's Health Seminar Series, which presents research on topical scientific issues related to sex and gender.

ORWH has sought to enhance the implementation of the SABV policy across NIH

3 NOT-OD-15-103: Enhancing Reproducibility through Rigor and Transparency - https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html

4 NIH Guide Notice NOT-OD-15-002: Consideration of Sex as a Biological Variable in NIH-funded Research - https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html

and among external stakeholders. The Trans-NIH SABV Working Group disseminated information on new SABV business practices to the ICOs, the larger biomedical research community, and the public. Resources for the ICOs were provided through road shows and online tools, including information from the Office of Extramural Research and ORWH websites. Program officials, institutional review groups (IRGs), reviewers, and grantees have been provided with appropriate guidance and tools related to grant applications and review processes. Tools and resources also have been targeted to the scientific community, including investigators; editors, publishers, and reviewers; professional associations and scientific societies; and other private and Federal partners. These resources have included numerous research symposia, workshops, seminars, presentations at national and international meetings, roundtables, and journal editor guidelines. Finally, significant media and outreach efforts have been undertaken to reach the public, including patients, families, health care providers, and patient advocacy groups. ORWH continues to make current and emerging information on the health of women and SABV policy available through its website, through the ORWH newsletter, in presentations and media interviews, and through practice guidelines. These efforts are continually evaluated and refined based on the guiding principle of "enhancing science and health with SABV."

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II. ORWH Research

Introduction: Research Mission

The NIH Office of Research on Women's Health (ORWH) is housed under the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the NIH Office of the Director (OD); its mission is to put science to work for the health of women. This includes stewardship of research on the diseases, disorders, and conditions that affect women's health. ORWH works across the NIH Institutes, Centers, and Offices (ICOs) to ensure that women are appropriately represented in all biomedical and behavioral research studies funded by NIH and promotes consideration of sex as a biological variable (SABV) to ensure that key sex differences in biomedical research and clinical trials are not overlooked.

ORWH promotes interdisciplinary and collaborative partnerships and invests in programs that strengthen the diversity of the biomedical workforce. ORWH research efforts focus on fostering co-funding initiatives, i.e., funding research to advance the health of women in collaboration with other ICOs; implementing trans-NIH strategic plans for women's health research; and ensuring compliance with legislative requirements related to research on the health of women.

The 21st Century Cures Act (Public Law 114–255), signed into law on December 13, 2016, requires that members of the advisory body known as the Coordinating Committee on Research on Women's Health (CCRWH), who serve as liaisons between ORWH and the ICOs, must be either directors or senior-level staff designees. The ICO directors must consult annually with the ORWH Director about their objectives to ensure that they are taking the health of women into account and are focused on reducing women's health disparities. In addition, the NIH Institutes and Centers' (ICs) strategic plans must document these priorities. The act also requires that applicable Phase III clinical trials report results in ClinicalTrials.gov by sex and gender and by race and ethnicity and expands the NIH inclusion policy to individuals of all ages. This Inclusion Across the Lifespan policy applies to grant applications and contract solicitations submitted on or after January 25, 2019. Implementation of the 21st Century Cures Act's requirements serves as a major milestone in women's health to ensure that women, people of all ages, and racial and ethnic minorities are appropriately represented in clinical research and will lead to evidence indicating whether the treatments studied at NIH would work for these populations.

Driving the NIH Women's Health Research Agenda

The commitment of ORWH to women's health research relies on supporting science that paves the way for effective clinical treatments for women. When the evidence base on females is expanded, clinicians will have more information on how specific treatments affect women and girls. ORWH fulfills this commitment by partnering with the ICOs to fund research that will address gaps or topics specific to women's health. Successful programs that have been developed through funding announcements include the Specialized Centers of Research Excellence (SCORE) on Sex Differences program, the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program, and the Administrative Supplement for Research on Sex/Gender Differences.

In addition to funding announcements produced by or with the support of ORWH, women's health research also may be initiated through an internal request for co-funding from an ICO. These

requests are submitted to ORWH monthly and carefully reviewed to determine whether such research would support the ORWH research mission and the goals of the 2010–2020 Trans-NIH Strategic Plan for Women's Health Research.

Increasing Consideration of Sex as Biological Variable in Preclinical Research

The health of women is affected by a complex intersection of multiple factors at the levels of the individual, family, community, and society (Bird et al., 2010; Early, 2016; Montez et al., 2016; Singh et al., 2017). Biological factors, such as sex, intersect with the social and contextual aspects of a woman's life to affect health status, disease presentation, treatment response, and quality of life. The area of preclinical research data related to female biology, physiology, and pathology is one in which women's health knowledge is particularly lacking. This gap was caused by the historical tendency of research studies to include primarily male animals, ignore the sex of cell study donors, and overlook potential differences in study effects between males and females.

Closing this gap in animal and cell model research knowledge is critical, because such information provides foundational knowledge about basic biological processes and pathways to treatment for both male and female humans. The current ORWH mission includes significant participation in NIH-wide efforts to ensure that studies appropriately address SABV. These efforts are a component of broad NIH efforts to increase rigor, reproducibility, and transparency.[5] A *Nature* article by Janine A. Clayton, M.D., Director of ORWH, and Francis Collins, M.D., Director of NIH, helped lay the groundwork for new policy and processes (Clayton and Collins, 2014). Since January 2016, investigators funded by NIH have been required to account for SABV in studies of vertebrate animals and humans.[6] The appropriate strategy for doing so depends on the research question under study and the current understanding of sex influences on that question.

ORWH is actively helping to implement this effort across NIH and with external stakeholders by providing supplemental funding to existing NIH grants to add the subjects, tissues, or cells necessary to study both sexes. NIH also provides funding to increase the power of studies to ensure that they can address influences of sex or gender.

To reinforce the consideration of sex in preclinical research and the SABV policy, ORWH is curating resources on SABV and making them publicly available. They include:

- FAQs that reflect field-specific questions identified during the peer review process for applications using males and females, including specific guidance on preclinical research using primary cells
- A web-based course on the major physiological differences between women and men, the influence of these differences on illness and health outcomes, implications for policy, and clinical research and care appropriate for interprofessional health education. The course was created by ORWH in collaboration with the Office of Women's Health (OWH) in the Food and Drug Administration (FDA)
- An e-learning course developed with the National Institute of General Medical Sciences (NIGMS) that is oriented toward researchers and clinicians and serves as a resource on SABV for designing research studies, employing statistical and power analyses, preparing NIH grant applications, and training the next generation of investigators.

5 NOT-OD-15-103: Enhancing Reproducibility through Rigor and Transparency. grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html

6 NIH Guide Notice NOT-OD-15-102: Consideration of Sex as a Biological Variable in NIH-funded Research. grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html

ORWH Programs to Advance Women's Health Research and Understanding the Influence of Sex and Gender on Health and Disease

Specialized Centers of Research Excellence on Sex Differences

In FY 2018, ORWH announced the new Specialized Centers of Research Excellence (SCORE) on Sex Differences program, which is supported by a cooperative agreement (i.e., a U54 grant mechanism) under funding opportunity announcement (FOA) RFA-OD-18-004. The SCORE on Sex Differences was based on its predecessor, the Specialized Center of Research (SCOR) on Sex Differences program, which was funded by a P50 grant. A significant change from the SCOR program to the SCORE program was the addition of a mandatory career education core (CEC) to support pilot research. The goals of the CECs are to make funds available for junior faculty or established investigators who wish to enhance or refocus their careers on translational research in the area of sex differences and to facilitate educational opportunities for participants. The current SCORE program is a disease-agnostic, interdisciplinary, translational research program on sex differences that serves as a national resource on translational research at multiple levels of analysis, identifying the role of biological sex differences in the health of both men and women.

The participating SCOREs are serving as vital hubs for piloting research funding in sex and gender research and are disseminating innovative, sex-based, translational research methods and best practices. In addition, they provide leadership in the development and promotion of standards and policies for the consideration of sex differences in biomedical research. ORWH is advancing sex differences research across NIH and coordinates cross-SCORE interactions by working in partnership with the NIH ICOs to implement and fund this program. Accounting for biological sex in research leads to a better understanding of the diversity of health outcomes, and this knowledge can be applied to the next generation of interventions and medical treatments.

In FY 2018, ORWH co-funded six SCOREs with three NIH institutes—the National Institute on Aging (NIA), the National Institute on Drug Abuse (NIDA), and the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK)—receiving an overall investment of $9.25 million. The FOA was reissued for FY 2019 under RFA-OD-19-013.

From FY 2013 to FY 2017, ORWH sponsored an annual SCOR directors meeting on NIH's main campus. These meetings highlighted the benefits of an interdisciplinary team science approach to translational basic research toward clinical practice. Research from the former SCOR-P50 program provided numerous insights into the sex differences observed in addiction and stress responses, such as gender-sensitive treatment for tobacco dependence and progesterone effects on impulsivity, smoking, and cocaine stress; in musculoskeletal diseases; in mental disorders, including depression and the brain's response to drug cues and to treatment; in pelvic floor dysfunction, fracture risk, and long-term outcomes; and in recurring urinary tract infections. Over the years, the SCOR program led to successful cross-organization collaborations, an increased team science approach, and high-impact peer-reviewed publications. The enhanced 2018 SCORE program builds on this foundation. More information on SCORE can be found at orwh.od.nih.gov/research/funded-research-and-programs/specialized-centers-research-sex-differences-score.

Administrative Supplements for Research on Sex/Gender Influences

In 2001, the Institute of Medicine (now called the National Academy of Medicine) published a report titled *Exploring the Biological Contributions to Human Health: Does Sex Matter?,* which highlighted the fact that women and men are

characterized by both sex and gender. In this report, "sex" referred to being male or female based on reproductive organs and biological functions assigned by chromosomal complement. "Gender" referred to socially defined and derived expectations and roles rooted in biology and shaped by the environment and experience. Sex and gender, as defined above, are important considerations in many areas of research, including basic biological, psychological, social, and behavioral studies. Consideration of these variables is critical to the accurate interpretation and validation of research findings that affect various aspects of women's health.

In 2013, ORWH initiated a trans-NIH program to catalyze exploratory research on sex/gender differences by providing administrative supplements to existing peer-reviewed NIH-funded grants. The administrative supplements initiative provided 1-year supplements of approximately $100,000 to funded research; new work and approaches were required to fall within the scope of the original parent grants. The initiative advanced research on sex/gender influences, predating the NIH SABV policy issued in June 2015.[7] The program supports three research approaches: (1) adding the opposite sex/gender (the addition of animal or human subjects, tissues, or cells of the sex opposite of those used in the parent grant to allow sex/gender-based comparisons), (2) increasing sample size (the addition of more animal or human subjects, tissues, or cells to a sample that already includes both males and females to increase the power of a study to analyze for a sex/gender difference), and (3) analyzing existing data (comparative analyses of extant samples/datasets/databases and/or data mining to investigate the role of sex/gender).

- In FY 2017 (FOA: PA-17-078), ORWH awarded 52 applications for a total of $4.5 million across 17 NIH Institutes and Centers (ICs), with an overall success rate of 35.37%.
- In FY 2018 (FOA: PA-18-658), ORWH awarded 44 applications for a total of $4.2 million across 19 ICs, with an overall success rate of 42.7%.

Since the inception of this program in FY 2013, ORWH has invested more than $33 million in administrative supplemental funding to support 343 investigators across the ICOs to explore research on sex/gender influences in preclinical and clinical studies. To further advance this important but underappreciated area of research, ORWH appropriated $3 million in additional funding for FY 2019. More information on the administrative supplements program is available at orwh.od.nih.gov/research/funded-research/administrative-supplements.

Research on the Health of Women in Understudied, Underrepresented, and Underreported (U3) Populations

In 2017, a new administrative supplement was established to explore health issues at the intersection of co-occurring contextual factors among women from populations that have been understudied and underrepresented in biomedical research and often underreported in surveillance activities (known as U3 populations). This supplement supports interdisciplinary, transdisciplinary, and multidisciplinary research focused on the effects of sex/gender influences at the intersection of many social determinants, including, but not limited to, race/ethnicity, socioeconomic status, education, health literacy, and socioecological contexts as modifiers in human health and illness. Projects funded under this program must include a focus on one or more NIH-designated health disparities populations, which include Blacks/African Americans, Hispanics/Latinos, American Indians/Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders, socioeconomically disadvantaged populations, underserved rural populations, and sexual and gender minorities (SGM). Projects that combine one or more of these populations are encouraged.

7 NOT-OD-15-102, NOT-OD-15-103

ORWH works in collaboration with the NIH ICOs to identify research areas that would benefit from an interdisciplinary approach focused on these populations of women. Since the program's inception in 2017, it continues to grow, with an expanding focus on a diverse range of projects targeting the health of U3 women. Projects funded in FY 2018 focused on behavioral science; prevention interventions; infectious diseases, including HIV infection; and environmental stressors and influences, such as the role of cultural resiliency and the built environment in postpartum depression among Mexican women.

As of 2018, more than 30 supplements were awarded, with over 80% of the NIH ICs participating. The funding announcement was reissued and expanded for FY 2019. A seminar/webinar series was developed to nurture discussion and interest in the complex issues that affect U3 women. It is anticipated that collaborations to further explore the many intersections among health, culture, context, social determinants, and other factors will further expand the knowledge base and lead to interventions for these populations.

ORWH R56 Program

The R56 program is a collaborative effort sponsored by three offices within DPCPSI: ORWH, the Office of Dietary Supplements (ODS), and the Office of AIDS Research (OAR). This collaboration greatly enhances the breadth, depth, and range of research topics of mutual interest available to the NIH ICOs. It supports innovative, potentially high-impact research that, if implemented successfully, could advance knowledge of women's health and/or sex/gender influences on human health and disease. It is a recognized grant mechanism designed to provide short-term funding for high-priority projects.

ORWH uses this mechanism to partner with the NIH ICOs to fund or co-fund meritorious research on women's health that otherwise would not be funded. The objective is to allow investigators to significantly improve their research proposals so that submission/resubmission applications can succeed in the highly competitive peer review and fiscal environments. Only the ICOs can apply for R56 funding; investigators cannot directly submit these applications.

In FY 2017, 12 projects were funded from six NIH Institutes and Centers (ICs), for a total of $3,598,936. Projects were funded in collaboration with the National Cancer Institute (NCI, four projects); the National Heart, Lung, and Blood Institute (NHLBI, one project); the National Institute of Allergy and Infectious Diseases (NIAID, one project); the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD, three projects); the National Institute on Drug Abuse (NIDA, two projects); and the National Institute of Dental and Craniofacial Research (NIDCR, one project). The research topics addressed were:

NCI:

- Biomimetic nanovesicles to overcome multiple physiological barriers for primary and metastatic triple-negative breast cancer therapy
- Nanosensor-based phenotypic screening for precision therapy of cancer stem cells
- Integrated nano-therapeutics to overcome tumor plasticity and resistance
- Nanoparticle transport through tissues.

NHLBI:

- Effects of inhaled nicotine on vascular miR-24 activity and abdominal aortic aneurysm formation.

NIAID:

- Role of Hofbauer cells in fetal infection/ inflammation.

NICHD:

- The genetics of primary ovarian insufficiency

- Cytoplasmic maturation in mouse oocytes
- Ovarian ultrasonography for the clinical evaluation of polycystic ovary syndrome.

NIDA:

- Women's response to e-cigarette cues
- Socio-moral processing in female stimulant abuse and psychopathy.

NIDCR:

- Analysis of MyD88-mediated immune activation in Sjögren's syndrome pathogenesis.

In FY 2018, ORWH funded six applications from five ICs, for a total of $1,796,525. Projects were funded in collaboration with NCI (one), NHLBI (one), NICHD (one), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, two), and the National Institute of Nursing Research (NINR, one). The research topics addressed were:

NCI:

- *In vivo* methodology for the discovery and validation of miRNA biomarkers in cancer.

NHLBI:

- Hypertension in adults who had intrauterine growth restriction: Beneficial effects of perinatal intervention.

NICHD:

- Role of the DNA helicase LSH in female meiosis.

NIDDK:

- Discerning the influence of maternal obesity, weight gain, and diet on the infant microbiota and programming of nonalcoholic fatty liver disease
- A practice-based intervention to improve care for women with urinary incontinence.

NINR:

- Sex-specific brain injury and symptoms in sleep apnea.

More information is available at https://orwh.od.nih.gov/research/funded-research-and-programs/co-funded-research.

Examples of R56 Grants Awarded

Grant # 1R01AI131613-01

Title: Role of Hofbauer Cells in Fetal Infection/Inflammation

Fetal inflammation and infection remain a major cause of neonatal mortality and morbidity. Hofbauer cells (HBCs), a novel understudied cell type, are placental macrophages of fetal origin located beneath the syncytium and adjacent to fetal capillaries. HBCs are involved in the placental response to a viral-bacterial polymicrobial infection. Previous studies showed that histological chorioamnionitis (HCA), microbial-driven infiltration of leukocytes to the maternal–fetal interface, was associated with a focal increase in the number of HBCs in the placental villus. The central hypothesis of this study is that herpes virus infection of HBCs suppresses their inflammatory responses to bacteria, inhibiting HBCs' ability to control bacterial growth and therefore exacerbating placental/fetal infection and chorioamnionitis. The potential impact of this study for public health includes the possibility of understanding how polymicrobial infection during pregnancy results in bacterial infection of the fetus, identifying the importance of Hofbauer cells in placental response to a viral-bacterial polymicrobial infection, and identifying a potential intervention to reduce bacterial infection of the fetus.

Examples of R56 Grants Awarded

Grant # 1R56DA044210-01

Title: Women's Response to E-Cigarette Cues

Cigarette smoking is still the largest cause of preventable death in the United States, killing almost a half-million people a year. In 2006 and 2007, e-cigarettes entered the U.S. market and were often promoted as a safer alternative to traditional cigarettes. Currently, an estimated 3.7–6.8% of U.S. adults use e-cigarettes, with the highest rates (14.2%) by people ages 18–24. Women may be at a disadvantage in attempts to quit smoking compared with men. They often have more difficulty setting a smoking quit date and have some unique barriers, such as weight and appearance concerns, greater social support for smoking, and smoking for mood enhancement. Women are specifically targeted in e-cigarette marketing and advertising. Thus, it's possible that exposure to women-marketed e-cigarette products could pose a new trigger for women that influences them to continue their tobacco addiction or increases the risk of relapse for those who have quit. The goal of the study is to examine exposures to e-cigarette cues and e-liquid flavors that are specifically marketed to women. This study is timely because of the need for public health awareness of the impact of exposure to e-cigarette use across several at-risk subgroups.

Grant # 1R56HL143459-01

Title: Hypertension in Adult IUGR Offspring: Beneficial Effects of Perinatal Intervention

Placental ischemia, the initiating event in preeclampsia (PE), is the leading cause of intrauterine growth restriction (IUGR) in the Western world. Numerous studies indicate that an increase in blood pressure (BP) is observed in individuals born following PE. The goal of this study is to determine whether maternal interventions improve fetal growth and mitigate the increase in BP in the offspring in two well-established rodent models of PE and IUGR. This study addresses a critical need to develop maternal therapeutic interventions that not only improve maternal health in PE but also mitigate fetal growth restriction and increased BP in the offspring.

Grant # 1R56DK114711-01A1

Title: Discerning the Influence of Maternal Obesity, Weight Gain, and Diet on the Infant Microbiota and Programming of Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) affects approximately 34% of obese children ages 3–18 in North America, and half have already progressed to the more severe nonalcoholic steatohepatitis (NASH) at the time of diagnosis. Maternal obesity, excess gestational weight gain (GWG), and gestational diabetes mellitus (GDM) are all associated with increased risk for childhood obesity and NAFLD. The goal of this study is to determine how the unique infant microbiome composition found in infants born to mothers with obesity, excess GWG, or GDM may promote weight gain and the early onset of chronic low-grade inflammation, including NAFLD, and whether a dietary intervention during pregnancy can promote healthier outcomes in children. This study offers the eventual possibility of a probiotic intervention to interrupt the transmission of risk for NAFLD from mother to child. Specific microbial groups may promote the early onset of chronic low-grade inflammation, which is a hallmark of obesity-associated metabolic disorders, including NAFLD.

ORWH Co-funding With the ICs in Targeted Research Activities

Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative

The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, described at www.braininitiative.nih.gov and www.braininitiative.org, catalyzes the development and application of innovative technologies to revolutionize our understanding of the human brain. ORWH, along with some of the NIH ICs and others whose mission and research priorities complement the goals of the BRAIN Initiative, provide ad hoc support for this work.

Despite the many advances in neuroscience that illuminate how individual brain cells, synapses, and simple circuits work, the higher complex functions of the brain are not clearly understood. The underlying causes of most neurological and psychiatric conditions also are not apparent because of the complexity of the disorders and of the human brain. The BRAIN Initiative arose to meet this challenge—to develop a more complete set of tools and methods for understanding how the brain functions, both in health and in illness.

The 10 NIH neuroscience ICs, whose missions and research portfolios best align with the goals of the BRAIN Initiative, manage the BRAIN awards, and they had given awards to more than 500 investigators as of January 2018, reflecting an investment of approximately $559 million. This investment has resulted in over 330 publications documenting remarkable advancements in technologies and methods, which should enable important insights into human brain function. As the BRAIN Initiative enters the second half of its 10-year term, NIH plans to build on the initiative's current emphasis on technology development with an added focus on the production and dissemination of resources for understanding the brain.

ORWH-supported Pain Research Activities

Chronic pain is a debilitating symptom of many chronic diseases, and it disproportionally affects girls and women across the life course. Because addressing pain is so important to the health of women, the co-funding of meritorious pain initiatives is a significant component of the ORWH research portfolio.

Common chronic pain conditions include headache, low back pain, fibromyalgia, cancer pain, arthritis, and endometriosis. These conditions often co-occur in an individual, and some of these disorders may share common mechanisms. Overlapping chronic pain conditions occur more often in women than in men and include migraine, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), endometriosis, fibromyalgia, inflammatory bowel disease, interstitial cystitis/bladder pain syndrome, temporomandibular joint disorders, and vulvodynia. They can be exacerbated by environmental and/or psychosocial factors. Research has documented differences in the development and persistence of pain conditions across the life course related to age, sex, gender, race/ethnicity, and socioeconomic status. To date, little is known about the long-term safety and effectiveness of pain medications for older adults, especially those with multiple health conditions or dementia. These knowledge gaps limit the effectiveness of pain management in older adults and hamper the ability to provide cost-effective and personalized pain care for the aging population.

During FY 2017 and FY 2018, ORWH engaged in several important NIH pain research initiatives. ORWH is a member of the NIH Pain Consortium, a collaboration of 25 ICOs that identify, coordinate, and support pain research initiatives and activities at NIH. The consortium funds the Centers of Excellence in Pain Education (CoEPEs), which act as hubs for the development, evaluation, and distribution of pain management curriculum resources for schools, including medical, dental, nursing, and pharmacy schools. ORWH was one of the original funders of the centers. The CoEPEs website, found at https://www.painconsortium.nih.gov/Funding_Research/CoEPEs, provides links to 14 modules on pain education. The website includes additional modules that focus on prescribing risks related to pain and opioid use.

In addition, ORWH staff members participated in the working group that developed the Federal Pain Research Strategy (FPRS). The FPRS addresses the recommendations of the National Academy of Medicine to develop a long-term plan for the Federal research agenda in the areas of pain prevention, acute and chronic pain, the transition from acute to chronic pain, and

disparities in pain. After the release of the FPRS in October 2017, the recommendations were widely disseminated to the NIH ICOs and other Federal agencies for use in their pain-related research agendas.

The NIH National Center for Complementary and Integrative Health (NCCIH) leads an interagency partnership with the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Nursing Research (NINR), ORWH, the U.S. Department of Defense (DoD), and the U.S. Department of Veterans Affairs (VA), known as the NIH-DoD-VA Pain Management Collaboratory, which was funded in the fall of 2017. This initiative prioritizes real-world research on non-pharmacological approaches to pain management and related conditions in military and veteran health care delivery organizations. Almost two-thirds of military veterans say they are in pain, and nearly 10% say the pain is severe.

ORWH is a long-term funding partner with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, which addresses chronic urological pain disorders, such as interstitial cystitis/bladder pain syndrome and vulvodynia. The MAPP Research Network also is evaluating the association between these pain conditions and other overlapping pain disorders, such as fibromyalgia, irritable bowel syndrome, and ME/CFS.

In FY 2017, NICHD and ORWH reissued an FOA on chronic vulvar pain of unknown etiology to encourage new applications in this area. ORWH also supported administrative supplements funded in FY 2017 and FY 2018 that focused on stress, sex, and immunity in the acute to chronic pain transition, as well as on the role of chronic stress and visceral pain in intestinal barrier dysfunction.

In FY 2018, ORWH joined several new NIH FOAs that are part of the HEAL (Helping to End Addiction Long-term[SM]) Initiative. Many of these funding opportunities will support research on chronic pain, ranging from basic research on the molecular, genetic, and biobehavioral basis of chronic pain to large-scale clinical studies of treatments. In some cases, wording was added to FOAs to encourage applications that will integrate SABV in biomedical research on pain and opioid use disorders.

Bladder Health Research

During FY 2017–FY 2018, the Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium continued to receive support from NIDDK and ORWH. Lower urinary tract symptoms (LUTS) are common in women, resulting in significant but underrecognized effects on quality of life, as well as public health and financial burdens. Stigma around LUTS, along with the belief among many women that these conditions are inevitable, frequently results in unreported and therefore untreated symptoms. Many women adopt unhealthy coping behaviors, such as limiting their physical activity, restricting fluid intake, or isolating themselves socially.

The features of a “normal bladder,” including healthy bladder function and behaviors that might promote bladder health over a lifetime, have yet to be identified. Additionally, efforts to delineate the causes of LUTS have focused primarily on biological factors, without sufficient consideration of the impact of behavior, mind, and mental functioning; cultural contributors; or social determinants of health. In response, PLUS has adopted the social ecological model (SEM), which considers interactions between social context and biology across the lifespan and views health behaviors as determined by intrapersonal factors, interpersonal processes and primary groups, institutional factors, community factors, and public policy.

Framing the PLUS Research Consortium goals broadly as "bladder health" allows for the possibility that findings will affect the understanding and, ultimately, the clinical management of numerous urological conditions. The consortium is obtaining information from adolescents and women of various ages through multiple complementary research approaches, including qualitative and quantitative research, to characterize the healthy bladder and identify personal behavior and other factors associated with normal bladder function. They also are identifying protective factors for long-term bladder health and risk factors for developing lower urinary tract conditions. The long-term goals are to obtain the information necessary to plan future studies—including interventions—to promote bladder health and prevent LUTS in women throughout their lives and to support institutional and societal policy changes. Two peer-reviewed articles based on this research were published in 2018. They can be found at plusconsortium.umn.edu.

Diabetes Prevention Program Outcomes Study

ORWH continues to partner with NIDDK to support the Diabetes Prevention Program Outcomes Study (DPPOS), a long-term follow-up of the women and men who participated in the landmark Diabetes Prevention Program (DPP) clinical trial. The DPP demonstrated that type 2 diabetes could be prevented or delayed in those at high risk for the disease (i.e., pre-diabetic), either through changes in diet and physical activity resulting in modest weight loss or through use of the diabetes drug metformin. Participants who took metformin showed a 58% reduction in risk compared with those who took a placebo. Notably, the DPP lifestyle intervention has been translated for practical delivery nationwide, an expansion made possible by additional research, congressional authorization of the Centers for Disease Control and Prevention (CDC)-led National Diabetes Prevention Program,[8] and coverage by several insurers. In April 2018, the Centers for Medicare and Medicaid Services (CMS) began providing coverage for this intervention. Given its successes, the DPP/DPPOS trial is a major biomedical research success story.

During FY 2018, DPPOS participants were seen annually for event outcomes; medical history; measurements of weight, height, and blood pressure; and blood and urine collections for glycemia and kidney function. Additional follow-up activities during these visits included oral glucose tolerance tests, fundus photography, ocular computed tomography, questionnaires on well-being and economics, and new neuropathy assessments.

This study continues to provide significant data. For example, analyses and publications in FY 2017 provided insight on women's health by describing the risk of diabetes and coronary artery calcification associated with androgens and irregular menses in women, the changes in visceral and subcutaneous adiposity related to sex hormones (Kim, 2017), and a sex difference in metformin's effect on the development of coronary artery calcium (Goldberg, 2017).

In 2018, analyses and manuscripts directly related to women's health were undertaken to describe the following associations: infertility and gravidity with the development of diabetes; infertility, gravidity, and gestational diabetes with coronary artery calcification; sex hormones with chronic kidney disease and renal function; and sex hormones with urinary incontinence. Other outcomes manuscripts will evaluate sex differences.

This well-established study is contributing important data to the study of pre-diabetes, diabetes, prevention of complications, and minority and women's health. Using evidence-based interventions, the DPPOS project is

8 The National Diabetes Prevention Program is described at https://www.cdc.gov/diabetes/prevention/index.html.

producing significant research findings. All 22 DPPOS clinical sites are following the same protocol through ORWH co-funding of the DPPOS Coordinating Center, which supports the activities of all sites through sample distribution and analyses. The DPP/DPPOS remains the largest study of pre-diabetes ever conducted, with the cohort composed of 67% women. Sex differences in the rates of outcomes have been and will continue to be examined. DPPOS was in its third phase at the close of 2018. The primary focus moving forward is to determine whether initiation of metformin during pre-diabetes leads to lower rates of cardiovascular disease and cancer. More information is available at https://repository.niddk.nih.gov/studies/dppos.

ORWH Research Dissemination and Engagement

In FYs 2017 and 2018, ORWH continued to leverage new and innovative strategies and technologies to engage with internal and external stakeholders. Research dissemination and engagement activities included the introduction of a quarterly ORWH newsletter; a redesigned website; new reports, publications, and videos; and meetings, conferences, and workshops promoting the health of women and the professional development of women in biomedical careers. ORWH has continued to work closely in these efforts with the ICOs; partners across the Federal Government; media, health, and advocacy organizations; and the general public. Specific activities for FYs 2017 and 2018 are described below.

Quarterly ORWH Publication: *Women's Health in Focus at NIH*

The inaugural issue of the ORWH publication, *Women's Health in Focus at NIH*, came out in March 2018. It was designed to showcase women's health research being performed across the NIH ICOs and to highlight relevant scientific advances that can improve the health of women. The publication also provides content of interest to women in biomedical careers. It includes feature stories, summaries of journal articles, announcements about recent and upcoming ORWH activities, profiles of prominent women

in science, best practices to advance women in science, staff updates, links to helpful resources on the health of women, and ORWH funding opportunities for research on women's health and the influences of sex/gender on health and disease. A "Director's Corner" includes messages from ORWH Director Janine A. Clayton, M.D. This ORWH quarterly publication can be viewed at orwh.od.nih.gov/about/newsroom/orwh-quarterly-publication.

ORWH Website Redesign: Putting Science to Work for the Health of Women

ORWH launched a redesign of its website in 2018 to better show its partnerships with the NIH ICOs and other agencies and offices within the U.S. Department of Health and Human Services (HHS) as they work to advance the health of women. The site highlights the work of these organizations and the role of ORWH as the focal point for women's health research within NIH. The new ORWH website provides timely and relevant content on women's health, including research reports, news articles, biomedical career topics, an A-to-Z guide on sex and gender influences on health and disease, online courses on sex and gender, podcasts by prominent guests, and videos on a variety of topics. The site has multiple points of entry across all platforms, including desktops, tablets, and smartphones. All ORWH digital resources and materials are widely accessible to audiences and comply with plain-language standards. The website can be found at orwh.od.nih.gov.

ORWH Reports and Videos

NIH Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2015–2016

October 2017

In 2017, the ORWH Advisory Committee on Research on Women's Health (ACRWH) published the biennial report for FYs 2015–2016. The report detailed the research investments and scientific advances made in women's health research and related programs across NIH during the reporting period. It described major ORWH programs, initiatives, and activities and research highlights from the NIH ICOs. It also documented NIH budget allocations for women's health research during the 2-year period, as well as the inclusion of women and minorities in NIH-funded clinical research during those years. It can be found online at orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Biennial_Report_WEB_508_FY-15-16.pdf.

Request for Information—Trans-NIH Strategic Plan for Research on Women's Health

October 2017

ORWH published a request for information (RFI) during the development process for the 2019–2023 Trans-NIH Strategic Plan for Research on Women's Health. Feedback was requested on three cross-cutting themes under consideration: (1) Expand the Exploration of Sex as a Biological Variable (SABV) in NIH Research, (2) A Multidimensional Approach to the Science of Women's Health, and (3) Quality of Life and Disease Burden over the Life Course. The themes were intended to stimulate new research areas, priorities, and approaches to put science to work for the health of women.

A Report of the 24th Annual Congress on Women's Health—Workshop on Transforming Women's Health: From Research to Practice

January 2018

ORWH sponsored a preconference workshop on sex and gender as critical contributors to overall health and disease. The *Journal of Women's Health* discussed the major topics of the workshop in a 2018 article. It addressed the fact that considering both sex and gender in research informs the development of prevention strategies and treatment interventions for both men and women. Topics included polycystic kidney disease, vaccine protection, depression, drug addiction, and cardiovascular disease. The

report can be found at https://doi.org/10.1089/jwh.2017.29016.orwh.

Understanding Traumatic Brain Injury in Women: Report Summary

February 2018

This report documented the proceedings of a workshop held December 18–19, 2017, by the National Institute of Neurological Disorders and Stroke (NINDS). The event was organized and sponsored by NINDS in collaboration with ORWH, the Center for Neuroscience and Regenerative Medicine (CNRM) of the Uniformed Services University (USU), the National Center for Medical Rehabilitation Research (NCMRR) within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the Defense and Veterans Brain Injury Center (DVBIC). The workshop brought together researchers and clinicians to identify knowledge gaps, best practices, and target populations related to research on women and sex differences in the field of traumatic brain injury (TBI). The event addressed existing knowledge of sex differences in TBI research and how those differences could be incorporated into future preclinical and clinical studies. More information can be found at https://www.ninds.nih.gov/sites/default/files/tbi_workshop_summary_-_december_18-19_2017_508c_0.pdf

Video Series: Pearls of Wisdom

In 2018, ORWH launched the "Pearls of Wisdom" video series on the "Women in Biomedical Careers" section of the NIH website, in which prominent women professionals in science and medicine, including several IC directors, share words of wisdom on overcoming barriers to success. The first set of videos in the series was produced in collaboration with the National Medical Association (NMA). Each vignette offers a unique perspective on an aspect of life and career, such as how to overcome obstacles, set and achieve goals, or stay motivated. Viewers are encouraged with candor, compassion, and wit to "see barriers as stepping stones," to always be prepared with a "plan B," and to "stay true to oneself." Biographies detailing the speakers' journeys also are provided on the website. During the reporting period, 14 women were profiled who have successful careers in fields such as ophthalmology, gynecological surgery, obstetrics and gynecology, gynecologic oncology, family medicine, and orthopedic surgery. To view the videos, go to https://womeninscience.nih.gov/resources/pearls_of_wisdom.asp.

Meetings, Conferences, and Workshops

ORWH remains current with the status of specific scientific areas related to its mission—strengthening research related to the health of women, ensuring that women are appropriately represented in biomedical and biobehavioral research supported by NIH, and developing opportunities for the professional advancement of women in biomedical careers. This is accomplished in part through NIH-sponsored meetings, conferences, and workshops, in which scientific experts and other stakeholders in women's health discuss current and emerging clinical and research developments. In some cases, ORWH sponsors events to provide a forum for educating researchers on the association between women's health and specific research topics. A list of meetings, conferences, and workshops sponsored or co-sponsored by ORWH, with brief descriptions of the focus of each event, is provided below.

The Human Microbiome: Emerging Themes at the Horizon of the 21st Century

Sponsored by ORWH and the Trans-NIH Microbiome Working Group (TMWG), August 16–18, 2017

This NIH-wide microbiome workshop was organized by a planning committee of the TMWG, which includes program staff from the 19 NIH ICOs that support human microbiome research through their extramural portfolios. The TMWG took stock of where the microbiome field stood

after a 10-year investment by NIH in the Human Microbiome Project and evaluated what would be needed for the field to advance over the next decade. Participants addressed the fact that because personalized health and nutrition are in the spotlight, it is clear that solutions will be needed to enable long-term monitoring and scientifically validated strategies for maintaining the health of our microbial communities. Rajeev K. Agarwal, Ph.D., of ORWH, noted that to further improve the benefits of personalized treatment, sex as a biological variable should be considered in all aspects of this research field. In addition, Federal Government agencies that currently support or conduct human microbiome–related research, including ORWH, participated in a joint agency panel on the last day of the workshop to identify agency-specific issues, as well as common themes regarding challenges to progress. They called out interests in and opportunities for microbiome work at their respective agencies, as well as potential collaborations between agencies. This transdisciplinary group of scientists identified knowledge gaps, technical hurdles, new approaches, and research opportunities to inform novel prevention and treatment strategies based on host/microbiome interactions over the following 10 years.

Working Together to Address Women's Health in Research and Drug Development: Challenges and Opportunities

Preconference Symposium for the 25th Anniversary of the Women's Health Congress

Sponsored by ORWH and the Food and Drug Administration (FDA), April 27, 2017

ORWH partnered with FDA to address women's health as it relates to current research and drug development. Janine A. Clayton, M.D., ORWH Director, provided opening remarks. Topics included progress in including women in clinical trials for FDA-approved products; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) clinical trials in pregnant women; drug labeling, registries, and clinical trials as they relate to pregnancy; the precision medicine initiative; and FDA transparency and communications for providers. An abstract of the symposium can be found at https://www.ncbi.nlm.nih.gov/pubmed/30325292.

Inclusion Across the Lifespan Workshop

Sponsored by ORWH, the Food and Drug Administration (FDA), the National Center for Advancing Translational Sciences (NCATS), the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Aging (NIA), the National Institute of Allergy and Infectious Diseases (NIAID), the Eunice Kennedy Shriver *National Institute of Child Health and Human Development (NICHD), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Mental Health (NIMH), the National Institute on Minority Health and Health Disparities (NIMHD), the National Library of Medicine (NLM), the Office of Behavioral and Social Sciences Research (OBSSR), the Office of the Director (OD), and the Office of Extramural Research (OER), June 1–2, 2017*

This workshop gathered clinical research experts to discuss barriers and opportunities related to the participation of pediatric and older populations in clinical trials. The meeting was held in response to both scientific need and a congressional mandate, issued through the 21st Century Cures Act, to include people of all ages in clinical trials. Discussion topics addressed the inclusion of participants from scientifically appropriate age groups, including study population issues (e.g., inclusion/exclusion criteria and age restrictions), study design and metrics, ethical challenges in the enrollment of vulnerable populations, and data collection and reporting to support age-specific and subgroup analyses. The workshop's primary outcome was a summary of opportunities and barriers to recruitment of children and older adults in clinical studies. See the video summaries at https://videocast.

nih.gov/Summary.asp?Live=23410&bhcp=1 (Day 1) and https://videocast.nih.gov/Summary.asp?Live=23414&bhcp=1 (Day 2).

The Science of Caregiving: Bringing Voices Together

Sponsored by ORWH and the National Institute of Nursing Research (NINR), August 7–8, 2017

NINR and its partners held a summit that provided perspectives on caregiving, including the importance of caregiving across the lifespan and current and future directions for research to improve the health of patients and caregivers. The summit was attended by researchers, advocates, health care providers, educators, and others interested in the science of caregiving. See a summary at https://www.ninr.nih.gov/sites/files/docs/Caregiving-Summit-Summary-508c.pdf.

Female Sex and Gender in Lung/Sleep Health and Disease

Sponsored by ORWH, the National Heart, Lung, and Blood Institute (NHLBI), and the Office of Rare Diseases Research (ORD), September 18–19, 2017

This conference addressed how lung and sleep biology and pathobiology are affected by female sex and female reproductive transitions. It focused on the importance of understanding how gender influences normal human function and the experience of disease. Marianne J. Legato, M.D., Ph.D., Professor Emerita of Clinical Medicine at Columbia University, delivered the keynote lecture. Her talk explored evidence linking experience to changes in the phenotype through the science of epigenetics, the discipline that describes how the environment produces changes in genomic expression. In addition, researchers reviewed the current understanding of the biological, behavioral, and clinical implications of female sex and gender on lung and sleep health and disease. The investigators formulated recommendations that addressed research gaps, with a view to achieving better health outcomes through more precise management of female patients with nonneoplastic lung disease. The meetings' topics were summarized in an article in the *American Journal of Respiratory and Critical Care Medicine* (2018 Oct 1;198[7]:850–858). The article can be found at https://doi.org/10.1164/rccm.201801-0168WS.

2017 Annual BIRCWH Meeting: Building Interdisciplinary Research Careers in Women's Health

Sponsored by ORWH, October 25, 2017

The Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program is a mentored career development program that connects junior faculty (i.e., BIRCWH Scholars) with senior faculty who have a shared interest in women's health and sex differences research. The 2017 annual BIRCWH meeting provided a forum for these young investigators, their mentors, and other research scientists to meet and present their research results and engage in mentoring and networking activities. The sessions included a panel on strategies to achieve an independent research career, a talk on cross-disciplinary research teams, and presentations by BIRCWH Scholars. The keynote address was presented by Afua Bruce, M.B.A., former Executive Director of the White House Office of Science and Technology Policy. A recording of the meeting can be found at https://videocast.nih.gov/summary.asp?Live=26431&bhcp=1.

NIH Sex as a Biological Variable (SABV) Workshop

Sponsored by ORWH and The Common Fund, October 26–27, 2017

This six-session workshop on sex as a biological variable (SABV) addressed sex differences in brain function and behavior, sex effects and interactions with external influences, sex differences in animal models, and sex differences in gene expression. The keynote speaker was Virginia M. Miller, Ph.D., Professor of Surgery and Physiology at the Mayo Clinic

College of Medicine. Dr. Miller's research focuses on how sex steroid hormones, such as estrogen and testosterone, affect blood flow to the brain, heart, and kidneys. She works collaboratively with researchers associated with the Rochester Epidemiology Project, the Mayo Clinic's Alzheimer's Disease Research Center, the Center for Translational Science Activities, and the Women's Health Research Center. At the workshop, researchers presented scientific results, challenges, and approaches to the inclusion of SABV in research design, spanning the entire continuum, from basic to translational to clinical research analyses and reporting. A panel discussed accounting for SABV in biomedical research. A recording of the event is available at https://commonfund.nih.gov/sexdifferences/workshop.

Putting Science to Work for Women's Health

Sponsored by ORWH and the National Academies of Sciences, Engineering, and Medicine's Government-University-Industry Research Roundtable (GUIRR), March 23, 2018

GUIRR convenes the senior-most representatives from government, universities, and industry to define and explore critical issues related to the national and global science and technology agenda that are of shared interest, to frame the critical questions stemming from current debate and analysis, and to incubate activities of ongoing value to stakeholders. GUIRR hosted a webinar with Janine A. Clayton, M.D., Director of ORWH. She discussed the ORWH mission for women's health research in 2018 and beyond, including helping to ensure that women are appropriately represented in NIH-funded clinical research and advancing women in biomedical careers. She noted that health trends of U.S. women have fallen behind those of women in peer countries and U.S. men, highlighting the need for the ORWH strategic vision. Dr. Clayton explained how ORWH is working across the NIH ICOs to enhance and expand women's health research.

Measures and Methods to Build Capacity in Sexual and Gender Minority Health Research

Sponsored by ORWH and the Sexual and Gender Minority Research Office (SGMRO), April 3–4, 2018

This workshop was organized in response to a call in the 21st Century Cures Act for increased support of sexual and gender minority (SGM) health research. It addressed section 404N of the act, which encourages IC directors to "facilitate the development of valid and reliable methods for research relevant to sexual and gender minority populations." Speakers included Brian Mustanski, Ph.D., Director of the Institute for Sexual and Gender Minority Health and Wellbeing at Northwestern University, and Bryn Austin, Sc.D., Director of the Sexual Orientation and Gender Identity and Expression Working Group of the Harvard T.H. Chan School of Public Health and Boston Children's Hospital.

Addressing Health Challenges of Women Across the Life Course

Sponsored by ORWH, May 3, 2018

ORWH hosted this preconference symposium prior to the 2018 Congress on Women's Health. ORWH Deputy Director Elizabeth Spencer, RN, opened the symposium by highlighting the office's multidimensional life-course approach. Victoria Cargill, M.D., M.S.C.E., ORWH Associate Director for Interdisciplinary Research, described the nature of interdisciplinary, multidisciplinary, and transdisciplinary research and the ways in which they create novel conceptual, theoretical, methodological, and translational innovations that integrate aspects of each discipline and move beyond discipline-specific approaches. Kara Hall, Ph.D., Director of the Science of Team Science (SciTS) Team at the National Cancer Institute (NCI), discussed the advantages of team science strategies, which typically are not addressed in traditional educational and training programs. The keynote speaker, Kathleen T. Brady, M.D., Ph.D.,

Vice President for Research and Director of the Clinical and Translational Research Institute at the Medical University of South Carolina, discussed the pressing health matter of opioid use among women.

Obesity and Fat Metabolism in HIV-infected Individuals

Sponsored by ORWH, the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Office of AIDS Research (OAR), May 22–23, 2018

This meeting was held to address evidence that obesity is emerging as a critical factor for individuals with HIV. Research indicates that fat metabolism is affected by HIV, and these effects may predispose individuals to the development of obesity. Women with HIV may be more adversely affected than men. Six sessions were held to address multiple topics, with speakers from NIH ICOs, academia, and the private sector. Results of the meeting included an action plan with specific recommendations for future obesity research in HIV; identification of research gaps, needs, opportunities, and plans to facilitate progress and catalyze new research directions; and knowledge exchange, including plans for further collaboration to advance the field. More information can be found at https://forumresearch.org/announcements/1574-nih-workshop-obesity-and-fat-metabolism-in-hiv-infected-individuals.

Women's Health in Interprofessional Education and Collaborative Care Meeting

Sponsored by ORWH and the American Dental Education Association (ADEA), June 26, 2018

At this meeting, Janine A. Clayton, M.D., ORWH Director, addressed the educational accomplishments of ADEA, including the development of dental education curricula that incorporate women's health and the fact that the association's efforts increased the number of women dentists. She explained the vision of ORWH in helping to set a research agenda for NIH through the individual ICOs' strategic plans, which integrate the health of women in their mission areas. Her remarks also explained the lack of reproducibility in science and the need for rigor and transparency, as well as the importance of the NIH sex as a biological variable (SABV) policy. Dr. Clayton described the key activities and resources made available by ORWH (e.g., Schweinhart and Clayton, 2018).

Enhancing Natural Product Clinical Trials

Sponsored by ORWH, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the National Center for Complementary and Integrative Health (NCCIH), the National Institute on Aging (NIA), the National Institute of Environmental Health Sciences (NIEHS), the Office of Dietary Supplements (ODS), and the U.S. Department of Agriculture (USDA), September 13–14, 2018

A workshop on enhancing natural product clinical trials (NPCT) was organized by the sponsoring organizations. The overall goal was to enhance the progression of natural product research from foundational data (e.g., from preclinical and epidemiological research) to actionable public health information. The workshop brought together transdisciplinary experts to discuss practices for rigor in obtaining, reporting, interpreting, and assessing foundational data for NPCT, as well as for NPCT decision-making and design. They also addressed which data should be collected during NPCTs to maximize the acquisition of information that could enhance future research design.

Sex Differences Across the Lifespan: A Focus on Metabolism

Sponsored by ORWH and the University of Colorado Center for Women's Health Research, September 26–28, 2018

At this national conference on women's health research, nationally and internationally known scientists convened to discuss sex differences across the lifespan. The cutting-edge research

areas addressed included sex as a biological variable (SABV), fetal origins of adult disease, the effects of sleep and circadian physiology on cardiometabolic health, and sex differences in diabetes. ORWH Associate Director for Clinical Research Margaret Bevans, Ph.D., presented information on "Integrating Sex to Advance Science for the Health of Women: A Lens into the Future."

Opioid and Nicotine Use, Dependence, and Recovery: Influences of Sex and Gender

Sponsored by ORWH, the Food and Drug Administration (FDA), the National Center for Complementary and Integrative Health (NCCIH), and the National Institute on Drug Abuse (NIDA), September 27–28, 2018

ORWH and the FDA's Office of Women's Health (OWH), in collaboration with the Center for Drug Evaluation and Research (CDER) and the Center for Tobacco Products (CTP), hosted this 2-day scientific conference on sex differences that may influence susceptibility to substance misuse. Experts in the fields of opioid and tobacco research, professional education, and clinical care presented research on biological (sex) and sociological (gender) influences on use, misuse, and recovery related to these drugs. They explained how these influences could have implications for optimal prevention and treatment approaches for women and addressed the ways gender influences affect public health from an environmental perspective. The key message of the conference was that to identify and treat women most at risk, researchers, educators, and clinicians must be able to recognize and consider both sex and sociological differences. Speakers included U.S. Surgeon General VADM Jerome Adams, M.D., M.P.H., who spoke on opioid and nicotine use, ORWH Director Janine A. Clayton, M.D., who discussed the sex as a biological variable (SABV) policy, and NIDA Director Nora Volkow, M.D., who delivered the capstone lecture, "Sex as a Biological Variable in the Opioid Crisis." The webcast recording of Day 1 is found at http://fda.yorkcast.com/webcast/Play/912d109a108c4eef98df97debd29c1751d. The webcast recording of Day 2 is found at http://fda.yorkcast.com/webcast/Play/8ddd038376d14abb91880712a78e30901d.

Recurring Events

Meetings of the Advisory Committee on Research on Women's Health (ACRWH)

43rd Meeting of the Advisory Committee on Research on Women's Health

Sponsored by ORWH, April 4, 2017

This advisory committee meeting featured a presentation on precision health care by Eric Dishman, Director of the *All of Us* Research Program. The NIH Working Group on Women in Biomedical Careers announced that it established a newsletter, as well as a web presence at https://womeninscience.nih.gov. John Burklow, Associate Director of the NIH Office of Communications and Public Liaison, discussed the work of Janine A. Clayton, M.D., Director of ORWH, in promoting the work of NIH. Her efforts have included scholarly papers, commentaries, interactions with Congress, scientific initiatives, media interviews, social media engagement, speeches, and domestic and international presentations.

44th Meeting of the Advisory Committee on Research on Women's Health

Sponsored by ORWH, September 13, 2017

This advisory committee meeting included an update by ORWH Director Janine A. Clayton, M.D., on efforts to support the sex as a biological variable (SABV) policy, stakeholder outreach, and ORWH funding and programs. Joshua Gordon, M.D., Ph.D., Director of the National Institute of Mental Health (NIMH), discussed women's mental health. Researcher Chloe Bird, Ph.D., from the RAND Corporation, presented "A Conceptual Model of Sex and Gender Influences on Health and Disease." Monica Basco, Ph.D., Associate Director for Science Policy, Planning, and Analysis at ORWH, discussed the status of the Trans-NIH Strategic Plan for Research on Women's Health. ORWH Statistician Ching-yi

Shieh, Ph.D., provided updates on data analyses from a workshop titled "Raising the Bar—The Health of Women in America: A National Perspective on Women's Health."

45th Meeting of the Advisory Committee on Research on Women's Health

Sponsored by ORWH, April 18, 2018

This advisory committee meeting featured a presentation by ORWH Director Janine A. Clayton, M.D., on the aggressive trans-NIH effort to speed scientific solutions to stem the opioid crisis and the effect of the epidemic on women's health and mortality. She also provided an update on the NIH Pain Consortium and its relationship to the opioid crisis. Other topics included the Adolescent Brain Cognitive Development (ABCD) Study, the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, and the request for information (RFI) on the Trans-NIH Strategic Plan for Women's Health Research.

NIH Vivian W. Pinn Symposia

2nd Annual NIH Vivian W. Pinn Symposium: Putting Science to Work for the Health of Women

Sponsored by ORWH, May 17, 2017

ORWH hosted the NIH Vivian W. Pinn Symposium during National Women's Health Week. This symposium addressed multiple domains that influence the health of women and addressed ways to reverse poor health trends. The roles of women in healthy families and communities also were highlighted. Davene B. McCarthy White, M.P.H., RN, NNP, received the inaugural ORWH Director's Award for caregiving in the field of nursing for her work with children and families in Washington, D.C. Jacquelyn Caglia, M.P.H., Associate Director of the Women and Health Initiative in the Department of Global Health and Population at the Harvard T.H. Chan School of Public Health, presented the results of a 3-year assessment of women's health conducted by the Commission on Women and Health. The resulting vision includes a broad accounting of women's contributions and needs in policy and governance to better provide for health and well-being. Afaf Ibrahim Meleis, Ph.D., FAAN, Professor of Nursing and Sociology and Dean Emeritus at the University of Pennsylvania School of Nursing and co-chair of the Commission on Women and Health, invited attendees to envision what women's status would be if their caregiving roles were acknowledged and supported. She discussed recommendations for moving toward a fuller accounting of women and health. Jennifer Karas Montez, Ph.D., Assistant Professor of Sociology and the Gerald B. Cramer Faculty Scholar in Aging Studies at Syracuse University, described declines in U.S. women's health, presenting data on trends in U.S. mortality rates. A recording of the event can be found at https://videocast.nih.gov/Summary.asp?File=23301&bhcp=1. and an event summary is available at https://orwh.od.nih.gov/resources/pdf/ORWH_VPinnSymposium2017_Final-508c.PDF.

3rd Annual NIH Vivian W. Pinn Symposium: Leveraging the Network to Advance Women in Science

Sponsored by ORWH, May 16, 2018

ORWH hosted the NIH Vivian W. Pinn Symposium during National Women's Health Week. The symposium addressed issues of importance to women in biomedical careers, with a panel of distinguished speakers offering mentoring and networking strategies to advance women in science. Panelists included P. Kay Lund, Ph.D., Director of the Division of Biomedical Research Workforce at the NIH Office of Extramural Research; Daniel Ford, M.D., M.P.H., Director of the Institute for Clinical and Translational Research at Johns Hopkins University and Principal Investigator of the university's Building Interdisciplinary Research Careers in Women's Health (BIRCWH) award; and Rachelle Heller, Ph.D., Professor of Computer Science at George Washington University's School of Engineering and Applied

Science. Invited speakers and guests had the opportunity to meet current and future mentors, as well as aspiring scientists, at a *Catalytic Connections* session. A recording of the event can be found at https://videocast.nih.gov/summary.asp?Live=27476&bhcp=1%20.

The Women's Health Seminar Series

Women's Health Seminar Series: Sex and Pain, What's the Story?

Sponsored by ORWH, the Food and Drug Administration (FDA), the National Center for Complementary and Integrative Health (NCCIH), the National Institute of Dental and Craniofacial Research (NIDCR), the NIH Clinical Center, the NIH Pain Consortium, the NIH Pain Special Interest Group, the National Institute on Drug Abuse (NIDA), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Nursing Research (NINR), December 7, 2017

ORWH introduced the Women's Health Seminar Series on December 7, 2017. This program features speakers who present the latest information on scientific topics important to the health of women across the life course. The inaugural seminar highlighted the timely issue of pain and the opioid epidemic and was titled "Sex and Pain, What's the Story?" The keynote address was given by Jeffrey Mogil, Ph.D., of McGill University, where he is the Research Chair in the Genetics of Pain Department, as well as the Director of the Alan Edwards Centre for Research on Pain. He explored the science of sex influences on pain and associated mortality and highlighted women-specific aspects of pain in relation to the opioid epidemic.

Women's Health Seminar Series: Sex Differences in Vaccine Efficacy

Sponsored by ORWH, March 20, 2018

This seminar featured a presentation by Sabra Klein, Ph.D., Associate Professor of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health. She is a leading expert on sex differences in immune responses and susceptibility to infection. Her talk addressed findings regarding mechanisms that underlie sex differences in immune responses, sex differences in vaccine efficacy in humans, and new scientific data showing sex-specific differences in immune responses over the life course. A recording is available at https://videocast.nih.gov/Summary.asp?File=23773&bhcp=1.

Women's Health Seminar Series: Sex and the Head–Heart Connection

Sponsored by ORWH, June 7, 2018

This seminar was designed to improve knowledge about (1) sex differences in heart and brain disease comorbidity, (2) how sex differences over the life course affect risk for and resilience against diseases of the heart and brain, (3) shared causes and pathophysiology of brain and heart diseases and how these differ by sex, and (4) current efforts and gaps in sex-specific research, education, and policies. Speakers also addressed what is needed to improve health outcomes nationally and globally. Nakela Cook, M.D., Chief of Staff and Senior Scientific Officer for the Immediate Office of the Director of the National Heart, Lung, and Blood Institute (NHLBI), was the keynote speaker, addressing the "Heart–Brain Connection: Implications of Sex Differences Across the Life Course." Jill M. Goldstein, Ph.D., Executive Director of the Women, Heart, and Brain Global Initiative at Massachusetts General Hospital and Professor of Psychiatry and Medicine at Harvard Medical School, spoke on the "Impact of SeXX on the Comorbidity of Depression and Cardiovascular Disease." Virginia M. Miller, Ph.D., Professor of Surgery and Physiology and Director of the Women's Health Research Center at the Mayo Clinic, presented "An Integrated Research Approach to Reducing Cardiovascular and Cognitive Comorbidities in Women." Ana Langer, M.D., Director of the Women and Health Initiative at the Harvard T.H. Chan School of Public

Health, gave a talk titled “What Does the Growing Burden of Non-communicable Diseases Mean for Women Globally: Current Trends, Future Challenges, and Opportunities.” A recording can be found at https://videocast.nih.gov/summary.asp?Live=27796&bhcp=1.

Meetings of the Sex and Gender in Health and Disease Scientific Interest Group

Founded by ORWH, the goal of the Sex and Gender in Health and Disease (SGHD) Scientific Interest Group (SIG) is to explore the influences of sex as a biological variable (SABV) and gender as a social construct on health and disease across the lifespan. It also promotes the dissemination of research and fosters interdisciplinary collaboration among NIH scientists who work on or are interested in aspects of sex-based research or in sex differences research relevant to health and disease. The SGHD SIG also aims to leverage the scientific expertise of neighboring research institutions. The inaugural meeting took place on January 23, 2018. Jeffrey Mogil, Ph.D., of McGill University, addressed the topic of sex and pain. The second meeting, on March 20, 2018, featured Anna Naumova, Ph.D., of McGill University, who spoke on “Sexual Dimorphism in DNA Methylation as a Modifier of Predisposition to Human Disease.” At the third meeting, on May 22, 2018, Susan T. Harbison, Ph.D., of the National Heart, Lung, and Blood Institute (NHLBI), described her research with *Drosophila melanogaster*. Her laboratory uses sleep and circadian rhythms in *Drosophila* as models to understand the forces that maintain genetic variation in complex traits.

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III. ORWH Biomedical Career Development Activities

Introduction

A major component of the ORWH mission is to promote the recruitment, retention, reentry, and advancement of women in biomedical careers. Accordingly, ORWH has initiated programs to nurture the participation and advancement of women in biomedical careers and to address career issues and barriers to advancement.

This chapter summarizes two major areas ORWH supported in fiscal year (FY) 2017 and FY 2018: (1) interdisciplinary research and career development programs and (2) career development opportunities for women in biomedical research. ORWH research and career development programs are based on the premise that interdisciplinary approaches are essential to moving the science associated with the health of women forward while increasing understanding of the influences of sex and gender on human health and disease. Career development programs also advance research on the health of women that can be translated into evidence-based clinical practice. These programs use NIH's K12 institutional career development mechanism.

Building Interdisciplinary Research Careers in Women's Health

ORWH designed, developed, and implemented the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) K12 program in 1999 to develop a cadre of women investigators who conduct research on sex/gender influences on health. BIRCWH provides for mentored research training and career development that prepares investigators for independent scientific careers that will benefit the health of women, advance research on sex and gender influences on health, and expand the use of interdisciplinary research methodologies. BIRCWH funding provides opportunities for training and development that would not otherwise be available to facilitate the transition to research independence for junior faculty researchers (known as BIRCWH Scholars) who are conducting interdisciplinary research on the health of women.

ORWH and the NIH Institutes, Centers, and Offices (ICOs) consider interdisciplinary mentoring teams an essential component of the BIRCWH program. They usually include mentors from diverse disciplines, such as medicine, dentistry, nursing, biotechnology, social sciences, bioengineering, anthropology, genetics, and other disciplines representing different areas of expertise. Together, principal investigators, sponsoring and cooperating departments, centers, or institutes form a collaborative unit with the common goal of supporting a BIRCWH Scholar in the transition from trainee to independent researcher.

Since the initial cycle of funding for the BIRCWH program in 2000, one major aspect of the program has continued to be enhanced and emphasized. Based on results from a different but related grant program first funded in 2009 that focused on research on causal factors and interventions that promote and support the careers of women in biomedical science, behavioral science, and bioengineering, BIRCWH has emphasized the importance of a *team science research approach*, as well as the utilization of interdisciplinary mentoring teams. The interdisciplinary team approach is applied to study the health of women across the lifespan, bridging basic and clinical science and incorporating new models of collaboration and institutional support.

The BIRCWH program also incorporates the goals and objectives of the latest Trans-NIH Strategic Plan for Women's Health Research, titled *Advancing Science for the Health of Women: 2019–2023 Trans-NIH Strategic Plan for Women's Health Research*, which is the follow-up to the 2010 plan, *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research*. The latest strategic plan focuses on the health of women and the influence of sex and gender on health and disease.

Since the BIRCWH program's inception, ORWH has made institutional career development grant awards to academic institutions that have sponsored more than 700 BIRCWH Scholars. This network has expanded the number of scientists and clinicians who have the interdisciplinary research skills to further the study of the health of women and the influence of sex and gender differences. At the end of FY 2018, 20 BIRCWH programs were actively funded across the country. Approximately 70% of BIRCWH Scholars had submitted at least one research project grant application after completion of their appointment. Among those who applied, about 49% of the scholars ultimately received an award from NIH or another Federal funding agency, demonstrating the success of this research training and mentorship program.

ORWH is responsible for the programmatic aspects of the BIRCWH program, but grants management resides within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). From FY 2000 through FY 2018, ORWH issued eight requests for applications (RFAs) through the *NIH Guide for Grants and Contracts*. Over this period, NICHD was joined in its funding support by many NIH ICOs, including the National Cancer Institute (NCI), the National Institute on Aging (NIA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Drug Abuse (NIDA), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), the NIH Office of Dietary Supplements (ODS), and the NIH Office of AIDS Research (OAR).

For more information on the 20 BIRCWH awardees funded in FYs 2017 and 2018, see Table 1.

BIRCWH Scholar Funding Success from FY 2000 to FY 2016

- About 40% (N=231) of BIRCWH Scholars submitted at least one NIH mentored career K-series grant application after their BIRCWH start dates. Of those, 45% received an award.
- About 70% of scholars (N=408) submitted at least one NIH research grant application after completion of their appointment, and 49% of the applicants received at least one NIH research grant.
- In addition to R01 grants, substantial numbers of BIRCWH Scholars applied for R03 grants (N=167, or 29%) and R21 grants (N=266, or 46%). Of scholars who submitted at least one application to these mechanisms, approximately 37% and 30%, respectively, received at least one R03 or R21 award.
- Female scholars had significantly higher K-series mentored research grant application rates compared with their male counterparts, but there was no significant sex difference in terms of grant award outcomes.
- Based on the research grants included in the analysis, neither the application rate nor the award rate shows a statistical difference between men scholars and women scholars.

Table 1. FY 2017–FY 2018 BIRCWH Programs

Institution	Lead PI
Brigham and Women's Hospital	Jill Goldstein, Ph.D.
Duke University	Nancy Andrews, M.D., Ph.D.
Emory University	Claire Sterk, Ph.D. (FY 2017) Ighovwerha Ofotokun, M.D., M.S. (FY 2018)
Johns Hopkins University	Daniel Ford, M.D., M.P.H.
Magee-Womens Research Institute & Foundation	Yoel Sadovsky, M.D.
Mayo Clinic	Virginia Miller, Ph.D.
Medical University of South Carolina	Jacqueline McGinty, Ph.D.
Oregon Health & Science University	Jeanne-Marie Guise, M.D., M.P.H.
Tufts University	Karen Freund, M.D., M.P.H.
Tulane University	M.A. "Tonette" Krousel-Wood, M.D.
University of California, Davis	Ellen Gold, Ph.D.
University of California, San Francisco	Claire Brindis, Dr.P.H.
University of Colorado	Judith Regensteiner, Ph.D.
University of Kentucky	Thomas Curry, Ph.D.
University of Minnesota	Sophia Vinogradov, M.D.
University of North Carolina	Kim Boggess, M.D.
University of Pennsylvania	C. Neill Epperson, M.D. (FY 2017) Maria A. Oquendo, M.D., Ph.D. (FY 2018)
University of Texas Medical Branch	Abbey Berenson, M.D., Ph.D.
University of Utah	Michael Varner, M.D.
Vanderbilt University	Katherine Hartmann, M.D., Ph.D.

NIH hosts an annual BIRCWH program meeting to bring together the scholars, principal investigators and their research staff, NIH staff, and others interested in the BIRCWH program. These meetings include keynote speeches, plenary panel discussions, mentoring sessions led by experienced NIH research program staff, and poster sessions. The accepted poster abstracts for both 2017 and 2018 were published in the *Journal of Women's Health* and can be accessed via the ORWH website at https://orwh.od.nih.gov/career-development/building-interdisciplinary-research-careers-womens-health-bircwh. A follow-up analysis of the program is currently being conducted, the results of which will be provided in the next report.

Women's Reproductive Health Research Career Development Program

Initiated by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) in 1998, the Women's Reproductive Health Research (WRHR) program was developed to provide obstetrician/gynecologists (OB/GYNs) who have recently completed postgraduate clinical training with the opportunity to further their education and experience in basic, translational, and clinical research. ORWH has provided support for this program since its inception. The primary objectives of the program are to (1) bridge clinical training with advanced research career development, (2) provide OB/GYN junior faculty with state-of-the-art training in women's reproductive health research in an academic department, (3) stimulate women's reproductive health research in a variety of disciplines, and (4) deliver a mentored research experience to help OB/GYN junior faculty attain careers as independent investigators.

Program eligibility is limited to OB/GYNs with an M.D. or D.O. degree who have completed residency training in obstetrics and gynecology and are beginning relevant basic, translational,

or clinical research. Subspecialty training is not required of candidates practicing general obstetrics and gynecology. WRHR scholars' scientific projects focus on subspecialty and emerging areas, including maternal–fetal medicine, gynecologic oncology, reproductive endocrinology and infertility, and female pelvic medicine and reconstructive surgery. They pursue a broad range of basic science, translational, and/or clinical research topics. More than 225 OB/GYN junior faculty members have been appointed to the WRHR program since its inception. In 2018, there were 15 WRHR sites in OB/GYN departments throughout the Nation, as listed below.

FY 2017–2018 Program Sites

Continuation of Wayne State University's Successful Development of Physician-Scientists as Independent Researchers in the Area of Women's Reproductive Health. Institution: Wayne State University, Detroit, Michigan. PI: Hsu, Chaur-Dong, M.D., M.P.H. Grants K12 HD001254-18 and K12 HD001254-19.

Fast Forwarding Women's Reproductive Health Research: University of Michigan WRHR Career Development Program. Institution: University of Michigan, Ann Arbor. PI: Fenner, Dee E., M.D. Grants K12 HD065257-08 and K12 HD065257-09.

Magee-Womens Basic and Translational Reproductive Health Training Program. Institution: Magee-Womens Research Institute & Foundation, Pittsburgh, Pennsylvania. PI: Edwards, Robert P., M.D. Grants K12 HD063087-08 and K12 HD063087-09.

OB/GYN Faculty Research Career Development Program. Institution: University of Alabama at Birmingham. PI: Jenkins, Todd R, M.D. Grants K12 HD001258-18 and K12 HD001258-19.

The Penn Center for Career Development in Women's Health Research. Institution: University of Pennsylvania, Philadelphia. PI: Driscoll, Deborah A., M.D. Grants K12 HD001265-18 and K12 HD001265-19.

Research Career Development in Obstetrics and Gynecology. Institution: Northwestern University, Chicago, Illinois. PI: Bulun, Serdar E., M.D. Grants K12 HD050121-13 and K12 HD050121-14.

University of Colorado Women's Reproductive Health Research Career Development Center. Institution: University of Colorado Denver. PI: Santoro, Nanette F., M.D. Grants K12 HD001271-18 and K12 HD001271-19.

Utah Women's Reproductive Health Research Career Development Program. Institution: University of Utah, Salt Lake City. PI: Silver, Robert M., M.D. Grants K12 HD085816-03 and K12 HD085816-04.

Women's Reproductive Health Research. Institution: University of California, San Francisco. PI: Murtha, Amy P., M.D. Grants K12 HD001262-18 and K12 HD001262-19.

Women's Reproductive Health Research Career Development Program. Institution: Augusta University, Augusta, Georgia. Principal Investigator (PI): Ghamande, Sharad A., M.D. Grants K12 HD085817-03 and K12 HD085817-04.

Women's Reproductive Health Research Career Development Program. Institution: University of Washington, Seattle. PI: Goff, Barbara A., M.D. Grants K12 HD001264-18 and K12 HD001264-19.

Women's Reproductive Health Research K12 Program. Institution: Oregon Health & Science University, Portland, Oregon. PI: Caughey, Aaron B., M.D., Ph.D. Grants K12 HD085809-03 and K12 HD085809-04.

Women's Reproductive Health Research Program. Institution: University of California, San Diego. PI: Nager, Charles W., M.D. Grants K12 HD001259-18 and K12 HD001259-19.

WRHR Career Development Program: Improving Women's Health through Career Development in Clinical Research. Institution: Women & Infants Hospital of Rhode Island/Brown University, Providence, Rhode Island. PI: Phipps, Maureen

G., M.D., M.P.H. Grants K12 HD050108-13 and K12 HD050108-14.

The Yale WRHR Career Development Center. Institution: Yale University, New Haven, Connecticut. PI: Taylor, Hugh S., M.D. Grants K12 HD047018-13 and K12 HD047018-14.

Research Supplements to Promote Reentry into Biomedical and Behavioral Research Careers

The ORWH/NIH Reentry into Biomedical Research Careers program assists individuals with high potential, including postdoctoral investigators, to reenter an active research career after a qualifying interruption for family or other responsibilities. The program began as a pilot in 1992 using administrative supplements to existing NIH research grants to support full- or part-time research. It includes three components that help reestablish awardees as independent competitive research scientists: (1) full participation in an ongoing NIH-funded research project, (2) an opportunity to update and enhance research capabilities, and (3) a carefully planned mentoring program developed by the mentor and the awardee. As of FY 2018, nearly 200 investigators had received awards under this program with support from ORWH and 25 NIH ICOs. An ORWH evaluation of the program in December 2006 showed that at an average time of 5 years post-award, more than 80% of reentry awardees remained in academia and in scientific research. More than 80% remained active in publishing and grant activities and indicated that the program had helped them advance their scientific careers. In FY 2018, NIH reissued the funding opportunity announcement with support from 25 ICOs. See https://grants.nih.gov/grants/guide/pa-files/pa-18-592.html.

NIH Working Group on Women in Biomedical Careers

The NIH Working Group on Women in Biomedical Careers (WgWBC) was established in 2007 and is co-chaired by the Directors of NIH and ORWH. Members of the working group lead trans-NIH efforts to address career barriers for women in science, including the development of innovative strategies to promote entry, recruitment, retention, and sustained advancement of women in biomedical and research careers. The group comprises NIH deputy directors, senior staff from the Office of the Director (OD), IC directors, IC scientific directors, and other NIH intramural and extramural staff. (FY 2017 and FY 2018 working group members are listed in Appendix C.)

In response to recommendations from the National Academy of Sciences' report titled *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, the WgWBC hosts several committees related to its mission. These include the Committee on Women of Color in Biomedical Careers, the Committee on Advancing Women in Independent Positions, and the Committee on the NIH Intramural Research Program. The working group and its committees have sponsored national workshops, seminars, and research symposia on career development research and interventions; issued reports on best practices; created public outreach websites; developed a funding grant program to study barriers that impede women's career development; and published on topics relevant to the advancement of women in biomedical careers. They have instituted flexible policies for families to address common roadblocks to balancing work and personal life. These can include time off to care for a family member or a personal disability, grant awards that allow for reimbursement of allowable costs for child care or parental leave, and opportunities to allow explanations in grant applications about how personal circumstances delayed an individual's transition to an independent career or reduced her scientific productivity.

NIH Women in Science Website and Newsletter Articles

ORWH maintains the website https://womeninscience.nih.gov for the NIH Working Group on Women in Biomedical Careers

(WgWBC). The website provides history, accomplishments, subcommittees, and a list of supported programs of the WgWBC. There are also pages for grant information, career development resources, and spotlights of prominent women in the sciences. In addition, the website hosts the Women of Color Research Network (WoCRN) page, which features NIH diversity efforts, prominent women-of-color researchers, and the WoCRN membership group.

The working group newsletter, titled *Advances & Insights: The NIH Women in Science Newsletter*, featured scientist spotlights, research and perspectives, and current news and reports. In FY 2018, articles that pertain to the advancement of women in science migrated to the ORWH quarterly publication, *Women's Health in Focus at NIH*, found at https://orwh.od.nih.gov/about/newsroom/orwh-newsletter.

These articles address career development and best practices for retention at universities and institutions and provide an overview of NIH policies and programs relevant to women in the sciences.

Activities of the Committee on Women of Color in Biomedical Careers

The Committee on Women of Color in Biomedical Careers, a subcommittee of the NIH Working Group on Women in Biomedical Careers, is charged with addressing the unique challenges facing women scientists of color. One aim of the committee is to increase their visibility and recognition. Toward that end, the committee regularly identifies and nominates exceptional women researchers for society awards and lectureships, such as the prestigious NIH Director's Wednesday Afternoon Lecture Series (WALS). In FY 2017 and FY 2018, six out of 55 WALS lecturers (11%) were women of color.

To promote networking among women scientists of color, the committee developed the Women of Color Research Network (WoCRN), a social media site that provides information, mentoring, and career development opportunities for women of color in biomedical careers and for all those who support diversity in the scientific workforce. More information is available at https://womeninscience.nih.gov/women-of-color/index.asp. This effort, supported by both ORWH and the National Institute on Aging (NIA), was awarded an NIH Office of the Director Honor Award in FY 2015 for its role as a national online resource supporting the NIH mission and minority women in biomedical sciences. It was migrated to the LinkedIn platform and can be found at https://www.linkedin.com/groups/8501207. The WoCRN also has regional chapters to facilitate local interactions and mentoring opportunities. During FY 2017 and FY 2018, content was added weekly to the WoCRN LinkedIn page for those interested in diversity in the scientific workforce.

Activities of the Committee on Advancing Women in Independent Positions

The Working Group on Women in Biomedical Careers issued a trans-NIH funding opportunity announcement titled "Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (RFA-GM-09-012)," also known as the Causal Factors and Interventions RFA. Through this effort, NIH funded 14 research grants that explored obstacles facing women scientists at all stages of their scientific careers. The grants totaled $16.8 million across 4 years, with support from 11 NIH institutes and centers and 4 offices within OD. Since receiving the awards, the principal investigators (PIs) have written more than 120 publications on causal factors and interventions, given more than 160 presentations, and received 24 related follow-up grants to continue their research. The PIs funded from the Causal Factors and Interventions RFA formed an independent group, the Research Partnership on Women in Biomedical Careers, to stimulate research collaborations. This group published a collection

of articles in the journal *Academic Medicine*, as well as a second collection in the *Journal of Women's Health* in early 2017.

Another activity from the committee was analyzing the receipt of research project grants (RPGs) of women scientists as compared with men. Results reported in the *Proceedings of the National Academy of Science* in 2018 determined that though women obtain only one-third of NIH RPG funding, they are as successful as men in obtaining first-time grants (Hechtman, 2018). Although the group found that women have similar funding longevity compared with men, contradicting the assumption of accelerating attrition, it also was found that women held fewer grants, submitted fewer grant applications, and were less successful at obtaining renewals than men (Hechtman 2018).

Workshop on Interventions to Promote and Support Women and Minorities in Biomedicine, Behavioral Science, and Engineering

In FY 2017, the Research Partnership on Women in Biomedical Careers held a workshop titled "Getting Beyond the Pipeline: Interventions to Promote and Support Women and Minorities in Biomedical, Behavioral Science, and Engineering Careers." The workshop was held at the Association of American Medical Colleges (AAMC) in Washington, D.C., and was sponsored by the Doris Duke Charitable Foundation. The overarching objective was to plan a multi-level, multi-institutional intervention for gender and underrepresented minority (URM) equity in academic medicine. The conference included presentations from the director of ORWH and representatives from the National Science Foundation, the American Medical Women's Association (AMWA), California's 6th Congressional District, and other leaders and educators in academic medicine. Panel discussions were held with the chair and principal investigators of the Research Partnership on Women in Biomedical Careers, key staff at NIH, the president and CEO of AAMC, and other relevant stakeholders. The conference provided an opportunity for ORWH to highlight the work of the research partnership and to strategize with the scientific community. The key challenge discussed was implementation of multi-center or multi-institutional initiatives to increase participation and advancement of women and URMs in biomedical, behavioral science, and engineering research careers.

Working Group Initiatives for NIH Employees

In FY 2017 and FY 2018, the NIH Intramural Research Program (IRP) focused on improving and enhancing the NIH employee work environment to support the advancement of women. The committee collaborated on several programs with the Office of Intramural Research (OIR), the Office of Equity, Diversity, and Inclusion (EDI), the Women Scientist Advisors (WSA), the NIH Equity Committee, and the NIH Civil Program. These initiatives are described below.

Keep the Thread Program

The IRP has continued its support for programs aimed at increasing flexibility for fellows. The "Keep the Thread" program aims to recognize and proactively address common roadblocks to balancing work and personal life. It offers current NIH Intramural Research Training Award (IRTA) and Cancer Research Training Award (CRTA) postdoctoral fellows several options for increasing flexibility and temporarily reducing effort while remaining connected to their research and the NIH community during times of intense family need. The program incorporates a variety of flexible arrangements, to be mutually agreed upon by the fellow and the principal investigator, with approval by the scientific director. These arrangements vary from increased use of telework and flexible scheduling to temporary reductions in effort. They also include necessary modifications of project timelines. More information about the program can be found at https://oir.nih.gov/sourcebook/personnel/

recruitment-processes-policies-checklists/keep-thread-policy.

Northwest Child Care Center

The Northwest Child Care Center on NIH's main campus opened in mid-2017. It provides an additional 170 child care slots on campus. Support for this center comes from the Office of Research Services (ORS), the Office of Research Facilities Development and Operations, the Child Care Board, and OD.

Back-up Care Program

Through the efforts of the Working Group on Women in Biomedical Careers and the NIH Child Care Board, ORS launched the Back-up Care Program in January 2012. The program offers short-term child care, elder care, and self-care to NIH employees. It continued throughout FY 2017 and FY 2018. More information about the program can be found on the ORS website at https://www.ors.od.nih.gov/pes/dats/childcare/Pages/NIHBack-upCareProgram.aspx.

NIH Resource Matrix

To increase awareness and encourage participation in the many supportive programs and resources at NIH, the Women's Employment Committee, in collaboration with OIR and ORWH, created the NIH Workforce Resource Eligibility Matrix. The matrix is a tool designed to assist the NIH workforce in identifying available resources based on category of employment or position. Information is available at https://hr.nih.gov/working-nih/work-life.

ORWH Support for Other NIH Career Development Programs and Activities

Office of Intramural Training and Education

The NIH Office of Intramural Training and Education's (OITE) mission is to enhance the training experience of students and fellows on all NIH campuses. The office works closely with the NIH ICOs to support the development of scientific and professional skills to enable junior investigators to become leaders in the biomedical research community. Many of the workshops, seminars, and career development resources also are available to individuals outside of NIH.

High School Scientific Training and Enrichment Programs: HiSTEP and HiSTEP 2.0

In FY 2018, ORWH provided funds to support students in the High School Scientific Training and Enrichment Programs (HiSTEP and HiSTEP 2.0). These programs expand the pipeline of students interested in biomedical and health care careers by providing internship opportunities for high school students from schools with large populations of financially disadvantaged students. The programs target students from Washington, D.C., Maryland, and Virginia, where greater than 30% of students receive free or low-cost lunches from the National School Lunch Program. Students from these lower-resourced schools traditionally struggle to obtain internships in research groups, even when they show great potential.

Local high school juniors are selected for HiSTEP through a two-part application process and participation in career exploration, leadership, and professional development training opportunities, and they are guided by HiSTEP staff members. HiSTEP 2.0 supports competitively selected high school seniors and HiSTEP alumni who have little or no research experience and provides them with the opportunity to spend 8 weeks performing biomedical research at NIH. Students are paired with and work side by side with scientists on the main campus of NIH in Bethesda, Maryland. Through these experiences, HiSTEP and HiSTEP 2.0 students develop their research and scientific skills; explore biomedical, translational, and/or basic science in depth; and sharpen their critical thinking skills. In addition to research experience, all students participate in a curriculum designed

to enhance leadership and communication skills, experience mentorship during and beyond the summer, and access resources that help them in the transition from high school to college. As a required part of the program, students present research results at a "Summer Poster Day," alongside other NIH summer interns.

In 2018, 25 students from 15 schools were selected for HiSTEP. Of the 25, 16 (64%) were women and nine (36%) were men. Students ranked the hands-on laboratory experience and the college application preparation sessions as their favorite aspects of the program. The entire 2018 HiSTEP cohort completed the program. The participants began their senior years with plans to apply for and attend college. When surveyed, 100% of the participants said they would recommend HiSTEP to a friend. Overall, 98% of HiSTEP alumni from the 2015–2018 programs said they would recommend HiSTEP to a friend.

The 2018 HiSTEP 2.0 cohort consisted of 27 students, of which 16 (59%) were HiSTEP alumni. The gender distribution in this cohort included 16 (59%) women and 11 (41%) men. In a survey, all HiSTEP 2.0 students (100%) said they would recommend the program to a friend who is interested in conducting biomedical research and said they felt more prepared for college after program completion. In fact, the students ranked the "Transition to College Series" as the most helpful component. By the end of the program, students indicated improvement in their abilities to: (1) communicate with peers and mentors, (2) present at laboratory meetings and posters presentations, (3) use networking skills to expand their professional networks, (4) further develop their research and scientific skills, and (5) better manage time and stress.

Representative feedback from HiSTEP and HiSTEP 2.0 students is listed below:

- "It provides a supportive environment to gain research experience and college preparation."
- "This experience really opens one up to experiences in science and it is a definite confidence booster."
- "I would recommend this program to a friend because this was a program that I enjoyed, and I felt as if I grew mentally, emotionally, and academically in a small amount of time."
- "It gives students a chance to learn and experience things that you won't get a chance to do in high school."
- "You get to work in a lab and have a community of support."
- "I have been able to break out of my shell and become very confident. I have learned so much about myself, but also from my peers. I've learned about many different types of STEM careers. A support system. A future!"
- "My network is the best it's ever been! Opportunity of a lifetime. Amazing new mentors. A support system of people like me going through this process for the first time. My love for public health was confirmed!"
- "Overall, a great learning experience! Perfect balance of hands-on (in the lab) and classroom-style learning."
- "This program exposed me to different resources and opportunities I couldn't get elsewhere. I gained experiences that will help me in the future."
- "Great full exposure to biomedical research with extra guidance."

Training in Mentorship, Leadership, Management, and Related Topics

For many years, ORWH has partnered with OITE to support the development and dissemination of materials to enhance mentoring and interpersonal skills in the intramural and extramural communities. OITE has developed programming to improve leadership and management skills of

its trainees. They are encouraged to participate in a "Workplace Dynamics Series" to improve research workplace environments. This four-part series aims to train fellows to build interpersonal and communication skills using experiential learning using examples relevant to research groups. It begins by enhancing self-awareness and understanding of others, transitions to examining differing communication and learning styles, builds understanding of workplace conflicts, provides strategies to communicate feedback, encourages skills in team dynamics and team behaviors, and closes with a session on capitalizing on diversity.

Postdocs, clinical fellows, and advanced graduate students who complete the Workplace Dynamics Series are eligible for a 2-day management course that provides an overview of common management concepts. Topics include emotional intelligence, personal and organizational resilience, hiring, managing conflict as a supervisor, establishing expectations and motivating others, and building an inclusive and diverse work group. This capstone course has provided valuable knowledge and skills that help advanced trainees transition to their first positions as direct supervisors.

OITE has developed resources for all trainees on topics such as stress management, mindfulness, holistic self-care, resilience, self-compassion, and wellness. The office facilitates in-person quarterly workshops to address the impact of stress on physical and mental health and to present strategies to enhance well-being. An additional workshop explores building resilience as a scientist. Every week, OITE offers at least five informal groups to discuss wellness topics. Two weekly guided meditation groups create an informal atmosphere in which to explore topics such as body–mind relaxation, breath awareness, and practicing stillness. The weekly wellness group explores topics such as sleep hygiene, understanding cognitive distortions, spiritual health, and social support. The weekly resilience group meets with a trained counselor to discuss conflict in workplace environments, managing the stress of job/school applications, and other work-related topics. The office also offers discussion groups for trainees who are parents and who have disabilities or chronic medical conditions. Finally, OITE offers a monthly discussion group for trainees with mental and emotional health challenges. Because individuals embrace wellness initiatives through different media, OITE recorded a YouTube video titled "Resilience in the Job Search" and created many blog posts on the topic, including an interview with Dr. Francis Collins, Director of NIH, on his approach to wellness. Additionally, OITE has wellness counselors on staff to meet individually with trainees to help them navigate life stressors and workplace environments.

In 2018, OITE hosted a second workshop, "How to Teach and Advise on Career Development Topics for the Next Generation of Biomedical Scientists: A Train-The-Trainers Event." The goal is to disseminate this leadership program and share best practices on engaging students individually and in groups. It was attended by academic deans, graduate and postdoctoral program directors, and career counseling staff members from STEM fields. One track prepared participants for standard career development needs, such as individual career meetings or workshops, decision-making, job search skills, and developing curricula vitae or résumés. A second track helped participants develop skills in talking with trainees, presenting workshops in assertiveness, and talking with mentors about careers, wellness, resiliency, and emotional intelligence. A third track provided guidance on delivering workshops on conflict, team dynamics, and other topics that encourage growth in interpersonal relationships in the biomedical workforce. Participants practiced difficult conversations with trainees related to stress, anxiety, and depression. The practice sessions were facilitated by a cohort of 10 therapists from

the community who coached participants on their verbal and nonverbal communication.

In 2018, participation nearly doubled from 2016 numbers; 230 participants attended from over 120 institutions. OITE is planning similar workshops every 2 to 3 years, as funding allows. Finally, the OITE Director has traveled to many universities and national scientific meetings to discuss wellness and resilience with institutional leaders, faculty, and trainees. These visits have supported many institutions in their efforts to improve the health and well-being of the biomedical workforce.

NIH Fogarty International Center Global Health Training Program

In FY 2017 and FY 2018, ORWH continued support for the Fogarty International Center Global Health Training Program,[9] a reissue of the Fogarty International Center Global Health Program for Fellows and Scholars. It provides mentorship, research opportunities, and a collaborative research environment for early-stage investigators from the U.S. and low- and middle-income countries. The program aims to enhance scientists' global health research expertise, with a focus on the careers of women in biomedical science. Many projects address women's health and maternal and child health. It includes a summer orientation and training initiative. In FY 2017, 49 of 90 scholars (54%) were women; in FY 2018, 45 of the 91 scholars (49%) were women.

NIH/National Medical Association Travel Award

Several NIH Institutes and Centers (ICs) contribute to the National Medical Association (NMA) Travel Award, which allows senior residents, fellows, and junior faculty interested in

9 FOA: https://grants.nih.gov/grants/guide/rfa-files/RFA-TW-16-002.html

careers in biomedical research and/or academic medicine[10] to attend the NIH-NMA Academic Career Development Workshop. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) coordinates the program. Other participating ICOs include ORWH, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI). ORWH continued its support for these travel awards in FY 2017 and FY 2018. Held in conjunction with the NMA Annual Convention and Scientific Assembly, the event covers topics ranging from grantsmanship to time management skills. Awardees must attend the entire workshop. NIH anticipates that this opportunity will allow more physicians from medically underserved communities to receive research training.

Online Courses

The Science of Sex and Gender in Human Health program[11] is a free online self-paced education program for physicians, pharmacists, and nurses. It was developed and sponsored by the Office of Women's Health (OWH) at the Food and Drug Administration (FDA) and ORWH. The program builds on the 2001 Institute of Medicine report titled *Exploring the Biological Contributions to Human Health: Does Sex Matter*,[12] funded by NIH and FDA. The three courses (each with five or six lessons) focus on sex- and gender-related differences from the perspective of: (1) basic science or biological bases, (2) health and behavior, and (3) disease expression and treatment. Since the first course was launched in 2006, there has been an exponential expansion of basic science evidence to support the concept of sex as a basic biological variable and the fact that every cell has a sex. It is important for clinicians to be familiar with the rapidly expanding findings in basic science and clinical research and be able to translate them into epidemiological and clinical contexts.

10 https://www.niddk.nih.gov/research-funding/research-programs/diversity-programs/travel-scholarship-awards/nih-national-medical-association

11 sexandgendercourse.od.nih.gov

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Hechtman, L. A., Moore, N. P., Schulkey, C. E., Miklos, A. C., Calcagno, A. M., Aragon, R., and Greenberg, J. H. (2018). NIH funding longevity by gender. *PNAS, 115 (31),* 7,943–7,948. https://doi.org/10.1073/pnas.1800615115

12 www.nap.edu/read/10028/chapter/1

IV. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

Historical Perspective

The establishment of policies for the inclusion of women and minorities in NIH-funded clinical research originates from the women's health movement. After the U.S. Public Health Service Task Force on Women's Health issued its report in 1985, NIH established a policy urging the inclusion of women in clinical research. This policy was first published in the *NIH Guide for Grants and Contracts* in 1987. Later that year, NIH published a policy encouraging the inclusion of minorities in clinical studies.

To ensure that NIH implements the inclusion policies, Congress made previous policy into public law through a section in the NIH Revitalization Act of 1993 (Public Law 103) titled *Women and Minorities as Subjects in Clinical Research*. In 1994, NIH revised its inclusion policy[13] to comply with the statutory language. The NIH Revitalization Act essentially reinforced certain existing NIH policies, stating that NIH should ensure:

- That women and minorities and their subpopulations are included in all clinical research
- That women and minorities and their subpopulations are included in Phase III clinical trials designed such that valid analysis can be performed
- That cost is not allowed as an acceptable reason for excluding these groups
- That it initiates programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as participants in clinical studies.

In October 2015, the Government Accountability Office (GAO) produced a report examining women's participation in NIH research, titled *Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research* (GAO 16–13).[14] GAO examined: (1) women's enrollment and NIH efforts to monitor this enrollment in NIH-funded clinical research and (2) NIH efforts to ensure that NIH-funded clinical trials are designed and conducted to analyze potential sex differences when applicable. GAO recommended that NIH examine and report more detailed data on women's enrollment in NIH-funded studies and collect, examine, and report data on the extent to which these studies include analyses of potential differences between men and women. NIH agreed with the report and is currently in the process of addressing the recommendations.

Since the NIH Revitalization Act was enacted, the overall number of women, minorities, and children included in NIH-funded studies has increased. However, as the GAO report pointed out, attention is still needed to ensure scientifically appropriate inclusion, as well as analyses and reporting of

13 https://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

14 https://www.gao.gov/products/GAO-16-13

population-specific information. In addition, the inclusion of groups in disease and condition areas should be monitored and reported.

In addition, the inclusion of groups in disease and condition areas should be monitored and reported. To address these issues, NIH has taken several steps: 1) IC-level enrollment data are now accessible online through NIH's RePORT website.[15] 2) As recommended in the GAO report and required by section 2038 of the 21st Century Cures Act, inclusion data by research, condition, or disease category are now available on the NIH RePORT website.[16] 3) NIH added questions regarding required valid analysis for NIH-defined Phase III clinical trials to the NIH-wide checklist used by program officers beginning in FY 2016. And 4) NIH has analyzed the percentages of NIH-defined Phase III clinical trials that need valid analysis, and data are included in this report, in Appendix D.

The 21st Century Cures Act and the Inclusion Across the Lifespan Policy

The 21st Century Cures Act (Public Law 114–255), enacted December 13, 2016, included several new reporting requirements for inclusion of sex/gender in clinical research. As a result, NIH updated its policy on the Inclusion of Women and Minorities as Subjects in Clinical Research on November 28, 2017, to require studies that are both NIH-defined Phase III clinical trials and applicable clinical trials to report the results of analyses by sex/gender and/or race/ethnicity to ClinicalTrials.gov. This requirement is effective for competing grant awards on or after December 13, 2017, as well as contract solicitations and intramural studies initiated after this date. Additionally, NIH held a workshop on age groupings and exclusions in clinical research on June 1–2, 2017,[17] and revised its Inclusion of Children in Clinical Research policy on December 19, 2017. The revision, now called "NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects," requires individuals of all ages (including children and older adults) to be included in clinical research unless there are scientific or ethical reasons not to do so. The policy also requires investigators conducting clinical research to submit individual-level data on sex/gender, race, ethnicity, and age of participants at enrollment in annual progress reports. The policy applies to all applications submitted on or after January 25, 2019. Also, in response to 21st Century Cures Act requirements, NIH has made available inclusion data by disease or condition category on the NIH RePORT website.

Inclusion Monitoring Activities

Communication and Outreach Efforts to the Scientific Community

NIH regularly updates application, contract proposal, and intramural project instructions and guidance to ensure that investigators address inclusion as required and report inclusion enrollment data at least annually. Numerous policy documents, podcasts, answers to frequently asked questions, and other resources are available for investigators and NIH staff on the ORWH and Office of Extramural Research (OER) websites. Tools to help investigators understand the new policies and their implementation, including a decision tree and infographic, are available on the OER website. These resources are intended to help the extramural research community understand and implement NIH requirements for monitoring inclusion in clinical research.

NIH staff members have authored several publications to communicate inclusion requirements to the scientific community and general public. The blog of the NIH Deputy Director for Extramural Research, "Open Mike," has published three entries explaining the new inclusion policies, available on the NIH Extramural Nexus website.[18] A Viewpoint essay

15 https://report.nih.gov/recovery/inclusion_research.aspx

16 https://report.nih.gov/RISR

17 Workshop report available at https://report.nih.gov/FileLink.aspx?rid=953.

18 https://nexus.od.nih.gov/all/?s=inclusion&submit=Search

published in the *Journal of the American Medical Association (JAMA)*, co-authored by Drs. Marie Bernard (National Institute on Aging), Janine Clayton (ORWH), and Michael Lauer (OER), explains the Inclusion Across the Lifespan policy and summarizes efforts by NIH to implement 21st Century Cures Act requirements regarding age of participants in clinical research.[19]

NIH conducts outreach to the extramural community through educational sessions at scientific meetings and conferences. For example, OER discussed the new inclusion policies at its NIH Regional Seminar[20] held in May and October of 2018. The NIH Office of Science Policy (OSP) presented updates on the Inclusion Across the Lifespan policy at the 2018 Advancing Ethical Research Conference. The Food and Drug Administration's (FDA) Office of Women's Health (OWH) is collaborating with ORWH to raise awareness of women and ethnic/racial minority enrollment in clinical trials in an initiative called Diverse Women in Clinical Trials.[21]

NIH Inclusion Outreach Toolkit

ORWH staff presented the *NIH Inclusion Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research* at the 144th Annual Meeting of the American Public Health Association. The toolkit is a resource intended to help principal investigators (PIs) and their research teams fulfill their responsibilities to women in clinical research by providing information on relevant Federal laws, regulations, and NIH policies. The toolkit features case studies with researchers' experiences with including women in their studies. Topics include oral health in pregnancy, dental caries prevention, HPV, and menopause.

Peer Review Expectations

Scientific Review Groups (SRGs) are instructed to focus on scientific considerations when assessing the enrollment for a proposed study described in an NIH grant application. The SRGs evaluate the inclusion plans and find them unacceptable if the applicant: (1) fails to provide enough information about the planned sample, (2) does not adequately justify limited inclusion or lack of inclusion of women or minorities, or (3) does not realistically address recruitment. Reviewers on NIH peer review panels are given specific guidance on reviewing inclusion based on sex/gender, race, ethnicity, and age when considering clinical research applications. For NIH-defined Phase III clinical trials, the SRGs also evaluate the description of plans for valid analyses and whether investigators need to examine differences in the intervention effect by sex/gender, racial, and/or ethnic groups. Valid analyses refer to stratified analyses that explore how well the intervention works among sex/gender and racial/ethnic groups. Although they may or may not have high statistical power, these trials provide essential information to inform future studies. Previous data suggesting that differences may exist could indicate a need to consider specific analyses.

Unacceptable inclusion plans must be reflected in the priority score of the application and documented in the minutes of the review session. Initial review groups make recommendations on the acceptability of the proposed study population with respect to inclusion policies. If issues are raised in review, program staff notify the PIs, who are required to address these issues prior to funding. Applications with unacceptable inclusion plans cannot receive funding; an award is not issued until an acceptable resolution is received. NIH staff members must be assured that the revised plans meet inclusion policy requirements.

Communication and Outreach Efforts Within NIH

The Center for Scientific Review (CSR) and OER provide training for reviewers and applicants. OER has online training tools designed for

19 https://jamanetwork.com/journals/jama/fullarticle/2703925

20 https://regionalseminars.od.nih.gov/sanfrancisco2018

21 https://www.fda.gov/consumers/womens-health-topics/women-clinical-trials

applicants.[22] These training and outreach efforts improve understanding of the inclusion policy and help extramural and NIH intramural investigators appropriately address these issues throughout the research funding process. Specifically, these tools help applicants understand how NIH monitors inclusion, reviews the importance of reporting the race and ethnicity of clinical research participants, and describes how grantees and applicants should report race and ethnicity. CSR, which handles approximately 70% of the grant applications that NIH receives, offers a robust applicant resource page that includes training, resources, and updates for scientific review officers and program officers.[23] Institute program officials/program directors and scientific review officers attended a May 11, 2018, training titled "Ensuring Inclusion in NIH Clinical Research: Policies and Procedures for Grants and Contracts." Staff members can access the archived training on the NIH staff intranet.

The Extramural Activities Working Group (EAWG), established by the NIH Director as a working group of the NIH Steering Committee, facilitates the governance for the policies, procedures, and utilization of resources for extramural research and research training. The Inclusion Governance Committee (IGC) was formed in 2011 as a subcommittee of the EAWG to discuss policy issues related to inclusion. The IGC is currently co-chaired by the ORWH Director and the National Institute on Aging Deputy Director. Members of the IGC are primarily senior-level staff from the NIH Office of the Director and various NIH Institutes and Centers (ICs); other participants represent business areas involved in the implementation of inclusion policy.

Monitoring Compliance and Inclusion Enrollment Outcomes

NIH staff members continue to monitor and document compliance with the inclusion policy and to work with grantees to ensure compliance. Program officers and staff provide technical assistance to investigators as they develop their applications and proposals. Program staff monitor actual enrollment progress in annual progress reports and provide consultation when necessary. In preparation for peer review meetings, scientific review officers remind reviewers of the guidelines for evaluating investigators' plans for the inclusion of women and minorities in clinical research. Also discussed during these preparatory meetings are the instructions and requirements for reviewing NIH-defined Phase III clinical trials, particularly how the proposed work considers plans for valid analyses of sex differences. Program staff note whether valid analyses of sex differences are required prior to awarding grants. When new and competing continuation applications selected for payment are deficient in meeting inclusion policy requirements, NIH staff members are required to withhold funding until the PI has satisfactorily addressed the policy requirements. Grants management staff ensure that appropriate terms and conditions of award are included in the *Notice of Award* and ensure that this information is appropriately documented in the official grant file. At the time of award and at the time of submission of progress reports, program officials monitor and verify that progress with inclusion is appropriate for the scientific goals under study.

Inclusion enrollment data aggregated across the ICs are presented in this report in summary figures and aggregate data tables (Appendix D), providing documentation of inclusion monitoring with some analysis. Caution should be used in interpreting these figures. Conclusions that can be reasonably drawn from the data are provided.

When assessing inclusion data, NIH avoids directly comparing enrollment figures with national census figures. The goal of the NIH policy is to ensure that the scientific knowledge acquired through NIH-defined clinical research ultimately will be generalizable to the appropriate population(s), not to satisfy any proportional target based on census data. The numbers of

22 https://grants.nih.gov/grants/funding/women_min/inclusion_training.htm

23 https://public.csr.nih.gov/ApplicantResources/Pages/default.aspx

women, men, and representatives of racial and ethnic groups included in a study depend on the scientific question(s) being addressed and may consider several factors, such as the prevalence among women, men, or racial and ethnic groups of the disease, disorder, or condition under investigation; gaps in scientific knowledge; and disparities in health risks or outcomes. A key principle of the inclusion policy is that inclusion is integral to conducting good science. Inclusion should not be considered based on absolute numbers of individuals of groups; rather, the focus should be on whether a given study has the right people for its scientific goals and how sex/gender, race, and ethnicity may affect outcomes in those groups.

NIH Human Subjects System (HSS)

NIH has monitored aggregate inclusion data for study populations since fiscal year (FY) 1994. All ICs have well-established practices for monitoring compliance with the NIH inclusion policy. A new Human Subjects System (HSS) replaced the Inclusion Management System (IMS) on June 9, 2018. This new system consolidates study-level human subjects and clinical trial information in one place. HSS facilitates data collection, allows submission of participant-level enrollment data in comma-separated values (CSV) format, and reduces the need for duplicate data entry in other systems, such as ClinicalTrials.gov. NIH staff members now use HSS to manage all human subjects' information associated with a grant, cooperative agreement, or contract, including plans for inclusion and inclusion enrollment data. HSS provides an electronic means to enter, store, approve, monitor, and report the planned and actual enrollment of research participants based on sex/gender, race, and ethnicity. The new features of HSS allow applicants/recipients to submit de-identified participant-level data in CSV format and to populate fields from ClinicalTrials.gov. HSS promotes increased transparency by displaying the same information to grant recipients and NIH staff.

Summary Report of NIH Inclusion Data for FY 2017 and FY 2018

Reporting of sex/gender, racial, and ethnic categories is typically based on self-identification by participants, who always have the option not to identify. Although inclusion is mandated for all clinical research projects conducted or supported by NIH, for the summary report, the primary focus of the racial and ethnic analyses is on studies involving populations in the U.S. Appendix D contains data tables describing inclusion data for all clinical research and NIH-defined Phase III clinical trials from FY 2008 to FY 2018.

Important Considerations When Interpreting NIH Inclusion Data

Analysis of aggregate NIH inclusion data demonstrates that substantial numbers of women and men and individuals of different races and ethnicities have been included as research subjects in NIH clinical research studies and NIH-defined Phase III clinical trials. In addition, multiyear data are provided to show inclusion trends over time. As explained in the section titled *Monitoring Compliance and Inclusion Enrollment Outcomes*, ORWH recommends using caution to avoid overinterpreting the figures and data tables provided in this chapter.

- **Portfolio Composition:** The NIH portfolio is diverse in terms of the types of clinical research studies it supports, the size of the studies, and the expectations for inclusion within them. The size of clinical research and clinical trial portfolios and the studies within those portfolios vary substantially across the NIH Institutes, Centers, and Offices (ICOs), depending on such factors as ICO budget, mission, and the scientific goals of a given study. Some ICOs do not conduct NIH-defined Phase III clinical trials or support very few of them.
- **Funding Life Cycle:** It is important to consider the nature of the funding life cycle at NIH and how that can affect inclusion

enrollment information. The average length of an NIH grant award is 4 years. This means that every year, approximately 25% of the NIH funding portfolio turns over to newly funded awards or competing continuation awards. However, funding can be as short as 1 year or can last up to 10 years. The total amount of funding can vary from year to year, and at times, spikes or dips in appropriations may affect inclusion enrollment. Changes caused by the funding life cycle may create noticeable shifts in inclusion enrollment data, particularly for ICOs with small clinical research or clinical trial portfolios. This life cycle also affects the reported enrollment numbers. In any given year, some projects have just begun, so enrollment is low. Other projects are in later years; their enrollment numbers are higher. Still other projects have ended, so their data are no longer reported. These fluctuations across studies also can lead to notable shifts in enrollment numbers from year to year.

- **Coding Categories:** The NIH-defined clinical research category includes not only NIH-defined Phase III clinical trials but many other types of clinical studies, as well, such as observational and epidemiological studies, exploratory studies, and other phases of clinical trials, all of which are monitored for compliance with the inclusion policy. The NIH-defined Phase III Clinical Trial category is a subset of all NIH-defined clinical research.

Summary of Key Trends

The following sections summarize data on the inclusion of women and minorities in NIH-funded clinical research and NIH-defined Phase III clinical trials. Appendix D summarizes all available inclusion data from FY 2008 to FY 2018. The key trends from the inclusion data summary are as follows:

- Investigators reported that in FY 2017 and FY 2018, a total of 20,068,789 and 12,814,162 participants, respectively, enrolled in NIH-funded clinical research **(Appendix D, Table 1A)**. If we exclude studies conducted outside the U.S., the enrollment count was 13,231,166 and 10,578,286 in the corresponding year **(Table 1B)**.
- Enrollment of women in all NIH-funded clinical research in FY 2017 was 47.2%. This figure increased to 52.4% in FY 2018 **(Appendix D, Table 1A)**.
- Enrollment of clinical research participants from racial minority groups across all NIH research was 50.2% in FY 2017 and decreased to 36.1% in FY 2018 **(Appendix D, Table 2E)**. However, enrollment of the Hispanic/Latino population increased from 6.9% in FY 2017 to 9.3% in FY 2018 **(Appendix D, Table 2F)**.
- NIH-defined Phase III clinical trials are a subset of NIH clinical research studies. The proportion of women participants enrolled in all NIH-defined Phase III clinical trials was 59% in FY 2017 and 62.4% in FY 2018 **(Appendix D, Table 1E)**.
- Despite the fact that racial minority inclusion in all NIH-defined Phase III clinical trials decreased from 50.6% in FY 2017 to 38.5% in FY 2018 **(Appendix D, Table 3A)**, the enrollment of ethnic minorities demonstrated a different scenario. In FY 2017, approximately 5.5% of participants who were recruited to NIH-defined Phase III clinical trials were Hispanic/Latino. This figure escalated to 11.8% in FY 2018, more than doubling the rate of the previous year **(Appendix D, Table 3F)**.

Source of Inclusion Data

The following summary is based on inclusion data tabulated from human subjects involved in NIH-funded clinical research and NIH-defined Phase III clinical trials. NIH defines human clinical research as patient-oriented, epidemiological,

behavioral, outcomes, or health services research that includes human subjects. Patient-oriented research is research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) in which an investigator directly interacts with human subjects. Excluded from this definition are *in vitro* studies that use human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical studies, and (d) development of new technologies. Studies falling under 45 CFR 46, Exemption 4 for human subject research are not considered clinical research by this definition. Exemption 4 is defined as "research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects." The inclusion data presented in this report reflect that definition. A revised justification of Exemption 4 took effect in January 2019.

Clinical trials are a subset of clinical research studies. They are research studies in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebos or other controls) to evaluate their effects on health-related biomedical or behavioral outcomes. Clinical trials test treatment, prevention, and diagnostic strategies and include studies of drugs, devices, surgical techniques, health care delivery systems, and strategies to change health-related behavior, such as diet or therapy.

Phase III clinical trials are a subset of clinical trials. Phase III clinical trials usually compare interventions to other standard or experimental interventions (biomedical or behavioral) in large groups of people, from several hundred to several thousand. Typically, these trials monitor adverse effects and collect information that will allow the interventions to be used safely.

Phase III clinical trials require valid analyses by sex/gender, race, and ethnicity. NIH program staff members monitor requirements for these analyses, and ICs report the number of Phase III trials requiring valid analyses in their triennial inclusion reports. The 21st Century Cures Act requires reporting of valid analyses for studies that are both NIH-defined Phase III clinical trials and applicable clinical trials. "Applicable clinical trial" is the term used in Title VIII of the Food and Drug Administration Amendments Act (FDAAA) of 2007 (Public Law 110–85) to designate the scope of clinical trials that may be subject to the registration and results reporting requirements of the FDAAA. Clinical trials that are subject to the regulation are, in general, clinical trials of drug, biological, and device products regulated by FDA. A pediatric post-market surveillance study of a device product required by FDA is also subject to the regulation.[24] Applicable NIH-defined Phase III clinical trials require reporting of results of valid analyses to ClinicalTrials.gov.

In FY 2015, NIH expanded inclusion monitoring to require submission of planned and actual enrollment data for additional funding mechanisms, such as career development (K) awards and individual fellowship (F) awards. In addition, NIH eliminated most previously allowable exceptions to inclusion monitoring for clinical research studies, such as secondary analyses, tissue repositories, early feasibility studies, studies with small sample sizes, and those determined by the ICs not to be clinical research.

The following summary of inclusion of women and minorities in NIH research was derived from HSS data to facilitate the congressional report required biennially by statute (Public Health Service Act section 492B, 42 U.S.C. section 289a-2). The data are aggregated across all the NIH ICs. Each IC has reviewed and approved its inclusion data used in this report. Individual IC reports are made available triennially on the NIH report

24 https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-014.html

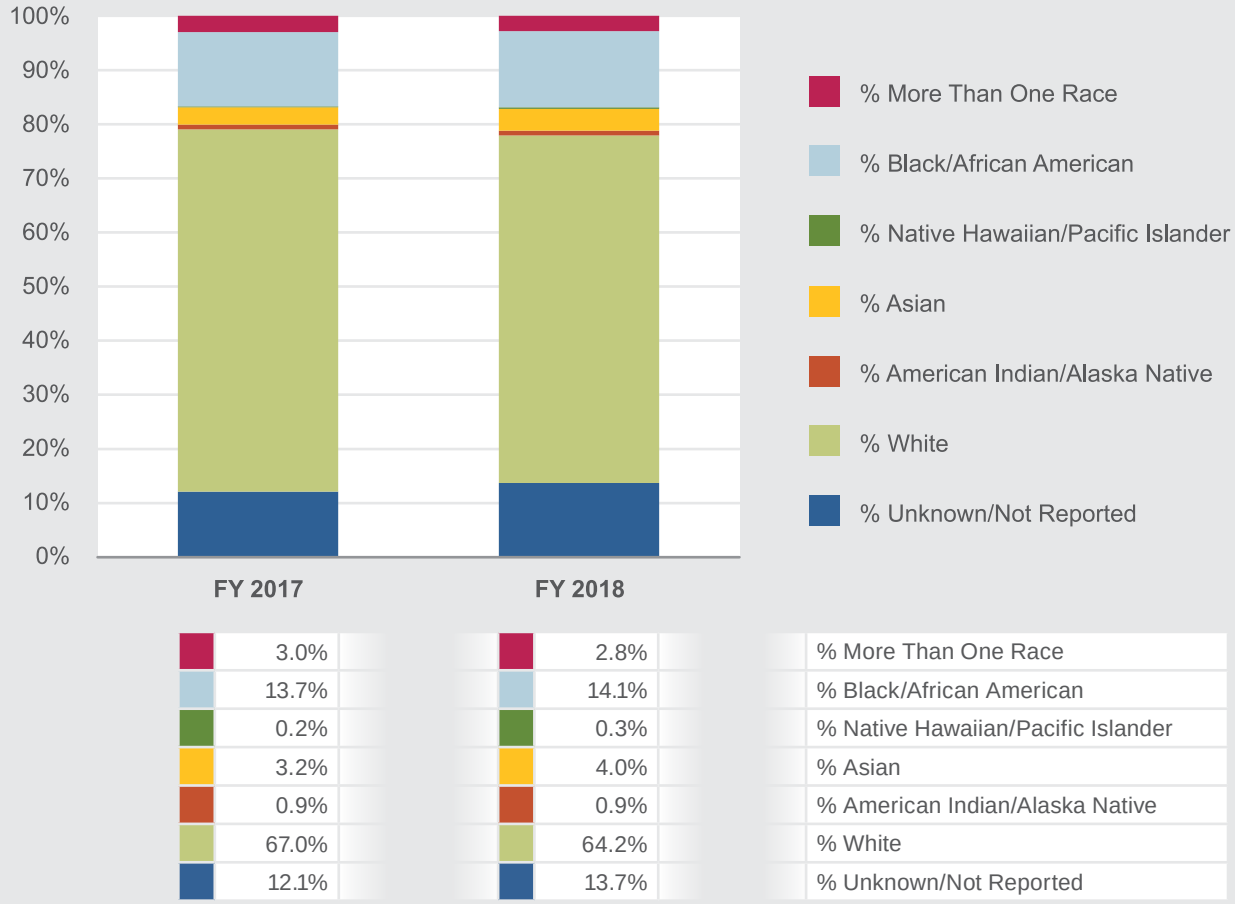
website. In FY 2017, investigators submitted 14,580 inclusion enrollment reports (IERs), with 12,932 IERs reporting enrollment of 20,068,789 participants. The remaining 1,648 IERs indicated that participants had not yet been enrolled. In FY 2018, investigators submitted 16,209 IERs, with 13,827 IERs reporting enrollment of 12,814,162 participants. The remaining 2,382 IERs for 2018 indicated that 13,827 participants had not yet been enrolled. The variation in enrollees from FY 2017 to FY 2018 was caused, in part, by the reported enrollment of one large epidemiology study from China with over 4 million participants that ended in 2017. Another domestic study that reported over 1 million participants also ended in 2017.

Inclusion Summaries

This report defines population subgroups by research participants' sex, race, and ethnicity. The percentage of female participants in NIH-funded clinical research is the proportion of enrolled participants who selected female as their sex. During FY 2018, out of a total enrollment of 12,814,162 participants, 6,711,564 were women, which accounted for 52.4% of participants in all NIH-defined clinical research. The enrollment count for men was 5,668,475, constituting 44.2% of the study population. Sex was unknown or not reported for 2.3% and 3.4% of participants in FY 2017 and FY 2018, respectively **(Appendix D, Table 1A)**.

Across all NIH-funded clinical research studies, the race of participants was unknown or not reported for 8.5% in FY 2017 and 12.4% in FY 2018 **(Appendix D, Table 2E)**. As for ethnic minorities, 8.8% of individuals did not report their Hispanic/Latino identity in FY 2017, and the rate increased to 12.4% in FY 2018 **(Appendix D, Table 2F)**. Subsetting clinical research conducted at U.S. sites demonstrated a higher percentage of unknown racial and ethnic identity. A total of 12.1% and 13.7% of study participants did not report their races in FY 2017 and FY 2018, respectively **(Appendix D, Table 2G)**. Likewise, the proportion of unknown Hispanic/Latino origin was approximately 12.2% in FY 2017 and increased slightly, to 13.1%, in the subsequent year **(Appendix D, Table 2H)**.

Figure 1: Enrollment for All NIH Clinical Research at U.S. Sites by Racial Categories for FY 2017 and FY 2018



	FY 2017	FY 2018
% More Than One Race	3.0%	2.8%
% Black/African American	13.7%	14.1%
% Native Hawaiian/Pacific Islander	0.2%	0.3%
% Asian	3.2%	4.0%
% American Indian/Alaska Native	0.9%	0.9%
% White	67.0%	64.2%
% Unknown/Not Reported	12.1%	13.7%

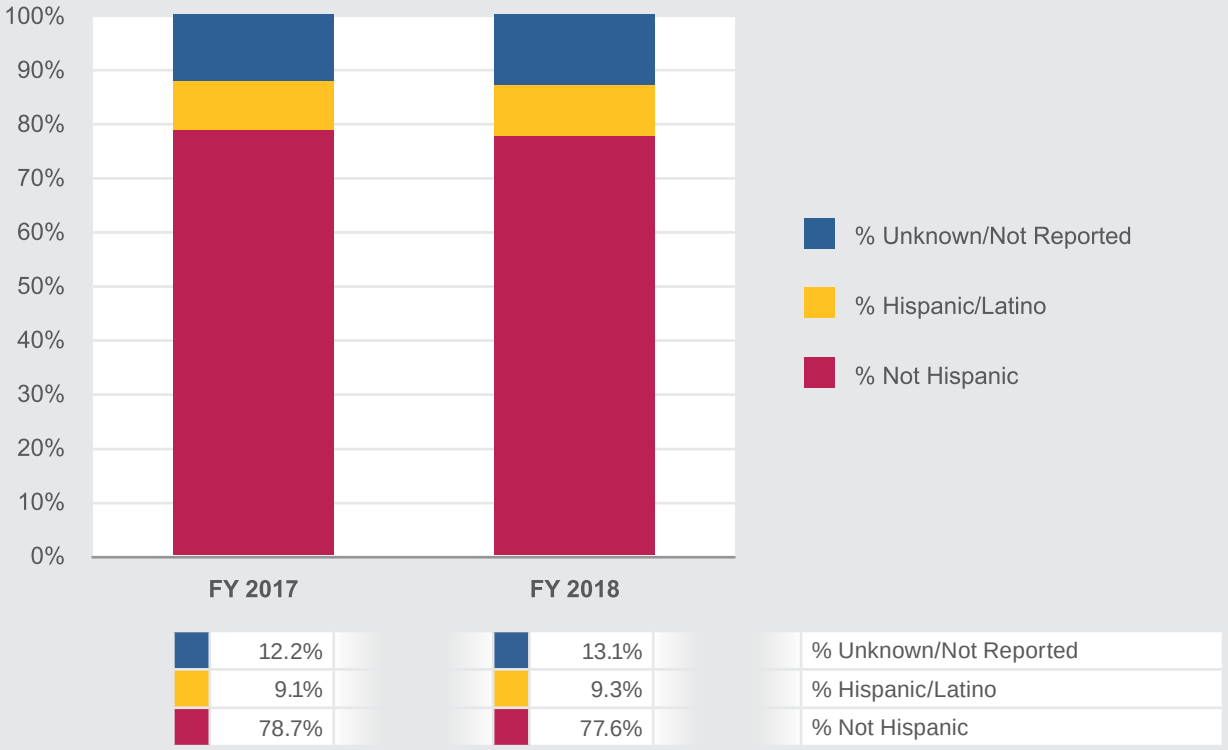
Figure 1 displays the racial composition of participants enrolled in all NIH-funded clinical research at U.S. sites for FY 2017 and FY 2018. Participation of White enrollees was 67% in FY 2017 but declined slightly to 64.2% in the subsequent year. In FY 2018, enrollment of participants identifying as more than one race was 2.8%, a minor decrease compared with the previous year (3%). Although the remaining racial minority groups had an increase in clinical research participation, the magnitude was marginal and never exceeded 1%.

The ethnic breakdown of participants in Figure 2 indicates that non-Hispanic participants decreased from 78.7% in FY 2017 to 77.6% in FY 2018. The proportion of Hispanic/Latino participants increased slightly, from 9.1% in FY 2017 to 9.3% in FY 2018. Overall, the magnitude of increase was negligible.

Inclusion Trends in NIH-funded Clinical Research

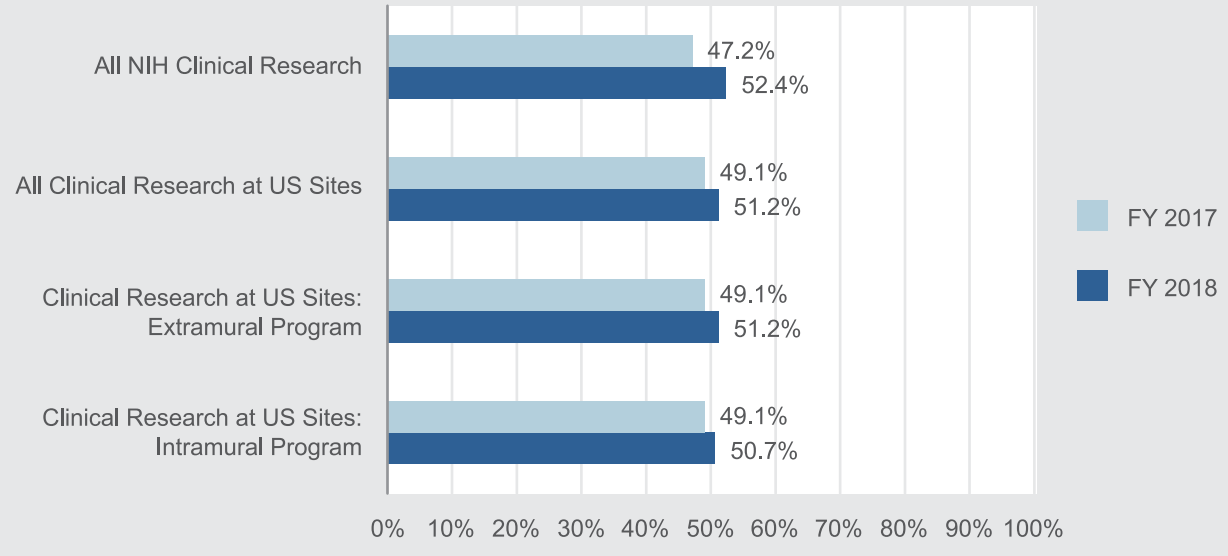
Data regarding enrollment of women and minorities for NIH-funded clinical research in FY 2017 and FY 2018 are presented in Figures 3 through 6 in the following pages. In each figure, the data are summarized for: (a) all NIH clinical research, (b) all clinical research at U.S. sites, (c) clinical research supported by the NIH Extramural Research Program conducted at U.S. sites, and (d) clinical research conducted through the NIH Intramural Research Program. All clinical research at U.S. sites includes studies conducted through the Intramural and Extramural research programs.

Figure 2: Enrollment for all NIH Clinical Research at U.S. Sites by Ethnic Categories for FY 2017 and FY 2018



	FY 2017	FY 2018
% Unknown/Not Reported	12.2%	13.1%
% Hispanic/Latino	9.1%	9.3%
% Not Hispanic	78.7%	77.6%

Figure 3: Percentage of Female Participants in NIH-funded Clinical Research for FY 2017 and FY 2018



Note: All NIH clinical research: Includes studies conducted in U.S. and foreign sites.

The information in this report represents new data collected prospectively. Studies that analyzed retrospective data using extant datasets were excluded from the report. The exclusion of retrospective data prevents possible inflation of enrollment counts, which may have been analyzed and reported previously.

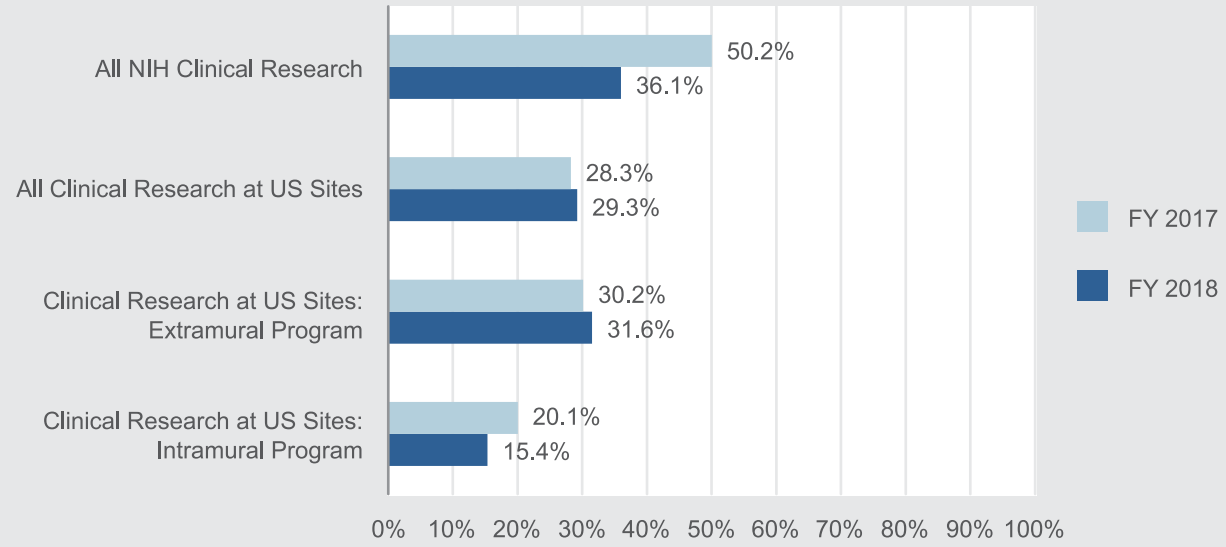
Figure 3 summarizes the proportion of women enrolled in NIH-funded clinical research for FY 2017 and FY 2018. For all NIH-funded clinical research presented in Figure 3, women accounted for 47.2% of research participants in FY 2017 and 52.4% in FY 2018. When studies recruiting only female participants are excluded from the tallies, the enrollment of women was 40.7% for FY 2017 and 41.1% for FY 2018 **(Appendix D, Table 1A)**.

Appendix D, Table 1B presents enrollment information for all NIH-funded clinical research at U.S. sites from FY 2013 to FY 2018. It shows that enrollment of women has been 49.1% or higher, whereas for men, the recruitment rate since FY 2013 has been 37.2% or higher.

Figure 4 summarizes the percentage of participants in NIH-funded clinical research who are members of racial and ethnic minority groups. For studies conducted at U.S. sites, the proportion of enrolled participants from minority groups was 28.3% in FY 2017, compared with 29.3% in FY 2018. U.S. site studies supported through the Extramural Research Program included a larger percentage of clinical research enrollees from minority groups than the Intramural Research Program in both FY 2017 (20.1% for intramural, versus 30.2% for extramural) and FY 2018 (15.4% for intramural, versus 31.6% for extramural).

To provide a more complete picture of minority enrollment in clinical research, Figures 5 and 6 provide an enrollment summary for female and male minority participants. The proportion of minority female participants was 49.3% in FY 2017 and 38.9% in FY 2018 **(Figure 5)**. For men, the proportion was 53% in FY 2017 and 34.7% in FY 2018 **(Figure 6)**. Moreover, enrollment of minority female participants from the Intramural Research Program was notably higher than enrollment of males in FY 2017 and FY 2018.

Figure 4: Percentage of Minority Participants in NIH-funded Clinical Research for FY 2017 and FY 2018



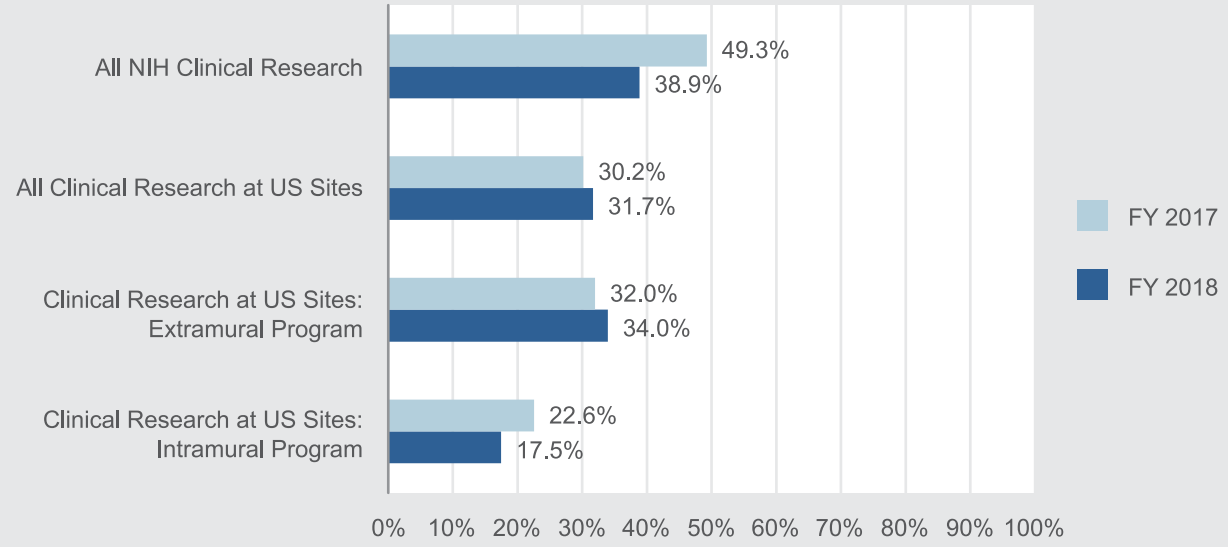
Note: All NIH clinical research: Includes studies conducted in U.S. sites and foreign sites.

Tables 4A through **4D** in **Appendix D** provide details on inclusion from FY 2013 to FY 2018 for male and female participants in clinical research who are members of minority groups. Tables **4I** through **4L** provide a detailed breakdown of enrolled participants by race and ethnicity of male and female enrollees for FY 2017 and FY 2018.

Inclusion Trends in NIH-defined Phase III Clinical Trials

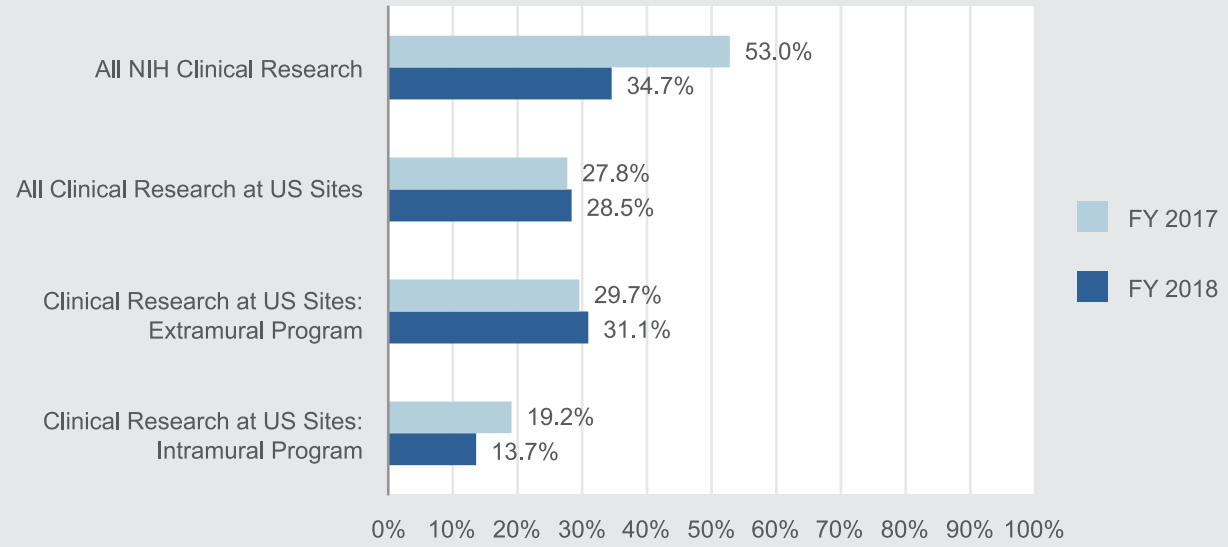
NIH-defined Phase III clinical trials are a subset of NIH clinical research studies. Enrollment for

Figure 5: Percentage of Female Minority Participants in NIH-funded Clinical Research for FY 2017 and FY 2018



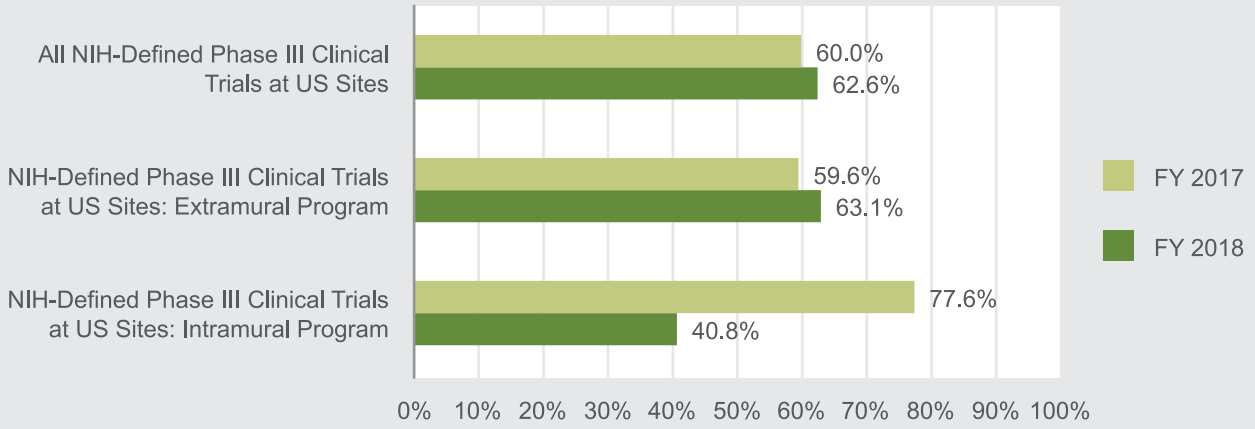
Note: All NIH clinical research: Includes studies conducted in U.S. sites and foreign sites.

Figure 6: Percentage of Male Minority Participants in NIH-funded Clinical Research for FY 2017 and FY 2018



Note: All NIH clinical research: Includes studies conducted in U.S. sites and foreign sites.

Figure 7: Percentage of Female Participants in NIH-defined Phase III Clinical Trials for FY 2017 and FY 2018



Note: All NIH clinical research: Includes studies conducted in U.S. sites and foreign sites.

Phase III clinical trials conducted at U.S. sites is presented in **Figures 7 through 10**.

Figure 7 illustrates the proportion of women enrolled in NIH-defined Phase III clinical trials in U.S. sites in FY 2017 and FY 2018, with additional percentages by intramural and extramural enrollment. The proportion of female participants in Phase III clinical trials in U.S. sites was 60% in FY 2017 and 62.6% in FY 2018. For extramural Phase III clinical trials, the proportion of female participants was 59.6% in FY 2017 and increased to 63.1% in FY 2018. However, in FY 2018, women's enrollment in the Intramural Research Program was only 40.8%, a significant decline from 77.6% in FY 2017.

A summary of data for minority enrollment across all NIH-defined Phase III clinical trials conducted at U.S. sites is provided in **Figures 8** through **10** and included in **Appendix D**.

Figure 8 illustrates NIH-defined Phase III clinical trials' enrollment data representing minority participants. For all Phase III clinical trials performed at U.S. sites, the minority enrollment

Figure 8: Percentage of Minority Participants in NIH-defined Phase III Clinical Trials for FY 2017 and FY 2018

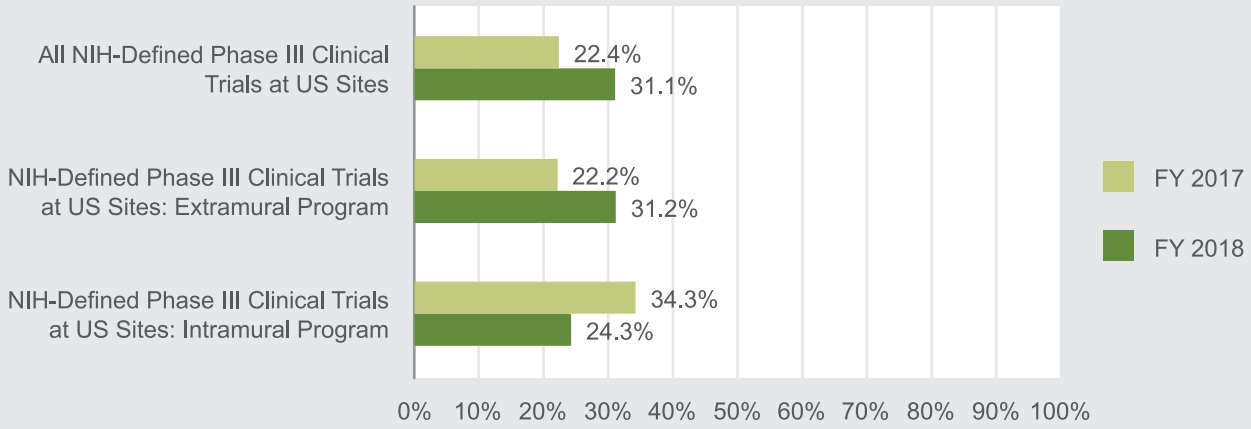
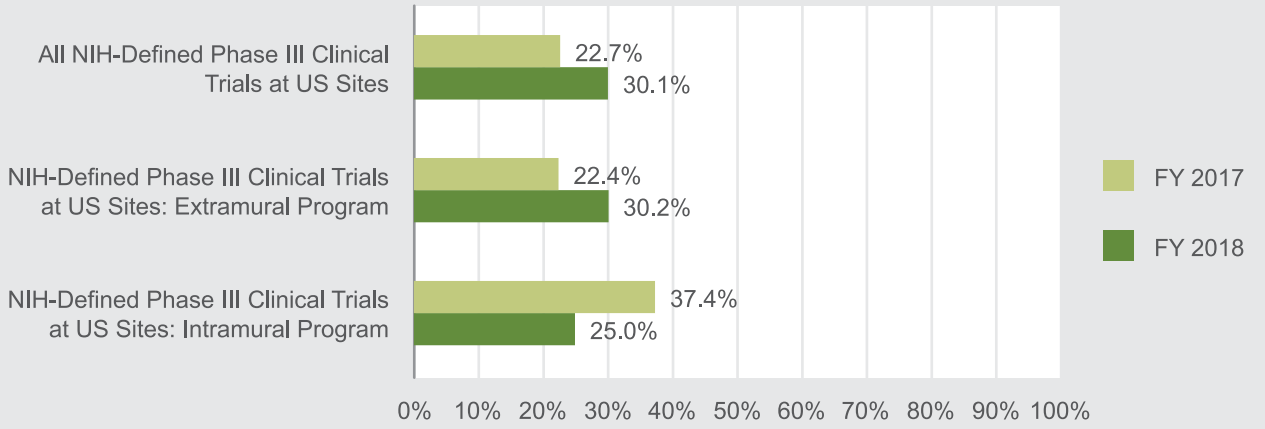


Figure 9: Percentage of Female Minority Participants in NIH-defined Phase III Clinical Trials for FY 2017 and FY 2018



rate was 22.4% in FY 2017 and 31.1% in FY 2018. Studies supported by the NIH Extramural Research Program had similar percentages.

Participants in Phase III clinical trials conducted through the Intramural Research Program included a larger percentage of enrollees from minority groups (34.3%) in FY 2017 than in FY 2018 (24.3%). **Tables 3A** through **3D** in **Appendix D** provide a summary of minority enrollment in NIH-defined Phase III clinical trials from FY 2013 to FY 2018. **Tables 3E** through **3L** provide a detailed breakdown of NIH-defined Phase III clinical trials' enrollment by race and ethnicity for FY 2013 through FY 2018.

To provide a more complete picture of minority enrollment in NIH-defined Phase III clinical trials, Figures 9 and 10 illustrate enrollment by sex/gender of minority participants. The proportion of participant enrollment in NIH-defined clinical trials for women who are members of minority groups increased from 22.7% in FY 2017 to 30.1% in FY 2018 **(Figure 9)**.

The proportion of minority male participants in NIH-defined Phase III clinical trials conducted

Figure 10: Percentage of Male Minority Participants in NIH-defined Phase III Clinical Trials for FY 2017 and FY 2018

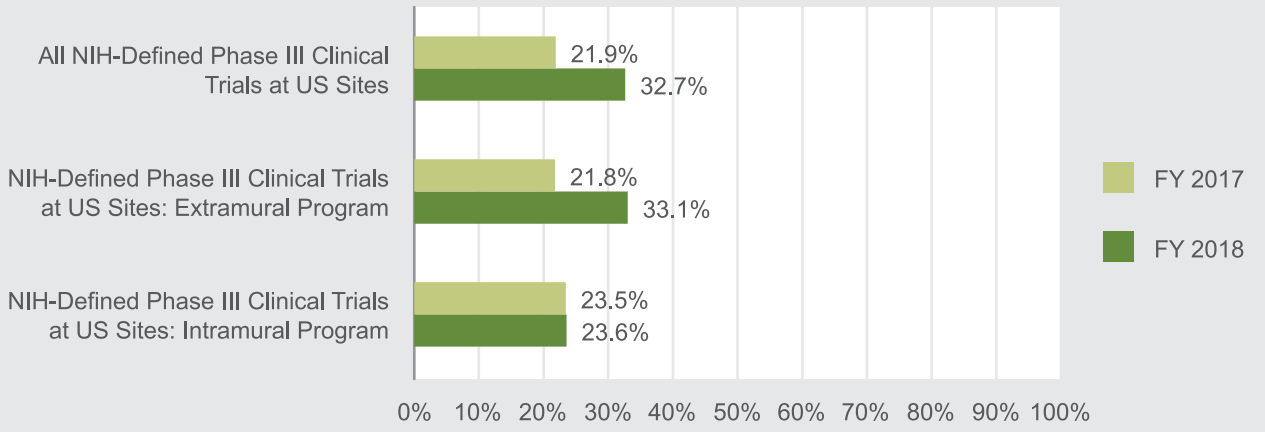
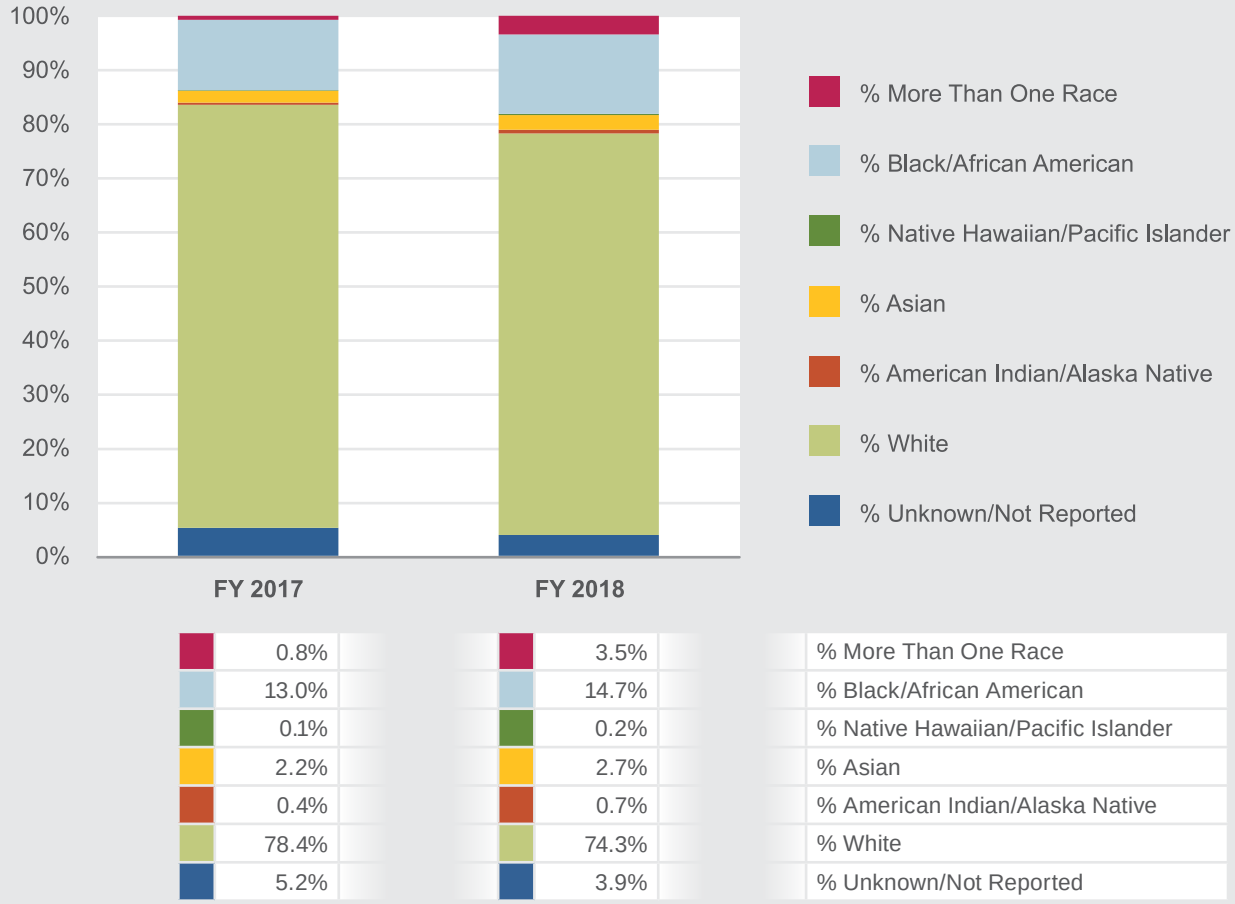


Figure 11: Enrollment for All NIH-defined Phase III Clinical Trials at U.S. Sites by Racial Categories for FY 2017 and FY 2018



FY 2017	FY 2018	
0.8%	3.5%	% More Than One Race
13.0%	14.7%	% Black/African American
0.1%	0.2%	% Native Hawaiian/Pacific Islander
2.2%	2.7%	% Asian
0.4%	0.7%	% American Indian/Alaska Native
78.4%	74.3%	% White
5.2%	3.9%	% Unknown/Not Reported

in U.S. sites had a noticeable increase, from 21.9% in FY 2017 to 32.7% in FY 2018 **(Figure 10)**. For clinical trials supported by the Intramural Research Program, enrollment rates for minority men were lower than those for minority women. In FY 2017, the difference was about 13.9 percentage points. However, the discrepancy was only 1.4 percentage points in FY 2018 **(Figure 9 and Figure 10)**.

Tables 4F through **4H** in **Appendix D** provide details on inclusion from FY 2013 to FY 2018 for minority male and minority female participants in NIH-defined Phase III clinical trials at U.S. sites. **Tables 4N** through **4P** further break down enrolled participants by race and ethnicity of male and female enrollees for FY 2017 and FY 2018.

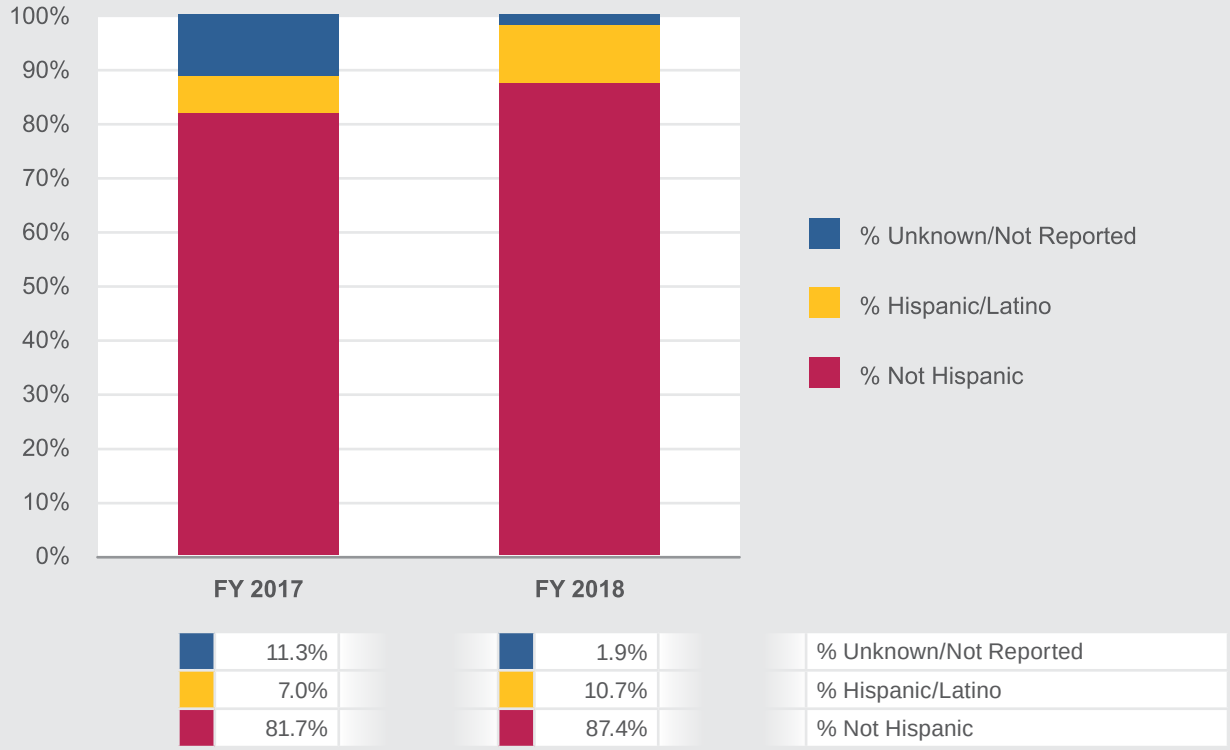
Racial and Ethnic Breakdown of Participants Enrolled in NIH-funded Phase III Clinical Trials at U.S. Sites

Figures 11 and 12 summarize enrollment data for self-reported race and ethnicity of research participants enrolled in all NIH-defined Phase III clinical trials at U.S. sites.

Figure 11 illustrates that in FY 2017 and FY 2018, Whites constituted 78.4% and 74.3% of enrollees in Phase III clinical trials, respectively, followed by Black/African American enrollees (13% in FY 2017 and 14.7% in FY 2018).

Figure 12 shows that Hispanic/Latino enrollment increased from 7% in FY 2017 to 10.7% in FY 2018. The proportion of unknown Hispanic/Latino

Figure 12: Enrollment for All NIH-defined Phase III Clinical Trials at U.S. Sites by Ethnic Categories for FY 2017 and FY 2018



	FY 2017	FY 2018
% Unknown/Not Reported	11.3%	1.9%
% Hispanic/Latino	7.0%	10.7%
% Not Hispanic	81.7%	87.4%

identity decreased from 11.3% in FY 2017 to 1.9% in FY 2018.

Summary

NIH uses several measures to address the inclusion of women and minorities in clinical research. During the peer review process for grant applications, the inclusion plan for clinical research is examined. NIH-defined Phase III clinical trials are required to have inclusion plans to inform enrollment targets. Peer reviewers assess the inclusion plans, and prior to each advisory council meeting, program directors examine the reviewers' comments on unacceptable inclusion goals and resolve issues with the investigators in writing. Program directors also review enrollment data submitted in the annual progress reports and determine whether the enrollment targets for inclusion are scientifically appropriate.

In summary, the aggregate enrollment data for the reporting period provide an overview of NIH clinical research participation and clearly show substantial inclusion of women and minorities in clinical research projects and Phase III clinical trials. The NIH HSS allows access to clinical inclusion records and cumulative reports, allowing program staff to monitor enrollment data. Overall trends in the data suggest a consistent pattern of 47.2% or greater enrollment of women in NIH-funded clinical research since 2008 **(Appendix D, Table 1A)**. Minority enrollment for NIH-defined Phase III clinical trials at U.S. sites was approximately 22.4% in FY 2017 and 31.1% in FY 2018 **(Appendix D, Table 3B)**. Minority men had lower enrollment rates than their female counterparts in the NIH Intramural Research Program in both FY 2017 and FY 2018.

V. NIH Budget for Women's Health Research

NIH Budgetary Expenditures for Research on Women's Health, Fiscal Years 2017 and 2018

NIH funding in research during fiscal years (FYs) 2017 and 2018 is presented in this budget summary, which focuses on diseases and conditions relevant to women. Budget officials at each NIH Institute and Center (IC) and the NIH Office of Budget contributed the data found in this chapter.

"Women's health conditions," as defined in section 141 of the NIH Revitalization Act of 1993 (42 U.S.C. § 287d), include all diseases, disorders, and conditions:

1. That are unique to, more serious in, or more prevalent in women;
2. For which the factors of medical risk or types of medical intervention are different for women or for which it is unknown whether such factors or types are different for women;
3. With respect to which there has been insufficient clinical research involving women as subjects or insufficient clinical data on women.

Research on women's health conditions includes research on preventing such conditions and applies to women of all ages and racial and ethnic groups.

In collaboration with the Department of Health and Human Services (HHS) Coordinating Committee on Women's Health (CCWH), ORWH reports the budgetary expenditures on women's health research throughout NIH. The reporting effort is coordinated by the Office on Women's Health in the Office of the Assistant Secretary for Health. The HHS Office of the Assistant Secretary for Financial Resources and other women's health offices and programs across HHS agencies contribute to the effort.

A variety of spending categories for diseases or disorders relevant to women are used for data collection and budgetary reporting on women's health research. The spending categories are periodically updated to reflect: (1) new disease categories, (2) new methods to standardize the proportion of the budget accounted for by women's health research when enrollment data are not available, and (3) the inclusion of men for comparison with women's health categories in which both men and women may be affected. In this case, the data collection process has evolved to account for studies in which men and women are both included and reported on. For example, in some reports prior to FY 2003 and FY 2004, the budgetary reporting on women's health research expenditures focused on single-gender studies, studies to evaluate sex/gender differences, and studies of diseases, disorders, and conditions unique to women. Previous reporting also used prevalence data as part of the reporting criteria and included research on diseases, disorders, and conditions that are not unique to one sex but for which there is documented evidence of greater prevalence in one sex by a ratio of at least 2 to 1 or for which a specific gender-related consideration exists.

For this report, budgetary expenditures are categorized as either: (1) inseparably combined, (2) supporting research on women's health only, or (3) supporting research on men's health only. As a result of discussions with the CCWH and the NIH Coordinating Committee on Research on Women's Health (CCRWH), uniform procedures for determining the appropriate categorical allocations were established. The guidelines for budget calculations are:

1. All funding for projects that focus primarily on women—such as the Nurses' Health Study, the Mammography Quality Standards Act, and the Women's Health Initiative—should be categorized as supporting women's health.

2. For research, studies, services, or projects that include both men and women, recommended methods to calculate the proportion of funds spent on women's health research are:

   a. If target or accrual enrollment data are available, multiply the expenditure by the proportion of female subjects included in the program. For example, if 50% of the subjects enrolled in a trial, study, service, or treatment program are women, then 50% of the funds spent for that program should be counted as supporting women's health research.

   b. Where both males and females are included, as may be the case for many basic scientific research projects, multiply the expenditure by 50%.

ORWH, with its advisory and coordinating committees, monitors the methodology used by the ICs for collecting budget data and provides input to the methods of the CCWH to optimize budget data collection methods.

Table 1 lists the overall NIH research expenditures in FY 2017 and FY 2018 for specific diseases, disorders, and conditions by women only, by men only, and for both women and men. The health categories and subcategories in this table were developed to accommodate all HHS agencies. The table shows zeros across all columns for subcategories that had nothing to report for the fiscal year. Because the table is additive, zeros may be shown for relevant subcategories. Even though a budget expenditure can apply to more than one subcategory, funding must be applied to a single primary subcategory. When a budget expenditure overlaps multiple subcategories, the ICO assigns the expenditure to the most scientifically appropriate subcategory. Because no overlap in reporting is allowed by the prescribed method of data collection for this report, the amount listed for each topic area may be understated.

Table 1. NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives, FY 2017 and FY 2018 (Dollars in Thousands).

Disease, Condition, or Initiative	FY17 Women	FY17 Men	FY17 Both	FY17 Total	FY18 Women	FY18 Men	FY18 Both	FY18 Total
I. Cancer								
Breast cancer *(including mammography & other services)*	720,986	89	3,755	724,830	697,033	179	4,425	701,637
Reproductive cancers:								
Cervical	92,508	1,598	7,478	101,584	103,225	1,086	7,726	112,037
Ovarian	139,785	87	48	139,920	155,022	179	507	155,708
Vaginal, uterine, and other	27,065	23	38	27,126	28,924	23	1	28,948
Lung cancer	204,498	223	131,689	336,410	223,275	465	161,524	385,264
Colorectal cancer	120,373	1,260	140,317	261,950	144,804	1,091	150,504	296,399
Other neoplasms	9,659	13,861	4,463,904	4,487,424	110,674	14,376	4,628,219	4,753,269
Subtotal	1,314,874	17,141	4,747,229	6,079,244	1,462,957	17,399	4,952,906	6,433,262

Disease, Condition, or Initiative	FY17 Women	FY17 Men	FY17 Both	FY17 Total	FY18 Women	FY18 Men	FY18 Both	FY18 Total
II. Cardiovascular/Pulmonary								
Blood diseases	66,459	77,346	465,957	609,762	69,192	73,404	457,584	600,180
Heart disease	164,217	181,213	749,117	1,094,547	169,742	171,047	810,360	1,151,149
Stroke	23,398	240	237,460	261,098	16,631	-	265,394	282,025
Other cardiovascular diseases/disorders	94,680	67,736	872,610	1,035,026	123,101	73,078	902,444	1,098,623
Pulmonary diseases	127,566	115,303	371,013	613,882	127,441	107,452	415,844	650,737
Asthma	56,804	44,381	134,969	236,154	58,765	49,676	151,706	260,147
Other	2,684	468	388,448	391,600	2,884	754	398,112	401,750
Subtotal	**535,808**	486,687	3,219,574	4,242,069	**567,756**	475,411	3,401,444	4,444,611
III. Reproductive & Maternal/Child/Adolescent Health								
Contraception	15,242	6,420	84,546	106,208	30,136	6,399	95,229	131,764
Infertility	4,231	-	12,833	17,064	3,581	-	14,377	17,958
Female reproductive physiology	70,024	178	251	70,453	74,912	254	-	75,166
Hysterectomy	603	-	-	603	1,150	-	-	1,150
Endometriosis/ leiomyomas *(fibroids)*	8,612	-	396	9,008	8,745	-	396	9,141
Pregnancy/ pregnancy prevention/ maternal health	230,716	1,390	598	232,704	254,205	1,443	15,878	271,526
Diseases related to DES exposure	-	-	-	-	-	-	-	-
Female genital cutting	-	-	-	-	-	-	-	-
Pelvic floor disorders	650	-	-	650	154	-	-	154
Other	17,601	11,325	519,402	548,328	5,783	11,317	658,830	675,930
Subtotal	**347,679**	19,313	618,026	985,018	**378,666**	19,413	784,710	1,182,789
IV. Aging								
Menopause	23,905	-	-	23,905	22,235	-	-	22,235
Menopausal hormone/non-hormone therapy	11,126	-	-	11,126	8,721	-	-	8,721
Alzheimer's disease	327,194	254,929	732,256	1,314,379	405,601	328,660	592,633	1,326,894
Malnutrition in the elderly	68	45	-	113	-	-	-	-
Osteoarthritis	55,169	4,864	58,621	118,654	52,128	5,726	52,411	110,265
Osteoporosis *(including fractures)*	74,623	7,277	18,955	100,855	79,262	9,819	9,736	98,817
Women's Health Initiative	-	-	-	-	200	-	-	200
Demography of aging	32,685	30,718	12,899	76,302	28,459	27,712	297	56,468
Aging economics	14,746	14,669	9,655	39,070	14,760	14,994	11,857	41,611
Other	158,672	139,494	509,648	807,814	169,700	148,648	1,028,877	1,347,225
Subtotal	**698,188**	451,996	1,342,034	2,492,218	**781,066**	535,559	1,695,811	3,012,436

Disease, Condition, or Initiative	FY17 Women	FY17 Men	FY17 Both	FY17 Total	FY18 Women	FY18 Men	FY18 Both	FY18 Total
V. Metabolism/Endocrinology/Gastrointestinal								
Diabetes	177,574	119,859	220,454	517,887	141,276	80,111	191,088	412,475
Obesity	202,228	91,674	114,100	408,002	211,153	96,497	136,684	444,334
Hepatobiliary diseases	1,495	2,613	237,904	242,012	1,821	2,457	284,036	288,314
Thyroid diseases/ conditions	11,307	2,839	631	14,777	10,586	2,630	40	13,256
Fecal incontinence	1,404	936	-	2,340	2,639	1,760	-	4,399
Irritable bowel syndrome	3,896	1,212	-	5,108	5,056	2,167	1,018	8,241
Other	699	668	138,938	140,305	2,139	1,480	156,008	159,627
Subtotal	**398,603**	219,801	712,027	1,330,431	**374,670**	187,102	768,874	1,330,646
VI. Substance Abuse								
Etiology *(unspecified)*	9,640	10,371	97,458	117,469	9,677	10,871	93,507	114,055
Epidemiology *(unspecified)*	29,288	31,297	51,271	111,856	29,291	32,164	49,502	110,957
Prevention *(unspecified)*	26,767	28,885	40,408	96,060	27,723	30,061	45,003	102,787
Treatment *(unspecified)*	82,449	93,234	147,373	323,056	81,063	91,151	143,024	315,238
Alcohol	20,084	23,293	121,682	165,059	22,573	24,620	115,467	162,660
Illegal drugs	118,699	128,623	214,221	461,543	119,366	133,128	226,353	478,847
Prescription drugs	16,100	17,768	29,296	63,164	27,708	31,086	52,530	111,324
Tobacco products	24,685	24,929	57,539	107,153	23,951	25,705	65,410	115,066
Other substances	1,686	1,634	12,003	15,323	1,651	2,097	13,992	17,740
Co-occurring substance abuse & mental disorders	2,038	1,232	4,256	7,526	1,463	1,271	5,589	8,323
Subtotal	**331,436**	361,266	775,507	1,468,209	**344,465**	382,154	810,377	1,536,996
VII. Behavioral Studies/Programs								
Violence *(including domestically abused women, spousal abuse, and elder abuse)* violence against women, trafficking, bullying	3,503	1,851	14,615	19,969	4,387	2,105	15,056	21,548
Tobacco use cessation	393	83	1,800	2,276	393	220	1,946	2,559
Physical activity/ exercise/nutrition (promoting healthy behavior)	2,072	1,014	256,454	259,540	5,768	1,811	293,896	301,475
Other behavior change/risk modification	14,545	13,946	519,262	547,753	15,597	11,928	542,919	570,444
Caregiving	185	159	20,775	21,119	258	158	16,351	16,767
Other	10,351	5,410	588,806	604,567	12,262	3,029	697,275	712,566
Subtotal	**31,049**	22,463	1,401,712	1,455,224	**38,665**	19,251	1,567,443	1,625,359

Disease, Condition, or Initiative	FY17 Women	FY17 Men	FY17 Both	FY17 Total	FY18 Women	FY18 Men	FY18 Both	FY18 Total
VIII. Mental Health								
Etiology *(unspecified)*	632	915	34,379	35,926	1,992	2,377	42,292	46,661
Epidemiology *(unspecified)*	-	-	507	507	199	-	1,626	1,825
Prevention *(unspecified)*	127	126	125	378	180	158	67	405
Treatment *(unspecified)*	259	223	3,791	4,273	365	297	3,209	3,871
Depression/mood disorders	17,651	585	129,688	147,924	14,468	510	136,161	151,139
Suicide	2,307	247	33,883	36,437	2,284	214	50,447	52,945
Schizophrenia	1,597	109	112,614	114,320	1,202	43	121,067	122,312
Anxiety disorders	3,950	1,214	46,620	51,784	3,388	393	48,980	52,761
Eating disorders	9,990	1,060	5,351	16,401	11,958	1,277	3,702	16,937
Psychosocial stress	5,048	759	24,913	30,720	7,464	1,475	28,458	37,397
Post-traumatic stress disorder *(PTSD)*	4,098	607	20,394	25,099	3,940	826	25,643	30,409
Other mental disorders *(excluding Alzheimer's)*	28,584	3,830	860,074	892,488	31,727	4,043	855,113	890,883
Autism	4,818	38,506	99,270	142,594	6,810	37,741	131,418	175,969
Subtotal	**79,061**	48,181	1,371,609	1,498,851	**85,977**	49,354	1,448,183	1,583,514
IX. Infectious Diseases								
AIDS/HIV	183,814	68,519	2,270,939	2,523,272	205,866	122,231	2,275,765	2,603,862
Tuberculosis	14,871	37,306	161,181	213,358	16,525	40,003	207,183	263,711
Sexually transmitted diseases *(STDs)*	26,280	22,592	126,592	175,464	31,680	25,099	110,944	167,723
Topical microbicides	89,615	-	3,134	92,749	72,425	-	2,671	75,096
Toxic shock syndrome	-	-	-	-	281	-	-	281
Tropical diseases *(including malaria)*	37,372	42,655	555,468	635,495	41,182	39,561	622,745	703,488
Other	1,624	665	600,880	603,169	4,121	2,002	595,643	601,766
Subtotal	**353,576**	171,737	3,718,194	4,243,507	**372,079**	228,896	3,814,951	4,415,926
X. Immune Disorders								
Rheumatoid arthritis	46,482	2,195	151,725	200,402	33,424	2,323	123,297	159,044
Lupus erythematosus	62,914	4,017	25,676	92,607	81,767	5,250	33,143	120,160
Multiple sclerosis	26,116	2,329	64,962	93,407	5,783	2,204	87,150	95,137
Myasthenia gravis	597	223	3,621	4,441	283	223	3,366	3,872
Scleroderma	9,368	369	1,111	10,848	11,198	631	997	12,826
Sjögren's syndrome	22,385	-	490	22,875	20,485	-	669	21,154
Takayasu disease	-	-	-	-	-	-	-	-
Other	3,182	2,893	193,798	199,873	3,758	3,303	152,405	159,466
Subtotal	**171,044**	12,026	441,383	624,453	**156,698**	13,934	401,027	571,659

Disease, Condition, or Initiative	FY17 Women	FY17 Men	FY17 Both	FY17 Total	FY18 Women	FY18 Men	FY18 Both	FY18 Total
XI. Neurological, Muscular, & Bone								
Trauma research:								
Brain	16,134	-	253,392	269,526	10,161	245	295,331	305,737
Other neurologic trauma	-	-	19,483	19,483	-	-	18,840	18,840
Bone fracture *(non-osteoporotic)* and muscle injury	142	160	24,247	24,549	597	155	23,335	24,087
Muscular dystrophy	1,750	35,969	30,108	67,827	1,605	39,601	28,393	69,599
Chronic pain conditions	14,418	138	138,298	152,854	11,396	376	148,039	159,811
Temporoman-dibular disorders	11,286	-	268	11,554	11,253	-	268	11,521
Vulvodynia	1,002	-	-	1,002	1,696	-	-	1,696
Fibromyalgia & eosinophilic myalgia	5,348	-	-	5,348	4,242	-	196	4,438
Migraine	8,095	-	5,201	13,296	4,587	-	9,302	13,889
Sleep disorders	3,720	647	56,581	60,948	4,035	777	82,519	87,331
Paget's disease	-	-	854	854	-	-	1,146	1,146
Parkinson's disease	7,949	827	125,847	134,623	6,103	656	135,065	141,824
Seizure disorders	6,980	113	113,153	120,246	6,745	113	133,222	140,080
Other	22,466	2,886	1,193,334	1,218,686	66,759	11,579	1,146,524	1,224,862
Subtotal	**99,290**	40,740	1,960,766	2,100,796	**129,179**	53,502	2,022,180	2,204,861
XII. Kidney and Urological								
Urinary tract infections *(cystitis, pyelonephritis)*	10,584	3,099	28,348	42,031	11,631	3,512	22,821	37,964
ESRD/trans-plantation	8,389	12,432	109,616	130,437	9,780	15,199	113,207	138,186
Urinary incontinence	10,286	-	-	10,286	10,762	-	-	10,762
Bladder pain syndrome, interstitial cystitis	10,653	1,117	588	12,358	9,407	1,023	835	11,265
Other	659	4,042	440,975	445,676	1,183	3,893	436,452	441,528
Subtotal	**40,571**	20,690	579,527	640,788	**42,763**	23,627	573,315	639,705
XIII. Ophthalmical, Otolaryngological, and Oral Health								
Eye diseases & disorders	26,096	9,977	709,540	745,613	23,425	12,559	743,483	779,467
Ear diseases & disorders	15,934	1	198,506	214,441	18,313	1	197,055	215,369
Dental and oral health	4,614	-	368,583	373,197	9,161	-	383,110	392,271
Other	684	590	2,502	3,776	709	609	2,773	4,091
Subtotal	**47,328**	10,568	1,279,131	1,337,027	**51,608**	13,169	1,326,421	1,391,198

Disease, Condition, or Initiative	FY17 Women	FY17 Men	FY17 Both	FY17 Total	FY18 Women	FY18 Men	FY18 Both	FY18 Total
XIV. Health Effects of the Environment								
Environmental estrogens	17,479	-	4,448	21,927	18,510	982	3,097	22,589
Health effects of toxic exposure *(excluding cancer)*	1,292	-	108,640	109,932	1,494	-	111,469	112,963
Toxicological research & testing program	-	-	103,828	103,828	31	31	102,778	102,840
Chemical/bio-logical warfare agents	-	-	7,304	7,304	-	-	6,569	6,569
Other	446	19	8,929	9,394	1,238	87	7,521	8,846
Subtotal	**19,217**	19	233,149	252,385	**21,273**	1,100	231,434	253,807
XV. Cross-Cutting Categories and Special Initiatives								
Treatment, prevention, & services	7,528	18,191	465,994	491,713	8,996	9,499	527,433	545,928
Access to health care & financing	1,118	712	7,509	9,339	2,107	1,055	10,246	13,408
Education & training for health care providers	1,008	912	94,151	96,071	4,362	1,858	82,940	89,160
Health literacy & bilingual information	465	100	31,273	31,838	799	808	33,493	35,100
Cultural influences	2,669	1,851	84,153	88,673	2,243	2,267	84,023	88,533
Disability research & services	659	1,422	104,555	106,636	52	1,045	109,079	110,176
Homelessness	15	231	13	259	172	310	9	491
Chronic fatigue syndrome	4,015	1,419	6,670	12,104	2,824	1,720	8,497	13,041
Breastfeeding	430	45	-	475	4,141	-	2,547	6,688
Organ donation	-	-	-	-	-	-	402	402
Genetic services/ counseling	15,151	11,766	12,659	39,576	17,548	15,489	37,160	70,197
Unintentional injury	17	266	56,268	56,551	25	133	47,763	47,921
Alternative & complementary therapies	38,809	35,937	136,699	211,445	42,309	34,115	148,669	225,093
Health statistics & data collection	2,394	2,078	250,067	254,539	2,360	1,060	113,809	117,229
Programs/offices on/ of women's health	197,785	16,148	1,747,784	1,961,717	120,031	22,730	2,035,981	2,178,742
Global health	27,490	111,796	1,820,710	1,959,996	31,121	120,112	1,996,396	2,147,629
Drug metabolism *(sex differences, pregnancy, etc.)*	1,276	518	4,435	6,229	1,210	835	4,050	6,095
Subtotal	**300,829**	203,392	4,822,940	5,327,161	**240,300**	213,036	5,242,497	5,695,833
TOTAL	**4,768,553**	**2,086,020**	**27,222,808**	**34,077,381**	**5,048,123**	**2,232,907**	**29,041,573**	**36,322,602**

Table 2 shows the dollar amounts and percentages of the NIH research budget in FY 2017 and FY 2018 for women and for men only, as well as for research including both women and men. Overall, the proportion of the research budget supporting women only was 14% for both FY 2017 and FY 2018. The proportion of the research budget supporting men only was 6% for both FY 2017 and FY 2018, which most likely reflects bias in the construction of data categories on diseases, conditions, and disorders relevant to women or occurring only in women.

Table 2. FY 2017 and FY 2018 Summary: NIH Research Budget by Sex (Dollars in Thousands)

Category	FY17, $	FY17, %	FY18, $	FY18, %
Women	4,768,553	14%	5,048,123	14%
Men	2,086,020	6%	2,232,907	6%
Both	27,222,808	80%	29,041,573	80%
Total	**34,077,381**	**100%**	**36,322,602**	**100%**

Reference

NIH Reform Act of 2006, H.R. 6164, 109th Congress. (2004)

Report of the NIH Institutes and Centers

National Cancer Institute

I. Executive Summary

The National Cancer Institute's (NCI) mission is to lead, conduct, and support cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives. To fulfill this mission, the NCI supports research across the cancer continuum from basic and translational research to clinical and population science studies in all types of cancer.

This report highlights progress being made in the basic understanding of cancer, cancer control, prevention, and treatment to help reduce cancer morbidity and mortality in women. Over the past 2 years, NCI-supported researchers have made significant strides in understanding a variety of cancers that affect women. One of the highlights are the findings from the TAILORx clinical trial. This is the largest precision medicine clinical trial completed to date, and its results will spare many women with the most common type of breast cancer from treatment with chemotherapy. Another precision medicine highlight in breast cancer was the case report of a metastatic breast cancer patient treated with an immunotherapy approach using the patient's own tumor-infiltrating lymphocytes. This patient experienced a complete regression with the experimental treatment despite being unresponsive to prior treatments. Progress was made in other cancers that affect women as well, including uncovering critical information about the viral oncogene that is responsible for the majority of HPV-associated cervical cancer and identifying the origin of the most common subtype of ovarian cancer. The latter finding that high-grade serous ovarian carcinomas originate in the fallopian tubes has significant implications for the prevention, early detection, and therapeutic intervention of this disease.

NCI supports numerous research initiatives and activities that address cancers specific to or primarily affecting women, especially those cancers with high incidence or mortality among women, as well as cancers that affect both sexes to a similar degree. NCI's National Clinical Trials Network (NCTC) conducts clinical trials in women's cancers and works to increase inclusion of women and underrepresented groups in all clinical trials. To this end, the NCTN supports both a breast and a gynecologic cancer steering committee.

It is well known that NCI scientists played a critical role in the development of a human papillomavirus (HPV) vaccine to prevent the development of cervical cancer. NCI continues to support research to improve the vaccination rates in the United States, particularly in underserved and high-risk populations. NCI also supports research to improve screening for and treatment of cervical cancer. In 2017, an analysis of a large collection of HPV type 16 cervical cancers revealed information about the genetics of the virus that has implications for the future prevention and treatment of cervical cancer.

Although far from comprehensive, the following summary provides a representative sample of the accomplishments, initiatives, and activities of NCI related to women's health in fiscal years 2017 and 2018. Disease areas included in this report are breast, cervical, colon, endometrial, and ovarian cancers.

NIH Strategic Plan for Women's Health Research

In the United States, the rates of death for all cancer types combined are declining among men, women, and children of all major racial and ethnic groups—yet there is more work to be done. As

the leader of the National Cancer Program, NCI is responsible for setting the cancer research agenda, ensuring that the nation's investment in cancer research has maximum impact, and directing progress against cancer. The NCI supports the implementation of NIH's strategic plan for women's health research by funding research to increase our basic understanding of all cancers and to advance cancer prevention, detection, and treatment for women. Herein, we report accomplishments and highlight initiatives and activities that work toward the following goals and objectives of the strategic plan:

- 2.5 – Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.
- 2.7 – Design drugs, biologicals, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.
- 2.9 – Encourage collaborative interactions among clinicians, bioethicists, and technologists regarding accessibility of new technologies, drugs, and other interventions relevant to women's health.
- 3.9 – Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behavior, and access to screening and therapeutic interventions.
- 5.2 – Expand collaboration with other NIH institutes and centers and Federal agencies in outreach activities on issues related to women's health.

II. Accomplishments

Breast Cancer

Reducing the Use of Chemotherapy in Early-Stage Breast Cancer – Results from a groundbreaking NCI-sponsored clinical trial, called TAILORx, showed that most women with a common type of early stage breast cancer (hormone receptor-positive, HER2-negative, and no lymph node involvement) do not benefit from adjuvant chemotherapy, saving thousands of women from unnecessary treatment. Sparano et al., set out to determine if a specific test that measures the expression of 21 genes associated with risk of breast cancer recurrence could be used to determine which patients would benefit from chemotherapy and which would not. The trial, which is the largest precision medicine trial completed to date, showed that up to 85% of patients had low or intermediate risk of recurrence based on the test and that chemotherapy did not benefit the vast majority these patients. The 15% of patients who have a high risk of recurrence do benefit from chemotherapy. These practice-changing results mean the majority of women with this type of early-stage breast cancer can be spared the short- and long-term effects of chemotherapy. There was a subset of younger women with an intermediate risk score that seemed to benefit from chemotherapy; therefore, more research is needed to understand how to better identify and treat these patients.

New Approach to Immunotherapy Leads to Complete Response in a Breast Cancer Patient Unresponsive to Other Treatments – In a case report, Zacharakis, et al., demonstrated that a hormone receptor–positive, metastatic breast cancer could be successfully treated with a type of immunotherapy called adoptive cell transfer. In this case, a modified adoptive cell transfer approach using tumor-infiltrating lymphocytes (TILs) was used to treat a patient who had not responded to previous treatments. This patient was treated as part of an ongoing Phase II clinical trial at the NIH Clinical Center, where a patient's tumor is sequenced to identify mutations and the patient's own TILs are tested to find which TILs recognize the identified mutations. Those TILs that recognize a subset of mutations are then expanded in a laboratory and infused

back into the patient to attack the cancer. This is an illustrative case report that highlights the power of immunotherapy.

A Common Inherited Variant Influences Breast Cancer Risk After Chest Radiotherapy for Survivors of Childhood Cancer – Childhood cancer survivors, particularly those who received radiation to the chest as part of their treatment, are known to be at elevated risk of developing breast cancer later in life. Morton, et al., conducted a genome-wide association study of nearly 3,000 female survivors of childhood cancers to identify whether inherited genetic susceptibility may influence which survivors later develop breast cancer. The investigators identified a common inherited variant that showed increased breast cancer risk among patients treated with radiation to the chest. The study provides strong evidence that germline genetics can modify the effect of radiation exposure on breast cancer risk after childhood cancer.

Multigene Hereditary Cancer Panel Testing for Triple-Negative Breast Cancer – Triple-negative breast cancer (TNBC) is a very aggressive type of breast cancer. Genes that are associated with high lifetime risk of developing TNBC, other than BRCA1, have not been established. Shimelis et al., identified five genes that, when altered, increased the risk of TNBC in women. The investigators tested 21 cancer genes from more than 10,000 TNBC patients participating in two studies, including approximately 1,200 African American women. This study is the first to establish a gene panel associated with lifetime risk of developing TNBC. The results suggest that all TNBC patients should undergo multigene panel testing, regardless of age at diagnosis or family history of cancer, for improved cancer risk assessment and determination of targeted therapeutic approaches for mutations in predisposition genes.

Estimating the Number of Women Living with Metastatic Breast Cancer in the United States – Cancer registries in the US, as in other countries around the world, do not document metastatic cancer recurrences, which account for a large majority of breast and other cancer deaths. Therefore, Mariotto et al., developed innovative methods of statistical modeling for metastatic breast cancer (MBC) incidence, prevalence, and length of survival to estimate the number of women in the United States living with MBC. The study showed that the number of women living with distant MBC, the most severe form of the disease, is growing. This is likely due to the aging of the population and improvements in treatment. The researchers also found that median and five-year relative survival rates for women initially diagnosed with MBC are improving, especially among younger women.

Differences in Breast Cancer Survival by Molecular Subtypes in the United States – Although incidence rates of breast cancer molecular subtypes are well documented, effects of molecular subtypes on breast cancer–specific survival are unknown in the U.S. population. Howlader and colleagues using SEER data that included the largest population coverage to date, found the best survival patterns among women with hormone receptor-positive/HER2-negative (HR+/HER2−) cancer. However, contrary to conventional thought, in advanced stage (stage IV) breast cancer patients, those with the HR+/HER2+ subtype experienced better survival than those with the HR+/HER2− subtype. This is likely attributable to major advances in HER2-targeted therapy.

Quantitative 3D Ultrasound Breast Scanner Gains FDA Marketing Clearance and Breakthrough Device Designation – Quantitative Transmission (QT) ultrasound has shown promise as a breast imaging modality and NCI has supported a multi-decade effort to bring this technology to women for the detection and diagnosis of breast cancer. This support includes funding to QT Ultrasound whose QT Ultrasound Breast Scanner (2000 Model A) was designated by the FDA as meeting an unmet

medical need for screening women at high risk for breast cancer. Malik and colleagues from QT Ultrasound published results showing improved imaging performance of the 2000 Model A prior to the FDA designation. The system is capable of visualizing normal and abnormal breast architecture exceeding other ultrasound and x-ray-based imagers. The company is working with the FDA to gain full approval of this device as a screening device for younger women at high risk for breast cancer.

Profiling Immune Cells in Breast Cancer and Normal Breast Tissue – Knowledge and understanding of the immune cells that reside in the tumor microenvironment is important to the success of immunotherapy. Azizi and colleagues used single-cell sequencing technologies to profile 45,000 individual immune cells from eight breast cancer patients. The resulting immune cell atlas revealed that there was a greater diversity of immune cell types in tumor tissue versus normal breast tissue. Moreover, important immune cell populations were dynamic in their activation states which has implications for the success of immunotherapy in breast cancer.

Inhibition of CDK4/6 Triggers Anti-tumor Immunity – Drivers of the cell cycle typically are involved in the initiation and progression of various cancers and are thus ideal targets for therapy. In particular, cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors can induce cell cycle arrest in tumor cells. CDK4/6 inhibitors are currently in clinical trials for breast cancer. Using preclinical mouse models, Goel at al., identified the molecular mechanisms of action involved in CDK4/6 inhibition and confirmed their findings in biopsies from breast cancer patients treated with CDK4/6 inhibitors. Their results show that CDK4/6 inhibitors increased tumor immunogenicity and provide a rationale for new treatment combinations comprising CDK4/6 inhibitors and immunotherapies such as checkpoint inhibitors.

Optimizing CAR T Cell Therapy for Breast Cancer – Chimeric antigen receptor (CAR) T cell therapy is a type of immunotherapy that uses a patients' own immune cells that are genetically engineered to attack their cancer. Currently, CAR T cell therapy is FDA-approved for certain types of leukemias and lymphomas. Bajgain et al., experimented with novel approaches to make CAR T cells effective in breast cancer. In preclinical testing, the investigators used CAR T cells directed against the mucin1 (MUC1) protein co-expressed with an engineered protein (4/7ICR) that enhanced the activity of the CAR T cells. The engineered 4/7ICR protein helps to transform the tumor microenvironment from suppressive to an environment that supports the CAR T cells. These finding support the translation of this approach into clinical testing in breast cancer patients.

International Consortium Adds 72 Genetic Variants to List of Known Breast Cancer Associated Genes – The OncoArray Network combines the forces of researchers from 300 institutions around the world to discover new cancer susceptibility variants for breast, ovarian, prostate, colorectal, and lung cancers. In 2017, the network published two studies (Milne et al., and Michailidou et al.) that together identified 72 previously unknown inherited variants associated with risk for breast cancer. This work adds to previous research bringing the total number of known variants associated with breast cancer to nearly 180. Furthermore, the research showed that 65 of the newly identified variants are common among all women with breast cancer. The remaining seven mutations predispose women to developing estrogen-receptor-negative breast cancer. These results provide further insight into the genetic susceptibility of breast cancer.

Acupuncture Reduced Pain Associated with Aromatase Inhibitor Treatment – Muscle and joint-related pain are the most common adverse effects experienced by women treated with aromatase inhibitors for early stage breast cancer. Up to 50% of women taking aromatase inhibitor therapy experience pain and stiffness affecting

knees, hips, hands, and wrists making it difficult to walk, sit, climb stairs, and perform simple tasks. In the largest, most rigorous study of its kind (a randomized clinical trial), Hershman and colleagues found that acupuncture significantly reduced the debilitating joint pain experienced by the women being treated with aromatase inhibitors. This finding suggests that acupuncture should be considered as a potential treatment option for muscle and joint pain in this population.

Treatment Decisions Effect Employment of Breast Cancer Patients – A diagnosis of cancer and its subsequent treatment can disrupt a person's ability to work both in the short and long term. Jagsi et al., conducted a population-based survey to assess how different treatments for women with breast cancer impacted the women's employment. The study, which primarily focused on different surgical treatments, showed that women who received the most aggressive treatment—a double mastectomy followed by breast reconstruction surgery—were almost eight times more likely to miss a month or more of work and three times more likely to stop working altogether than women who underwent a lumpectomy. Overall the results showed that treatments have a profound effect on employment outcomes.

Cervical Cancer

HPV 16 E7 Oncogene Genetic Conservation is Critical to Carcinogenesis – There are more than half a million cases of cervical cancer a year worldwide, and human papillomavirus (HPV) type 16 causes about half of all these cases. It is not known why HPV 16 is uniquely highly carcinogenic compared to other HPV types, or why the majority of HPV 16 infections will clear on their own while a few will persist and lead to cervical precancer and cancer. Sequencing a large collection of samples from over 5,000 HPV 16 infected women with and without cancer, Mirabello and colleagues observed that a particular genetic sequence of the E7 oncogene is common to virtually all cervical cancers caused by HPV 16 worldwide. This work further demonstrated that the E7 oncogene is the fundamental contributor to carcinogenesis in these HPV 16 cancer cases. This large genomic analysis shines new light on the influence of viral genetic diversity on carcinogenicity of the high-risk HPV 16 type and presents a highly specific target for prevention and treatment of cervical cancer.

Cervical Cancer Screening May Be Less Effective in Obese Women – Previous studies have linked obesity with increased cervical cancer incidence and mortality, though the reasons have not been well understood. In a population of 1,000,000 women undergoing state-of-the-art cervical cancer screening, Clarke et al., found that overweight and obese women had an increased risk of cervical cancer compared to normal weight women, likely due to less effective cervical cancer screening. Evidence from this study suggests that in overweight and obese women, reduced sensitivity of HPV testing, Pap cytology, and colposcopy (visualization of the cervix) leads to decreased detection and treatment of cervical precancers, contributing to reduced efficacy of cervical cancer screening. Improvements in equipment and/or procedures to assure adequate sampling and visualization of women with elevated body mass might reduce cervical cancer incidence.

New Targets for Immunotherapy-based Treatment of HPV-related Cancers – Immunotherapies designed to treat cancers caused by the human papillomavirus (HPV), including cervical, anal, and oropharyngeal cancers, have traditionally targeted protein antigens produced by the virus itself. However, such treatments have had little success in the regression of HPV-related cancers. Stevanovic et al., showed that immunotherapy treatments that resulted in complete regression of metastatic cervical cancer largely targeted two non-viral antigens. These findings suggest a new paradigm

for targeting non-viral antigens in immunotherapy of virally-associated cancers.

Colon Cancer

Obesity Tied to Higher Risk of Colorectal Cancer in Younger Women – Colorectal cancer incidence and mortality are increasing among people younger than 50 years of age. In the Nurses' Health Study II, a prospective cohort study of US female nurses aged 25 to 42 years at study enrollment, Liu et al., found that those women classified as obese (BMI greater than or equal 30) had a nearly doubled risk of early-onset (younger than age 50) colorectal cancer compared with women with a BMI of 18.5 to 22.9. Specifically, women aged 20 to 49 who were considered overweight or obese based on BMI had up to twice the risk for colon cancer before age 50 compared to women with the lowest BMIs. The study analyzed more than 85,000 women free of cancer and inflammatory bowel disease at the time they enrolled in the Nurses' Health Study. These finding may shed light on the previous studies that found colorectal cancer rates increasing among younger people.

Endometrial Cancer

Phase III Trial Confirms Pelvic Radiation as Standard of Care for High-Risk, Early-Stage Endometrial Cancer – Clinical trials in the early 2000s found that external beam radiation therapy to the pelvis following surgery to remove early-stage endometrial cancer reduced tumor recurrence rates compared with post-surgical observation alone. These trials established adjuvant pelvic radiation as the standard treatment for early stage (I-II) patients. In recent years, however, physicians have begun treating early-stage patients at higher risk of recurrence with an alternative approach of vaginal cuff brachytherapy followed by chemotherapy. The phase III Gynecology Oncology Group trial, GOG-249, led by Randall at al., showed there was no statistically significant increases in recurrence-free survival (RFS) or overall survival (OS) in the brachytherapy followed by chemotherapy arm. However, risk of pelvic and para-aortic nodal recurrence and frequency of short-term side effects were greater for this arm. Therefore, the trial demonstrated that adjuvant pelvic radiation should remain the standard of care.

Health Disparities

"Quadruple Negative" Breast Cancers in African American Women – Triple-negative breast cancers that lack androgen receptor (AR) expression are considered "quadruple negative" breast cancers and there is increasing evidence that AR expression has prognostic usefulness in triple-negative breast cancer. Davis and colleagues analyzed AR expression across breast cancer subtypes and among African Americans and whites. Overall, AR-negative patients are diagnosed at a younger age compared to AR-positive patients, with the average age of African American AR-negative patients being 49. AR-negative patients are more likely to have a basal-like subtype, and this is associated with an increased time to progression and decreased overall survival. Thus, AR could be used as a prognostic marker for breast cancer, particularly in African American patients.

Examining Breast Cancer Incidence Trends by Race and Ethnicity – Recent reports of converging black and white breast cancer incidence rates have gained attention, potentially foreshadowing a worsening of the black-white breast cancer mortality disparity. However, these incidence rates also reflect the sum of non-Hispanics and Hispanics that may mask important ethnic-specific trends. Davis Lynn et al., examined breast cancer incidence trends among non-Hispanic white women, Hispanic white women, and non-Hispanic black women in the NCI SEER 13 Registries Database. They then used statistical modeling of breast cancer incidence rates for 2015-2030 to project slowly increasing incidence rates for non-Hispanic white and Hispanic white women, and slowly decreasing rates for non-Hispanic black women. The investigators

concluded that a worsening of the black-white racial mortality gap seems unlikely; however, they call for continued monitoring of race- and ethnic-specific breast cancer trends by age and tumor characteristics to learn more about what causes disparities in incidence and to develop targeted prevention strategies.

Comparing Breast Cancer Molecular Features and Survival by African and European Ancestry – African Americans have the highest breast cancer mortality rate. While racial differences in intrinsic breast cancer subtypes are known, (e.g., black women are more likely than white women to have triple-negative breast cancer), it is not known if other inherent genomic differences contribute to survival disparities. Huo et al., used data from The Cancer Genome Atlas (TCGA) to identify a modest number of genomic differences but a significant clinical survival outcome difference between blacks and whites in the TCGA data set. These data could form the basis for the development of molecular targeted therapies to improve clinical outcomes for the specific subtypes of breast cancers that disproportionately affect black women.

Psychosocial Impact of BRCA Testing in Young Black Breast Cancer Survivors – Genetic counseling and genetic testing (GC/GT) are recommended for women who have or may have a risk of developing hereditary breast or ovarian cancer. Studies that have demonstrate minimal psychological consequences for women receiving GC/CT for hereditary breast or ovarian cancer have predominantly studied the experiences of white women. Gonzalez et al., conducted a prospective follow-up of a subset of participants from a population-based study of black breast cancer survivors receiving GC/GT for BRCA1 and BRCA2 mutations. This study demonstrated minimal negative psychosocial outcomes following GC/GT among young black breast cancer survivors, irrespective of test results.

Ovarian Cancer

High Grade Serous Ovarian Carcinomas Originate in the Fallopian Tube – Ovarian cancer is the leading cause of death from gynecologic cancers and high-grade serous ovarian cancer (HGSOC) is the most common histologic subtype of ovarian cancer. Until recently it was thought that HGSOC originated from the ovarian surface epithelium. Labidi-Galy et al., showed that most, if not all, HGSOC originate in the fallopian tubes. These results provide insight into the etiology of ovarian cancer. The investigators also found that there is a window of several years between the development of abnormal cells, or lesions, in the fallopian tubes and the start of ovarian cancer. This has significant implications for the early detection of HGSOC, as currently about 70% of women with HGSOC are diagnosed with advanced stage disease.

CancerSEEK – A Blood Test that Can Detect 8 Common Cancers – In 2018, a consortium of international and NCI-supported researchers and their colleagues (Cohen, et al.) reported the development of CancerSEEK, a blood test that measures the levels of eight proteins and the presence of mutations in 16 cancer-associated genes to detect early-stage cancers. When this test was applied, in a retrospective analysis, to blood samples from 1,005 patients with eight different types of non-metastatic cancer, the presence of cancer was correctly identified 70% of the time. For five of the eight cancer types, including ovarian cancer, for which no screening tests are currently available, the sensitivity of detecting cancer ranged from 69% in esophageal cancer to 98% in ovarian cancer. Because the sensitivity of detection of the test in not yet high enough to be used for routine cancer screening, additional studies are underway.

Molecular Subtypes of High-Grade Serous Ovarian Cancer Gene are Associated with Surgical Outcomes and Survival – Despite an increase in knowledge about molecular

subtypes of high-grade serous ovarian cancer (HGSOC), subtypes are not currently used in clinical decision making. Wang et al., used data from more than 2,000 HGSOC cases to define molecular subtypes of HGSOC and identified five subtypes. The investigators then applied the classification scheme to a separate cohort of HGSOC cases with detailed surgical outcome and survival information. Molecular subtypes were significantly associated with rate of optimal surgical debulking and with overall survival. One subtype in particular, the mesenchymal subtype, was associated with the least favorable surgical outcome. Thus, molecular subtyping may have future utility in guiding neoadjuvant treatment decisions for women with HGSOC.

Chlamydia Infection Associated with Increased Risk of Ovarian Cancer – Pelvic inflammatory disease (PID), which is often caused by sexually transmitted infection, has been associated with ovarian cancer. However, some studies have not conclusively established a link between sexually transmitted infections and ovarian cancer. Trabert et al., conducted a study to characterize the association between ovarian cancer risk and prior infection with Chlamydia, one of the primary causes of PID worldwide. The presence of the plasmid-encoded Pgp3 protein, a marker for prior chlamydia infection, was consistently associated with increased ovarian cancer risk. Importantly, markers of other infectious agents analyzed were not associated with ovarian cancer risk, further supporting the specificity of the chlamydia-ovarian cancer association.

Targeting Mutant p53 in Ovarian Cancer Cells – The tumor suppressor p53 is mutated in half of all cancers. Certain mutations cause the p53 protein to gain novel functions in cells that play a role in cancer progression. Selective degradation of these “gain of function” p53 mutants has emerged as a potential therapeutic option to specifically target cancer cells harboring these mutant proteins. Padmanabhan et al., identified a small molecule that causes rapid degradation of specific mutant p53 leading to cancer cell death. These results confirm that understanding the biology and distinct pathways that regulate mutant p53 will allow new therapeutic options to treat ovarian cancer.

MICU1 as a Therapeutic Target in Ovarian Cancer – Cancer cells have the ability to control cellular metabolism in irregular ways and deranged metabolism is linked to tumor growth and drug resistance. Chakraborty et al., identified the protein MICU1 as a critical component responsible for aberrant metabolism in ovarian cancer cells. Further, the investigators showed that MICU1 played a role in drug resistance in these cells. Thus, MICU1 may be exploited as a therapeutic target to normalize deranged metabolism to inhibit tumor growth and overcome therapy resistance.

Identification of 12 New Susceptibility Loci for Epithelial Ovarian Cancer Subtypes – Approximately 4% of inherited epithelial ovarian cancer (EOC) can be attributed to known common genetic variants. Thus, additional susceptibility loci or markers are likely to exist. Phelan et al., pooled data from multiple genome-wide association studies involving a total of 25,509 women with EOC and 40,941 controls (women without cancer) to identify common genetic loci associated with different histologic subtypes of EOC. The investigators identified nine new risk loci for different EOC subtypes: six for the serous subtype of EOC, two for the mucinous subtype of EOC, and one for the endometrioid subtype of EOC. In addition, they identified three new risk loci for high-grade serous EOC in women who have a BRCA1 or BRCA2 mutation. Further analyses at each locus identified candidate susceptibility genes, including OBFC1, a new candidate susceptibility gene for low-grade and borderline serous EOC.

Use of an HDAC Inhibitors for a Subset of Ovarian Cancer – Histone deacetylases (HDACs) are established targets against cancer.

A number of HDAC inhibitors are FDA approved for treating lymphomas. Fukumoto and colleagues showed that ovarian cancers that have mutations in the ARID1A gene are selectively sensitive to inhibition of HDAC2. This finding is consistent with the fact that high HDAC2 expression is known to be associated with poor outcomes in this type of cancer. The investigators went on to show that inhibition of HDAC2 with an FDA-approved HDAC inhibitor (SAHA/Vorinostat) suppressed tumor growth and improved survival in a mouse model of ARID1A-inactivated ovarian cancer. This suggests the use of HDAC inhibitors may be a new therapeutic option for this subset of ovarian cancers.

III. Initiatives

The Human Papillomavirus Serology Standards Laboratory (HPV-SSL) – Antibody responses in HPV prophylactic vaccine trials have been assessed using different methods. The lack of standardized assays, procedures, and reagents accessible to the scientific community has precluded the comparison of different studies evaluating immunogenicity of HPV vaccines. In January 2017, the HPV-SSL was established and is jointly supported by NCI and the Bill and Melinda Gates Foundation. The goals of the HPV-SSL include the development of qualified secondary assay standards, critical reagents, and immunogenicity assays that will be made available to the scientific community. This initiative will enable comparisons of data across different vaccines and different studies, thus facilitating vaccine development and implementation of new vaccine indications and new vaccine candidates.

HPV Vaccine Uptake in NCI-designated Cancer Centers Catchment Areas – In FY 2017, NCI awarded supplements to 12 NCI-designated Cancer Centers to investigate local barriers and implementation strategies used to promote uptake of the human papillomavirus (HPV) vaccine in regions of the U.S. where adolescent uptake is low. The short-term goals for these one-year supplements are to identify low-uptake areas within the cancer center catchment area and to conduct an environmental scan focused on identification of local barriers and implementation strategies used to promote adolescent uptake of the HPV vaccine. The long-term goal is to use this information to develop or expand applied research to increase HPV vaccination uptake in regions where low uptake has been documented by the 2015 National Immunization Survey-Teen.

Multilevel Communication Strategies to Promote HPV Vaccination Uptake – In FY 2017, in partnership with the Centers for Diseases Control and Prevention, NCI funded a Prevention Research Program Supplemental Interest Project to promote the development and testing of multilevel health communication strategies to increase human papillomavirus vaccination rates in underserved or high-risk populations.

Accelerated Control of Cervical Cancer – In FY 2018, NCI launched a Cancer Moonshot initiative project to accelerate control of cervical cancer. The project objectives include: validating the effectiveness and cost-effectiveness of novel screening methods as the basis for implementation of cervical cancer screening and triage strategies in high- and low-resource settings; improving efficiency of cervical cancer screening in high-resource settings; and developing practical and accurate screening strategies that improve coverage for low-resource settings that can be integrated with vaccination programs.

Feasibility and Planning Studies for Development of Cancer Health Disparities SPOREs – In 2018, NCI funded planning grants designed to facilitate the development of Specialized Programs of Research Excellence (SPOREs) to investigate cancer health disparities. Among the FY 2018 funded projects, NCI funded three projects in breast cancer that are working to identify and better understand mechanisms contributing to treatment resistance and racial disparities in triple-negative breast cancer

outcomes (P20CA233374 and P20CA233216); and to identify biomarkers, in particular from the gut microbiome, that are predictive of treatment response, and develop individualized risk assessment, diagnosis, and treatment for underserved women who are at risk of dying from the most aggressive forms of breast cancers (P20CA233307).

Breast, Ovarian, and Endometrial Cancer Proteomic Characterization – The NCI Clinical Proteomic Tumor Analysis Consortium (CPTAC) is a national effort to accelerate the understanding of the molecular basis of cancer through the application of large-scale proteogenomic analysis. To characterize molecular aberrations correlated with women's cancers, CPTAC used standardized and optimized procedures to comprehensively characterize (proteomic and genomic characterization) breast, ovarian, and endometrial cancers from treatment-naïve patients. Datasets generated from tumor samples and adjacent normal tissues are publicly available on the CPTAC data portal.

Human Tumor Atlas (HTAN) Network – In FY 2018, through the Cancer Moonshot Initiative, NCI funded the HTAN. This is a collaborative network constructing 3-dimensional atlases to describe important transitions during cancer, such as the transition of pre-malignant cancers to malignant tumors, the progression to metastatic cancer, the response to cancer treatment, and the development of resistance to treatment. Among the funded projects, three atlases are focusing on breast cancer and have begun to characterize ductal carcinoma in situ to map the natural history of breast cancer and its progression to life-threatening disease (U2CCA233254); quantify the response of patients with triple-negative breast cancer to immunotherapy or combinations of targeted therapy and immunotherapy (U2CCA233303); and describe the development of resistance to targeted CDK4/6 inhibitors in patients with estrogen receptor-positive and/or progesterone receptor-positive breast tumors (U2CCA233280).

IV. Other Activities

Clinical Trials

NCI Supports Clinical Trials Through a Number of Mechanisms – The National Clinical Trials Network (NCTN) is a collection of organizations that support clinical trials at more than 300 sites across the United States and Canada. NCTN members lead numerous active clinical trials in women's cancers. Examples from 2017-18 include: a study evaluating the efficacy of a metabolite of tamoxifen to treat women with estrogen receptor-positive breast cancer and women who do not respond to tamoxifen and aromatase inhibitors (NCT02311933); another study evaluating if the Mirena intrauterine device alone or in combination with the drug everolimus is an effective treatment for endometrial hyperplasia, a pre-cancerous growth of the lining of the uterus, or early-stage endometrial cancer (NCT02397083).

The NCI's intramural program also conducts clinical trials in women's cancers. Since January 2017, six trials have opened at the NIH Clinical Center. These studies are evaluating new treatments for breast, ovarian, fallopian tube, and endometrial cancers (NCT02889900, NCT02948426, NCT03427411, NCT03394027, NCT03197025, NCT03189108).

In addition to treatment trials, NCI continues to support studies to improve prevention and screening tools for early detection of women's cancers. In FY 2018, NCI and the Bill & Melinda Gates Foundation funded a large study that will enroll 20,000 girls, ages 12 to 16 years, residing in Costa Rica to evaluate if a single dose of the human papillomavirus (HPV) vaccine is just as effective as the recommended two doses. This would reduce challenges to vaccine uptake in many parts of the world and improve cancer prevention through HPV vaccination (NCT03180034).

In 2017, NCI launched The Tomosynthesis Mammography Imaging Screening Trial (TMIST), the first large-scale breast cancer screening trial in nearly 25 years (NCT03233191). Conducted through the NCI Community Oncology Research Program (NCORP), TMIST will involve up to 100 participating sites and enroll 165,000 asymptomatic women in the U.S. and Canada, between the ages of 45 and 74, to compare the incidence of advanced cancers in those screened for four years with digital breast tomosynthesis (3D) versus standard digital (2D) mammography. In addition, the Digital Breast Tomosynthesis Guided Tomographic Optical Breast Imaging (TOBI) trial is evaluating the combinatory role of digital breast tomosynthesis and TOBI, which uses near-infrared light as a measurement tool to improve sensitivity and specificity of diagnose of breast cancer (NCT02033486).

Funding Initiatives

Prevention of Human Papillomavirus (HPV)-related Cancers in HIV-infected Individuals: United States-Latin American-Caribbean (LAC) Clinical Trials Network Partnership Centers – This FOA will support a network between a research institution in the United States and partnering institution(s) in low- and middle-income countries in the LAC region. It invites proposals for clinical trials focused on optimizing clinical prevention interventions among HIV-infected individuals, including immunoprevention (vaccination), screening and triage, and precancer treatment. Results are expected to influence the development of clinical practice guidelines to improve preventive clinical care and reduce the burden of highly preventable HPV-related cancers in HIV-infected individuals. (RFA-CA-18-018)

Linking the Provider Recommendation to Adolescent Human Papillomavirus (HPV) Vaccine Uptake – Characteristics of the provider, parent/patient, and clinical setting, can all affect whether a provider makes a recommendation, and whether that recommendation results in uptake of the HPV vaccine. This FOA will support research on how the healthcare delivery system enhances or inhibits the effectiveness of a provider's recommendation of the adolescent HPV vaccine. (PAR-18-008)

Reducing Over Screening for Breast, Cervical, and Colorectal Cancers Among Older Adults – While ongoing efforts to promote screening have been successful, there is growing concern that these tests may be overused subjecting adults to unnecessary risks. This FOA invites applications of research projects that aim to understand the factors that drive screening overuse and to develop and test interventions that will reduce overuse for breast, cervical, or colorectal cancer screening among average-risk older adults in healthcare delivery systems. (PA-18-005)

Traceback Testing: Increasing Identification and Genetic Counseling of Mutation Carriers through Family-based Outreach – Traceback testing is a framework for identifying and genetically testing previously diagnosed but unreferred patients with ovarian cancer and other unrecognized mutation carriers to improve the detection of families at risk for breast or ovarian cancer. This FOA aims to support pilot research projects using a "Traceback" approach to genetic testing of women with a personal or family history of ovarian cancer and reaching out to their family members to identify unaffected individuals at increased risk for cancer in different clinical contexts and communities, including racially/ethnically diverse populations. (PAR-18-616)

Inclusion

Clinical Trials Steering Committees for Women's Cancers – The NCI NCTN supports steering committees with disease-specific strategic priorities. The steering committees increase information exchange at early stages of trial development, increase efficiencies of collaboration among trial sites, and reduce trial redundancy. Among the NCTN steering committees, the Breast Cancer Steering

Committee (BCSC) and the Gynecologic Cancers Steering Committee (GCSC) develop, evaluate, and prioritize concepts for large Phase II and all Phase III clinical trials for their respective cancers. Please see the workshops and conferences section for additional details on the BCSC and GCSC planning meetings held during 2017-2018.

Workforce and Science, Technology, Engineering, and Mathematics (STEM) Efforts

Sallie Rosen Kaplan Postdoctoral Fellowship for Women Scientists – Observational, longitudinal, and intervention studies have shown women in science are significantly more likely to leave research careers earlier than men, specifically at the transition from mentored scientist to independent investigator. The Sallie Rosen Kaplan Fellowship equips NCI's female postdoctoral fellows for the competitive nature of the job market and helps them transition to independent research careers through a competitive, annual, one-year program to strengthen leadership skills by providing additional mentoring opportunities, networking, seminars, and workshops. The program is for current women NCI postdoctoral fellows training at NCI's intramural research locations in Maryland.

NCI Small Business Innovation Research (SBIR) Program Outreach Events to Women-targeted Organizations – NCI supports technology development for women's cancers and by women-owned small business through the SBIR program. NCI SBIR completed several outreach events to women-targeted organizations. These include workshops, webinars, and presentations at organizations and national conferences, such as the annual Graduate Women in Science National Conference, Women's Business Development Center (WBDC) in Chicago, a Women in STEM event at the Philippine Embassy and the Life Science Women's Conference in Austin, Texas.

Workshops and Conferences

The National Clinical Trials Network Breast Cancer and Gynecologic Cancers Steering Committees (BCSC, GCSC) held the following clinical trial planning meetings in 2017 and 2018:

- **Omitting surgery in patients with complete clinical/radiologic response to neoadjuvant chemotherapy: a paradigm shift –** This planning meeting was held by BCSC to develop recommendations for a clinical trial to determine if surgery can be omitted for a subset of breast cancer patients who have a complete clinical/radiologic response to neoadjuvant chemotherapy.
- **Moving forward in cervical cancer - Enhancing susceptibility to DNA repair inhibition and damage –** GCSC convened a planning meeting to review the biologic understanding of HPV-related cervical cancer and its susceptibility to DNA damage repair modulation, and to identify potential drivers to maximize new therapeutic strategies for the treatment of advanced or metastatic cervical cancer.
- **Designing trials for endometrial cancer populations using targeted agents** – Results from an early 2016 GCSC planning meeting on diagnostic strategies for molecular subtypes of uterine carcinomas were published in 2017 (PMID: 29137450) and 2018 (PMID: 29477660).

Breast and Gynecological Cancers Specialized Programs of Research Excellence (SPOREs) Workshops – The NCI-funded SPORE grants bring basic and clinical/applied scientists together to support projects that will result in new approaches to the prevention, early detection, diagnosis, and treatment of human cancers. In 2018, NCI convened two workshops to identify preclinical and translational research challenges, highlight advances, define needed resources and technologies, and foster collaborations among the Breast Cancer SPORE

sites and among the cervical, endometrial, and ovarian SPOREs (GYN SPORE workshop), including patient advocates and NCI staff.

NCI-Progesterone & Breast Cancer Workshop – In 2018, NCI convened extramural investigators to examine the role of the hormone progesterone in the mammary gland and clarify its activity in breast cancer.

Technology

Examples of NCI SBIR Supported Technology for Women's Cancers

- On Target Laboratories is developing tumor-targeted fluorescent dyes to improve cancer surgery. One of the laboratories' lead development candidates is OTL38, a near infra-red (NIR) dye probe. OTL38 has been proven safe and effective in a completed Phase II clinical trial for the treatment of ovarian cancer. In April 2018, it was announced that the first ovarian cancer patient was treated in a pivotal phase III study that will assess the efficacy of OTL38 to identify additional ovarian cancer lesions not detectable by current means. (R43CA192569 and R44CA192569)
- Immunomedics is a leading biopharmaceutical company in the area of antibody-drug conjugates (ADC). In 2018, FDA granted a priority review designation to a biologics license application (BLA) for sacituzumab govitecan, an ADC, developed by Immunomedics for the treatment of patients with metastatic triple-negative breast cancer who previously received at least two prior therapies for metastatic disease. (R43CA171388)

Conclusion

NCI is committed to improving the health of women, specifically as it relates to prevention, detection, diagnosis, and treatment of cancer. The accomplishments described above are selected examples of scientific progress made across the cancer research continuum over the past two years. Many more advances were made, including in the basic understanding of cancer biology, that are not discussed here. There are also additional NCI-supported research initiatives and activities not described—for example, long-term population health studies such as the Nurses' Health Study that investigates risk factors for the development of cancer and other diseases in women. Finally, NCI is committed to disseminating research advances to the scientific community and the public, and sustains numerous resources related to women's health. NCI's website, cancer.gov, serves a diverse range of audiences, including Spanish speakers (cancer.gov/espanol), and NCI's Cancer Information Service provides the latest, most accurate information about cancer treatment, clinical trials, early detection, and prevention for cancer patients, their families, and the public.

NCI will continue to push progress in women's cancers and cancers that affect women to help all women live longer, healthy lives.

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National Eye Institute

I. Executive Summary and Overview of Women's Health Research

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90-489 with the mission to conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

Worldwide, the prevalence of moderate to severe visual impairment and blindness is 285 million, with 65% of visually impaired and 82% of all blind people being 50 years and older. Many eye diseases and conditions affect women disproportionately or in unique ways. Clinical analyses indicate that two out of three blind people are women, a gender discrepancy that holds true for both developed and developing countries (Zetterberg, 2016). This gender difference may in part be explained by the longevity of women; however, there are sex-dependent biological differences across the lifespan, which may affect symptoms, conditions and risks associated with this vision loss.

For example, estrogen levels significantly decrease during menopause and in postmenopausal women, and a decrease in estrogen levels in known to correlate with an increased risk of glaucoma, wet (neovascular) and dry age-related macular degeneration (AMD), cataracts, dry eye disease (DED), low vision, and other ocular functions. Hormone replacement therapy (HRT) in women and estrogen (E2) treatment in animal models has been shown to reduce intraocular pressure (IOP) associated with glaucoma; however, despite this, the mechanisms are not known. Women also have higher rates of autoimmune diseases such as lupus, rheumatoid arthritis and multiple sclerosis. These conditions often have serious effects on the eyes, causing vision loss and the rates of these diseases are increasing as the population ages, especially among women.

Many of NEI's strategic planning efforts are germane to women's health. This includes a diverse portfolio of both basic and clinical research directed at advancing our understanding of sex/gender differences in ocular diseases and conditions. These include diseases such as dry eye and Sjögren's, AMD, glaucoma, corneal dystrophies, myopia, cataracts, infectious diseases and other eye conditions affecting aging women and the role of dietary supplements in eye health. Other areas include research on sex-related effects linked to basic developmental retinal processes, population-based studies to understand the prevalence of these diseases and its impact on women, as well as epidemiology studies to determine the efficacy, toxicity, and safety of drugs to treat these conditions. In addition, an NEI representative serves as a Women's Health Liaison to the Office of Research on Women's Health (ORWH) and works to coordinate efforts across the Institute and ORWH to encourage input and/or partnerships in areas of joint interest.

II. NEI Implementation of Research of the NIH Strategic Plan for Women's Health Research

NEI's research and initiatives in 2017-2018 address several aspects of the following goals and objectives of the NIH Strategic Plan for Women's Health Research (WHR):

Goal 1: Increase Sex Differences Research in Basic Science Studies:

1.2: Explore sex differences in the structure and function of cells, tissues, organs, and physiological systems.

1.4: Include sex parameters in the design of experiments using animal models.

Goal 2: Incorporate Findings of Sex/Gender Differences in the Design and Application of New Technologies, Medical Devices, and Therapeutic Drugs:

2.2: Develop novel animal, in vitro, and computational models to study sex differences.

2.3: Develop the information systems needed for collecting, sharing, and comparing clinical data.

2.6: Exploit high-resolution bioimaging technologies.

2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases.

Goal 3: Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women:

3.1: Conduct research to understand the role of hormones and hormonal changes on conditions throughout the lifespan.

3.3: Encourage research on safe and effective interventions for conditions affecting pregnant women.

3.5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

III. Scientific Accomplishments

Below is a summary of vision research findings for which significant sex/gender differences were reported:

a. Retinal Eye Development

Sex differences have been observed during retinal development of the eye. Previous studies provide evidence that sex hormones play a role in cilia formation on retinal ganglion cells (RGC) and may affect the trabecular meshwork which affects aqueous outflow and the IOP associated with glaucoma (Boycott and Hopkins, 1984). Research to determine if estrogen and other sex hormones are an effective treatment for glaucoma are in progress. Another study, recently co-funded by the ORWH demonstrated that genetic variations within the homeobox Rx gene of mouse eyes may also be influenced by sex hormones (Goal 1.2; R01-EY025295; R21-EY027427).

Sex-related effects have also been linked to a retinal neuroprotective pathway associated with stressed photoreceptor damage (R01-EY016459; Hooper et al., 2018). Understanding these effects during development will lead to a better understanding of stem cell differentiation, and subsequently improved in vitro protocols and transplantation methods of adult-, iPSC-, ESC-derived retinal, corneal and other ocular tissues. This project promotes the development of scientist studying eye-related sex differences by funding a training grant through the Women's Health Program (T32-EY7132).

b. External Ocular Diseases

i. Dry Eye Disease (DED)

Dry eye is a common chronic disease that affects approximately 6 million women as compared to 3 million men, and its prevalence is expected to

increase. Dry eye is associated with discomfort of the eye including a constant stinging or burning sensation in the eye, and if left untreated may result in blurred or loss of vision. It's also the most common reason for patients seeking eye care after refractive errors, indicating the significant impact dry eye can cause on an individual's quality of life.

Dry eye results from a reduction in secretion of fluid by the lacrimal glands, or from defects in the surface of the eye, mucin or mucous production, and/or the lipid or fatty components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders, such as Sjögren's syndrome, lupus, and/or rheumatoid arthritis but also occurs in association with aging, medications, exposure to the environmental, and eye surgery including laser correction surgery (van Nimwegen et al., 2015; reviewed in Sullivan, 2004).

Current treatments for DED aim to suppress the pain and damage by treating with steroids to control inflammation, antibiotics, and artificial tears; however, these treatments have met with limited success. The volume of tears on the eye is the result of a balance between tear production and tear loss and many researchers are developing drugs to restore and maintain normal tear volume. Restasis, a drug that has been approved by the FDA, has been shown to increase natural tear production in the eye; however, this drug is not very effective and only works for some people. Another treatment for dry eye is the surgical insertion of lacrimal or punctal plugs to block the eyes drainage ducts keeping the tears in place (reviewed in Schultz, 2014).

Supporting better treatments for dry eye, the NEI has recently sponsored the development of new drugs such as, P-321 Ophthalmic Solution, which functions as an inhibitor of the epithelial sodium channel (ENaC) to restore tear film volume to relieve the symptoms of moderate to severe DED. Parion Sciences Inc. has completed a phase 1/2a clinical study in 53 patients with dry eye disease and NEI has awarded a Small Business Innovative Research (SBIR) Grant for an FDA-approved Phase 2 clinical trial to pursue the next steps in the clinical development of this drug. (R44-EY020705; R43-EY020705; Parion ARVO Presentation, 2016; http://www.parion.com/).

Dry Eye Assessment and Management Study-DREAM: The NEI funded a Phase III clinical trial, called DREAM, to examine the effectiveness of omega-3 supplementation treatment for DED. Despite being a widespread, growing problem with serious consequences, at present DED is inadequately treated. Omega-3 fatty acids have gained popularity over the past decade because some laboratory studies demonstrated that they combat or prevent diseases associated with inflammation, including DED. However, a follow-on study investigating the use of omega-3 fatty acids in the treatment of dry eye, particularly postmenopausal women showed that supplements are no better than placebo for typical patients who suffer from moderate to severe DED. This study has recently been published in the New England Journal of Medicine and addresses Goals 2.3 and 2.7 of the NIH Strategic Plan for WHR (U10-EY022881; Asbell et al., 2018).

ii. Sjögren's Syndrome

Sjögren's syndrome is a chronic autoimmune disease that occurs primarily in women (with female patients outnumbering males by a ratio of 9:1) and attacks the salivary and lacrimal glands resulting in severe dry eye. Lacripep, is a new drug that is currently being developed as a treatment for dry eye. This is a topical eye drop that functions differently from conventional approaches. Rather than seeking to suppress inflammation, it aims to eliminate inflammatory triggers by restoring the natural basal tearing mechanism and health of cells in contact with tears. Each dose of Lacripep remains in the tears because it's lipid soluble and is released into the eye slowly. NEI is funding a grant to support a Phase I/II clinical trial to evaluate the efficacy and safety of this drug in patients with primary

Sjögren's Syndrome. The study is currently recruiting participants. The development of these new drugs to treat dry eye and Sjögren's maps closely to Goal 2.7 of the NIH Strategic Plan for WHR. (TearSolutions Inc., http://tearsolutions.com).

The NEI continues to co-fund, with the National Institute of Dental and Craniofacial Research (NIDCR) and the ORWH, the Sjögren's International Collaborative Clinical Alliance (SICCA), a group who is developing an International Sjögren's Syndrome Biorepository and Data Registry. The purpose of this registry is to promote cutting-edge research in the area of Sjögren's syndrome with emphasis on diagnosis, epidemiology, causes, prevention and treatment. The coordinating center is at University of California, San Francisco and multiple international sites (USA, Argentina, China, Denmark, Japan, India and United Kingdom) have been established. Currently, over 300 people are successfully enrolled. This registry is currently being used for secondary data analysis associated with Sjögren's syndrome which is included within the WHR Strategic Plan (http://www.sjogrensregistry.org/index.php; https://sicca-online.ucsf.edu/).

iii. Corneal Endothelial Dystrophy

Corneal dystrophies are a group of genetic and progressive eye disorders in which one or more parts of the cornea (the clear outer layer of the eye) lose their normal clarity because of a buildup of cloudy material. There are over 20 corneal dystrophies that affect all parts of the cornea; however, some dystrophies cause severe visual impairment while a few causes no vision problems and are only discovered during a routine eye examine. Other dystrophies may cause repeated episodes of pain without leading to permanent loss of vision. Corneal dystrophies affect women and men in equal numbers, except for Fuchs' endothelial corneal dystrophy (FECD) which affects women about four times as often as men (Higa et al., 2011; Zoega et al., 2006). Because some individuals are asymptomatic, determining the true frequency of these disorders in the general population is difficult.

The peak prevalence of Fuchs' dystrophy is seen in females who are between 50-59 years old; however, this peak is not observed in males. Preliminary evidence suggests that decreasing estrogen levels after menopause in females may be a risk factor that accounts for the sex disparity in the prevalence of FECD (Zoega et al., 2013). To further explain this sex disparity, NEI and the ORWH are co-funding a research training grant to investigate the contributions of estradiol and estrogen receptors on corneal health and the development of this disease. Currently, corneal transplants are the only effective treatment; however, in some cases, cornea specialists are able to treat this condition by performing limbal stem cell transplants to repopulate the damaged corneal epithelial cells (Goals 1.2 and 3.1; K08 EY029007; Sangwan et al., 2012).

FECD often clusters within families and most forms are inherited as autosomal dominant traits; while a few are inherited as recessive traits. Most recently, a genome-wide association study (GWAS) on DNA samples collected from patients with FECD as well as controls revealed a common genetic variation in the TCF4 gene and the LAMC1 locus, encoding a basic transcription factor and a protein coding gene, respectively. The study also detected a differential sex-specific association at LAMC1, with greater risk in women, and TCF4, with greater risk in men. Combining GWAS results with biological evidence, we gain a deeper understanding of the underlying pathogenic mechanisms of FECD which will hopefully lead to the development of sex-specific biomarkers and improved treatments (Goal 3.5; R01 EY23196; R01 EY16514; R01 EY16835; Afshari et al., 2017).

iv. Thyroid Eye Disease

Graves' eye disease, also known as thyroid eye disease, is an autoimmune condition that causes

hyperthyroidism and tends to affect 2% of all women (7:1 compared to men) between the ages of 20 and 40. Excessive thyroxine is produced from the enlarged thyroid glands causing swelling of the muscle and other tissues around the eye resulting in proptosis (bulging of the eye), corneal exposure, optic nerve compression and ultimately loss of vision. The most commonly utilized treatment for Graves' hyperthyroidism is radioactive iodine (RAI) therapy; however, studies show that treatment shouldn't be started during pregnancy or lactation and should cease 6 months before pregnancy. To further develop safe and effective treatments during pregnancy, NEI is funding 3 research project grants to identify immune cells including T cells, B cells, and fibrocytes that are unique to Graves' disease and are being used to develop new therapeutics (Goal 3.3; reviewed in Burman, 2004).

c. Myopia

Nearsightedness or myopia, is the most common refractive error of the eye and it's become more prevalent in recent years. Epidemiological data in children indicate that myopia is more common and progresses more quickly in girls than in boys. These findings have traditionally been attributed to gender specific behavioral differences such as time spent outdoors; however, there is increasing evidence that sex hormones play an important role as determinants of susceptibility to myopia (Rudnicka et al., 2016). The NEI is currently funding several grants on refractive error and is continuing to work with the ORWH to investigate the influence of systemic sex hormones on ocular growth and myopia in animal models (Goal 3.1; R01-EY12392).

d. Visual Processing

Visual processing refers to how visual information is interpreted or processed by the brain, by interpreting size, perception, distance, motion, and be able to discriminate between differences and similarities among shapes. The cerebral cortex has several regions that specialize in analyzing visual motion. One of the most prominent is area MT+, which contains multiple regions each specialized in different aspects of motion perception. A recent paper was published reporting a strong and highly replicable sex differences in visual motion processing among neurotypical adults. Sex differences were not captured by the standard MT+ fMRI response that is used to predicts individual differences in perception; however, measures of motion duration thresholds, the minimum duration needed to accurately perceive motion direction were considerably shorter in cohorts of males than females.

Overall, the data shows a difference in motion processing between males and females and demonstrates the importance of sex as a factor in the design and analysis of perceptual and cognitive research (Murray et al., 2018). The use of bioimaging technology in order to develop this as a sex-specific biomarker implements Goals 2.6 and 3.5 of the WHR Strategic Plan.

In addition to supporting a research grant, NEI funds an NIH fellowship to promote training in this field. (F32-EY025121; R01-EY09295).

e. Lens-Cataracts

Age-related cataracts are the number one cause of blindness worldwide and occurs when the lens of the eye becomes progressively opaque, resulting in blurred or loss of vision. Three types of cataracts include nuclear cataracts, cortical cataracts, and subcapsular cataracts, and occur in the central, peripheral, and posterior regions of the lens, respectively. The incidence is higher in women than men and their onset coincide with estrogen deficiency that occurs after menopause. Studies on the effects of estrogen; however, are conflicting with some reports stating that estrogen in women may protect against the development of all three forms cataracts (reviewed by Zetterberg, 2016).

Epidemiological studies (The Beaver Dam Eye Study; The Blue Mountains Eye Study) show a

modest protective effect of estrogen exposure on cataract risk. In these studies, a later onset of menopause was associated with a decreased risk of cortical cataracts; whereas, a younger age at onset of menstruation was associated with a protective effect regarding nuclear cataracts; and HRT was associated with a lower prevalence of nuclear cataracts. Data also showed that current use of HRT in women over 65 years of age was associated with a lower prevalence of cortical cataracts (Klein et al., 1992; Mitchell et al., 1997; Ostberg et al., 2006).

More recently, however, another study suggested the opposite effect, i.e., postmenopausal women who receive HRT were at greater risk for developing cortical cataracts. As shown in the clinical trial/epidemiological study, the longer a woman took HRT – the greater the severity of the cataract (AREDS2 Research Group, 2013; Lindblad et al., 2010).

Research also showed that concentrations of lutein (L) and zeaxanthin (Z), in the central retina and lens epithelium protect against UV light damage and oxidative stress which are associated with cataract development. Data from the Second Carotenoids in Age-Related Eye Disease (CAREDS2) clinical trial, an ancillary study of the Women's Health Initiative (WHI) demonstrated that there is an increased risk of cataract development among women with high macular pigment optical density (MPOD) in their retina (R01EY025202; Lawler et al., 2017).

The discovery of ocular estrogen receptors (ERs) indicates that estrogen protection may result from direct interactions with receptors in the eye; however, another study demonstrates that estrogens protective effects may result from indirect effects on other tissue. Studies using a transgenic mouse model, overexpressing ERΔ3, a form that inhibits ER function demonstrated that cortical cataracts spontaneously form in ERΔ3 female mice after puberty and progresses with age. This cataract formation can be prevented if the females are ovariectomized before sexual maturity and both male and female mice develop cataracts after neonatal treatment with estrogen (Goals 2.2 and 3.1; Davis et al., 2002). These data are consistent with some of the epidemiological results suggesting that decreased estrogen levels induce cortical cataracts.

Another potential mechanism through with estrogen exerts its effects is the oxidative stress pathway. Smoking and UVB exposure are cataractogenic, suggesting that oxidative stress plays a role in the development of cataracts. Studies in animal models showed a protective role of estradiol against oxidative stress (R01-EY15863; Beebe et al., 2010). These findings support the potential effects of estrogen on cataract development and further demonstrate the importance of estrogen in lens physiology. The role of estrogen addresses Goals 3.1, whereas, the population-based studies address Goal 2.3 of the NIH Strategic Plan for WHR.

f. Retinal Diseases

i. Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a major cause of blindness and visual impairment among elderly individuals in the United States. The macula is a specialized region near the center of the retina responsible for the high-resolution vision that permits activities such as reading. AMD is described as either the dry form or the wet (neovascular) form. Both types are characterized by deterioration of the RPE and photoreceptors; however, only the wet type results in growth of blood vessels on the retina causing edema and hemorrhaging in the central part of the macula. Several genetic and environmental risk factors have been identified with this condition including age, smoking, obesity, sex/gender (females at greater risk for wet AMD), and ethnicity with a higher risk in Caucasians (AREDS 2000; Owen et al., 2012).

The Nurses' Health Study (NHS), supported by the NEI and the ORWH showed an association between women who received hormone

replacement therapy (HRT) after menopause and 34% higher risk of early AMD, whereas, a 48% lower risk of the late-stage neovascular form of the disease was observed. Another study by the Korea National Health and Nutrition Examination Survey revealed that age, duration of lactation, and duration of oral contraceptive pills are associated with late AMD. These findings suggest a role for estrogen in the pathogenesis of AMD; however, the reason for this sex difference is unknown. The levels of estrogen are currently being used as a biomarker for screening of patients at risk and the prevention of AMD among the postmenopausal women (Goal 3.5; Snow et al., 2002).

The principle focus of these following studies doesn't address the biological basis of the disparities; nonetheless, increased knowledge of the disease will have a disproportional benefit to women's health given the incidence of the disease. Currently, treatments for both the wet and dry form of AMD are limited. During the past decade, treatments for the wet form have been developed using antibodies against anti-vascular endothelial growth factor (anti-VEGF) which slows or prevents the blood vessel growth in the back of the eye; however, it doesn't prevent the retinal atrophy that occurs in the photoreceptors and RPE (Schmidt-Erfurth et al., 2014). The health of the retina is known to be dependent on the health of the RPE, and certain vitamins and antioxidants have been shown to be important in maintaining retinal health. Another approach that is currently being investigated is to prolong the life of the photoreceptors and the RPE. The NEI Audacious Goals Initiative (AGI) is currently supporting the development of gene therapies to rescue dying photoreceptors as well as stem cell therapies to replace functional photoreceptors and RPE in hopes of restoring vision (RFA-EY-16-002).

Age-Related Macular Degeneration-AREDS: The AREDS is an NIH Intramural Research Program-based, multi-center clinical trial/epidemiological study designed to assess the clinical course, prognosis, and risk factors of AMD and to evaluate the effects of antioxidants and zinc in slowing the progression of the disease. The study demonstrated that high-dose antioxidant supplements (beta-carotene, vitamins C and E, and zinc) can slow the progression of AMD. Data from AREDS and other studies suggested that lutein/zeaxanthin and omega-3 fatty acids might also be beneficial in slowing down the development of AMD and cataract. A second study, AREDS 2, confirm this hypothesis. Another clinical trial, The Complications of Age-related Macular Degeneration Prevention Trial, assessed the safety and efficacy of laser treatment in preventing vision loss in patients in whom the disease is manifested bilaterally. This study recently reported that low-intensity laser treatment was ineffective in preventing complications of AMD or loss of vision (AREDS Research Group, 2001; AREDS2 Research Group, 2013; Chew et al., 2013).

Second Carotenoids in Age-Related Eye Disease-CAREDS2: The dietary plant pigments, lutein (L) and zeaxanthin (Z), and the lutein metabolite meso-zeaxanthin, comprise macular pigment in the macula of the retina. There is a large body of evidence suggesting that these pigments can protect against damage that contributes to AMD. Data from this CAREDS2/WHI indicates that individuals with low optical density of macular pigment are more likely to develop AMD, and that older women who had the lowest 20% of macular pigment optical density (MPOD) were about 40% more likely to have died over 14 years of follow-up. These results may be due to multiple shared risk factors for low MPOD and common chronic diseases, which are also risk factors for AMD (R01-EY025292; Lawler et al., 2017). These clinical trials address Goals 2.3 and 2.7 of the NIH Strategic Plan for WHR.

ii. Glaucoma-Optic Neuropathies

Glaucoma is a neurodegenerative disease characterized by damage to inner layers of the retina and the optic nerve, which is the bundle

of nerve fibers connecting the eye to the brain. This damage is due to degeneration of retinal ganglion cells (RGC) and their axons. Worldwide, glaucoma is the second leading cause of visual impairments and irreversible blindness. The pathogenesis of this condition remains unknown, however elevated intraocular pressure (IOP) is frequently associated with the disease. Therefore, most drugs to date are aimed at decreasing IOP by decreasing fluid outflow in the hope that progression of optic nerve atrophy will be slowed.

There are two main types of glaucoma, angle-closure glaucoma (ACG) and the more common type, primary open-angle glaucoma (POAG). ACG is more prevalent in women with the female-to-male ratio as high as 5:1 in some populations; whereas, reports show that POAG is more common in men which maybe correlated with increased risk of vascular disease (Quigley and Broman, 2006; Tham et al., 2014). The basis for the increased risk of ACG in women may be anatomical, with women having a shallower anterior chamber in the structure of the eye leading to reduced aqueous outflow and elevated IOP (reviewed in Tehrani, 2015).

The Nurse's Health Study (NHS), supported by various branches of the NIH, and has contributed considerably to research on glaucoma (Pasquale and Kang, 2011). These studies suggest that women with longer reproductive periods are associated with decreased risk of POAG suggesting that endogenous estrogen is protective against glaucoma. In addition, IOP has been shown to decrease during pregnancy and increases after menopause, suggesting a role for estrogen in regulating IOP (Ebeigbe et al., 2012). The data on hormone replacement therapy (HRT) in postmenopausal women shows it to be beneficial in reducing IOP in some studies (Na et al., 2014; Newman-Casey et al., 2014). These studies, however, have been limited by methodological issues, particularly small sample size. The results support the notion that there are unique, sex-specific risk factors for glaucoma in women, and the risk associations between reproductive factors, including menopause, late menarche, oophorectomy, oral contraceptive use and glaucoma continue to be studied. To further understand the neuroprotective effect of estrogen, the NEI is collaborating with the ORWH to co-fund a study to further investigate the role of estrogen in preventing retinal ganglion cell loss due to elevated IOP in animal models (R01-EY27005).

Recently, the development of a new class of drugs, rho kinase inhibitors have also been shown to lower IOP by decreasing conventional outflow and have protective effects against optic nerve degeneration. One of these inhibitors Netarsudil, has been evaluated in two Phase 3 clinical trials using equal populations of males and females. By comparison, the safety and efficacy of this treatment to an existing, but less effective drug, timolol in patients has been completed and approved by the FDA and now on the market as Rhopressa (Aerie Pharmaceuticals, Inc.; Serle et al., 2018).

Currently there is no curative treatment for glaucoma; however, all available medical and surgical treatments target IOP. The real hope for advancing glaucoma care is to discover therapies that target the RGCs to stave off or even restore vision loss. Promising candidates for neuroprotection in glaucoma that target RGC viability is being investigated in two NEI sponsored clinical trials that are underway at Stanford University. The first trial is a phase I study to evaluate the effectiveness of a recombinant human nerve growth factor (Dompe Farmaceutici) in treating POAG in men and women as well as in ACG. The second trial is a phase II study of NT-501 encapsulated cell therapy (Neurotech, Inc.), an intravitreal device that secretes ciliary neurotrophic factor (CNTF). Both trials are currently recruiting patients (Goldberg 2018; Presentation: American Academy of Ophthalmology 2017). The

development of these drugs and devices are relevant to Goals 2.3 and 2.7 of the NIH Strategic Plan on WHR.

g. Infectious Diseases

i. Herpes Zoster Ophthalmicus

Herpes Zoster Ophthalmicus (HZO), is a complication of Herpes Zoster (HZ) or shingles affecting the eye which is a common and serious disease caused by reactivation of the chicken pox virus that can result in chronic eye disease and incapacitating pain. Population-based studies show that the prevalence of HZ is about twice as more common in women than men, and that female patients with HZ may suffer from ocular complications more frequently than men.

Analysis of 3 independent databases show that sex and race may be risk factors for ocular herpes and postherpetic neuralgia (eye pain); however, larger and more statistically relevant epidemiology studies to determine the prevalence of HZO and PHN between men and women are needed. To further understand this association the NEI and the ORWH are currently co-funding a grant to perform secondary data analysis on data obtained from the electronic medical records of patients with HZO in 4 multi-national, multi-ethnic databases. Analysis will further assess the prevalence of HZO in males and females as well as determine if vaccines for HZ will prevent HZO. The efficacy of the vaccine in women vs men and disparities will be determined, as well as subgroups of women and men and/or minorities that will benefit from specific interventions (Goal 2.3; R01-EY028739; Borkar et al., 2013; Yawn and Gilden, 2013).

NEI is also funding a clinical trial to determine if prolonged treatment with a low dose of the antiviral valacyclovir is different in men vs women and if the effectiveness of antivirals treatments improve outcomes by reducing eye disease and/or chronic pain in HZO patients. This study is currently recruiting patients (Goal 2.7; U10-EY026869).

ii. Zika Virus Syndrome

The emergence of the Zika virus (ZIKV) has been accompanied by a rise in birth defects that are unique to fetuses and infants infected with ZIKV before birth. These infants show severe CNS defects such as microcephaly and ocular abnormalities including atrophy of the retina, optic nerve and RPE (Guevara and Agarwal-Sinha, 2018). Researchers have recently identified the involvement of novel pathways unknown to play a crucial role in ZIKV pathogenesis. Moreover, in the wake of rapidly spreading ZIKV infection and lack of treatment options, the identified genes/pathways specifically perturbed by ZIKV infection could allow the rational design of therapeutic strategies to treat or prevent ZIKV infection and its complications (Kumar-Singh et al., 2018). The ORWH is interested in studies on the cause of these ocular abnormalities due to ZIKV during pregnancy, and the NEI is currently funding research grants in this area (Goal 3.3; R01-EY-026964; R01-EY-027381).

IV. Areas of Interest and Initiatives

The NEI and the National Advisory Eye Council (NAEC) have established a 5-year strategic plan called, *Vision Research, Needs, Gaps, and Opportunities*. The August 2012 completed report includes goals and objectives relevant to women's health research. NEI is interested in all studies that gather comprehensive knowledge of (i) the molecular basis of ocular health and disease and use that knowledge to improve diagnosis, treatment, and prevention of eye disease; (ii) translational basic research into clinical studies; (iii) use clinical, epidemiological, and statistical tools to identify populations at risk of blinding eye diseases and visual disorders; (iv) evaluate new therapeutics to improve vision; and (v) regenerative medicine approaches for restoring visual function lost because of genetic abnormalities or disease processes are encouraged by the NEI. All proposed projects

require a group of animals/humans of the opposite sex (female) for comparative analyses of sex differences and mediated effects and treatment outcomes.

i. *Population-Based Studies:* Research on diseases that are known to have a higher incidence and prevalence in women than men are encouraged. In collaboration with the ORWH, a lot of progress has been made identifying and studying sex differences as it relates to vision research. The prevalence and incidence of many ocular diseases have been shown to be greater in females than men and occur at different stages of the life span. For example, the effects of ZIKV and its effects on the eye and visual system begins in utero. Complications such as ocular herpes, which may be more prevalent in women, results from the reactivation of the varicella zoster virus. Myopia is another example of an ocular disorder that is more frequent in girls than boys; whereas, visual processing disorders can occur at all stages of the lifespan. And, diseases such as DED, cataracts, glaucoma, and AMD are more common in adulthood and appears to be more prevalent in women especially during and after menopause.

Many epidemiology studies on diseases of the retina, cornea, lens, and other areas of the eye show an inherent sex biases in subject populations. In addition, several fundamental processes such as during eye development also demonstrate clear sex differences. These findings lend strong support to recent efforts to include sex as a biological factor in vision and neuroscience research, by either matching the sex of the animals and human subjects and/or including it as a factor in the analysis of the data.

The NEI recently published a Funding Opportunity Announcement with the goal to fund meritorious vision related research projects that involve secondary data analyses using existing database resources. The announcement includes sex-based differences in their analysis which addresses Goal 2 of the NIH Strategic Plan for WHR (PAR-16-168).

ii. *Opioid Health Crisis:* Discomfort from ocular pain, principally associated with ocular surface disorders and postherpetic neuralgia, are common reasons for patients seeking eye care. Ocular pain is associated with a significant decrease in patient quality of life and is strongly associated with the use of antidepressants and pain medications, especially among women. This is adding to our nation's current opioid crisis (Satitpitakul et al., 2017). In an effort to end opioid misuse/addiction and yet control chronic ocular pain, NEI is sponsoring the development of non-addictive pain medicines to control/treat eye diseases including those with nerve damage which leads to neuropathic pain. Both the NEI and the ORWH are currently participating in the NIH sponsored Initiative, Helping to End Addiction Long-term (HEAL) (https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative ; RFA-NS-18-043).

iii. *Training:* The NEI recognizes the importance of training research scientist to study sex differences in all aspects of vision science, and promotes training and career development of postdocs and scientist to get the research experience necessary to become highly competitive for positions as an independent scientist in vision science. Resent statistics shows that women remain underrepresented in the science and engineering fields, and therefore, NEI is participating with other NIH Institutes and Centers on the Blueprint and BRAIN Initiatives to promote postdoctoral training of women in basic and clinical research (RFA-NS-18-007; RFA-MH-18-510).

iv. *Audacious Goals Initiative (AGI):* The NEI AGI (see http://www.nei.nih.gov/audacious) addresses Goals 1, 2, and 3 of the NIH

Strategic Plan for Women's Health. Its focus is on regenerating neurons and neural connections in the eye and visual system. In consultation with the National Advisory Eye Council, the NEI initiative is targeting the photoreceptor and retinal ganglion cells, because the loss of either cell type by disease or injury leads to severe visual disorders and blindness. This includes loss of photoreceptor cells as occurs in AMD or damage to retinal ganglion cells (RGC) resulting in glaucoma or optic nerve pathologies, all of which are conditions that are more pronounced in women. One challenge in vision research is how to restore vision by promoting photoreceptor cell and RGC survival, as well as functional retinal regeneration. These areas of research are relevant to Goals 1 and 2 of the NIH Strategic Plan for WHR (RFA-EY-14-001; RFA-EY-16-002; RFA-EY-17-003).

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National Heart, Lung, and Blood Institute

I. Executive Summary

The National Heart, Lung, and Blood Institute (NHLBI) supports basic, translational, and clinical research to prevent, treat, and cure heart, lung, blood and sleep (HLBS) disorders. A key part of understanding health and disease is to understand sex as a biological variable. In many cases, both normal biology and disease susceptibility and progression differ between men and women. Accounting for these sex differences is precision medicine at its most fundamental level. For example, more women than men are diagnosed with and die from chronic obstructive pulmonary disease (COPD). Although the reasons for this disparity are unclear, ongoing research points to many contributing factors, including differences in lung anatomy between men and women, sex-specific differences in gene regulation and function, and distinct behavioral risk factors, including a steeper decline in the prevalence of smoking among adult men over the past 50 years. Further study of these differences may yield improved prediction, diagnosis, and intervention for COPD among both women and men.

The NHLBI Strategic Vision expresses the Institute's commitment to understanding sex differences to improve women's health and develop precision medicine approaches for women. From its inception, NHLBI has valued and prioritized including women in clinical research. NHLBI's Framingham Heart Study, launched in 1948, was one of the first epidemiological studies to address cardiovascular disease (CVD) and was designed from the beginning to include women and men. Inclusion of women in NHLBI-funded studies and trials remains a priority. In fiscal year 2018, nearly 57 percent of all prospectively enrolled participants in NHLBI-funded clinical studies were female. These studies, including the ongoing Framingham Heart Study and the Women's Health Initiative (WHI) continue to provide an evidence base to understand and address the burden of heart, lung, blood, and sleep disorders in women.

This report describes recent research studies and programs that are helping to reveal sex and gender differences in in heart, lung, blood, and sleep disorders, their pathobiology, and in treatment efficacy and response. This research is providing valuable insights into ways to reduce disease in women, even as it helps pave the way for more personalized delivery of care for all patients.

Research areas and topics covered in this report include the health of women during and after pregnancy, like studies that examine the impact of sleep disorders and hypertension during pregnancy on women's heart health over the short and long term. Additionally, we report on studies that explore the role of sex hormone levels in diseases ranging from thrombosis to asthma. We also highlight the wealth of knowledge that has come out of the WHI and ancillary studies, including those that underline the importance of physical activity on health and reduced mortality in women.

NHLBI also supports a variety of community outreach and educational programs for women intended to raise awareness about heart disease and its risk factors and empower women to reduce their risk. During American Heart Month 2018, NHLBI's #MovewithHeart theme encouraged all Americans to improve their heart

health by exercising more. Our American Hearth Month activities and *The Heart Truth* campaign seek to raise awareness that heart disease is the leading cause of death for women in the U.S., increase knowledge of the risk factors that render women susceptible to heart disease, and encourage women to talk to their doctors, learn their personal risk, and take action to reduce it.

Also addressed are the health disparities experienced by women in minority populations. We summarize NHLBI's support for several large observational studies that are exploring the development of HLBS diseases and risk factors and their association with biological, demographic, social, environmental, and genetic determinants of risk in racial and ethnic minority populations.

Lastly, we emphasize NHLBI's role in promoting gender equality in the scientific workforce and highlight our efforts to create funding structures to support the recruitment and retainment of women throughout a scientific career trajectory.

II. Scientific Accomplishments and Activities

Asthma and Airway Inflammation

Sex hormones and Asthma

Asthma is more common in boys than in girls, but also more common in adult women than men, suggesting that shifting sex hormones with age influence disease susceptibility and progression. NHLBI-funded studies show that in both males and females, sex hormones contribute to inflammation in the lungs in response to allergens. However, estrogens are more potent than androgens at stimulating a major inflammatory pathway implicated in asthma. These findings are helping advance our understanding of how an individual's sex and age can interact to influence asthma risk, and may help lead to more effective treatments that take these factors into account.

Sex hormones and Pollution-Induced Inflammation

In an animal model of pollution-induced lung inflammation, NHLBI-funded investigators discovered that both sex and hormonal status can influence micro RNA expression in response to air pollutants, indicating a sex-specific regulation of the inflammatory response.

Cardiovascular Disease (General)

Breast Arterial Calcifications and CVD

Although breast arterial calcifications (BAC) found during mammography are not associated with breast cancer risk, they are associated with some risk factors for cardiovascular disease (CVD). NHLBI is funding a study to gain insight into ethnic differences in BAC incidence, severity, and association with CVD risk factors. This work will shed light on the potential value of BAC mass as a new tool for CVD risk stratification and thus for CVD prevention. A recent publication from the work showed that a deep learning system was nearly as accurate as human experts in the ability to detect BAC in mammograms.

Non-Obstructive Coronary Artery Disease

The NHLBI-funded *Women's Ischemia Syndrome Evaluation (WISE)* study was launched in 1996 to follow 1,000 women referred for chest pain, in order to address challenges in diagnosing ischemic heart disease in women. Of those women, two-thirds had no signs of obstructive coronary artery disease (CAD) on angiography, but still had an increased risk of heart attack, heart failure, and stroke. A recent analysis of this cohort found that within nine years of

referral for angiography, one in five women had died, mostly from cardiovascular causes.[25] Another recent analysis found that heart failure hospitalizations was the most frequent event (ref) , which was validated to be heart failure with preserved ejection fraction (HFpEF)(ref), and deaths from any cause within the WISE cohort were associated with a rise in the inflammatory protein interleukin-6 (IL-6) in the blood.[26] This suggests that inflammation could be a target for therapy in non-obstructive CAD and HFpEF, and that proteins like IL-6 could help identify women with non-obstructive CAD who are at risk of developing heart failure.

Sex Hormones and Atherosclerosis

An NHLBI-supported study from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort showed that sex hormone levels were associated with coronary artery calcium (CAC) progression among women. CAC and its progression, measured by non-contrast cardiac computed tomography, are markers of subclinical atherosclerosis and predict CVD, even among low-risk women. This study concludes that a more androgenic hormone profile of higher free testosterone and lower sex hormone binding globulin (SHBG) is associated with a greater CAC progression up to 10 years in post-menopausal women. Sex hormone levels may help identify women at increased risk for CVD who may benefit from additional risk-reducing strategies.

Sex Hormones and Thrombosis

Studies have linked increased sex hormone levels, such as during pregnancy or oral contraceptive (OC) use, with an increased risk of thrombosis – blood clotting that can cause a heart attack or stroke. In 2017, NHLBI launched a program to better understand the mechanisms of hormone-induced thrombosis. Grants funded in 2018 are looking at how platelets (clotting cells) are activated during pregnancy and OC use, new biomarkers for predicting thrombosis, and potentially protective mechanisms.

Heart Disease

Mental Stress–Induced-Myocardial Ischemia in Women

Mental stress-induced myocardial ischemia (MSIMI) is common in patients with coronary artery disease (CAD) and can increase the risk of heart attack, stroke, and mortality. In an NHLBI-funded study of patients who had recently been hospitalized for MI, researchers found that young women, with a mean age of 50 years old, were twice as likely to develop MSIMI compared to men of a similar age. In addition, women were more likely to experience a lack of dilation in their arteries, known as microvascular dysfunction, and an increase in peripheral vasoconstriction during stress. These circulation events may be contributing to the increase in MSIMI in women, and could inform clinicians when assessing the risk for such events.

Genetic Variants Associated with Peripartum Cardiomyopathy

Sex-specific studies are essential when a condition is unique in women. An NHLBI-funded study examined genetic risk factors in a large series of women with peripartum cardiomyopathy, and found an association with variants in a gene called TTN, remarkably similar to variants previously found in patients with idiopathic dilated cardiomyopathy. These variants were the most prevalent genetic predisposition in each disorder.

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Genetic Risk Factors for Atrial Fibrillation

AFib is the most common type of rapid, irregular heartbeat in the U.S., and a risk factor for stroke and heart failure. There have been many advances in AFib treatment, but earlier intervention is needed, especially for women, who have higher rates of death and disability from AFib than men. Recently, in a large genome-wide association study that included about 60,000 people with AFib, NHLBI-funded researchers found that a number of genes known to be involved in heart development during early life also are associated with susceptibility to AFib. These genes could help identify people at risk for AFib and serve as targets for more effective therapies.

Hypertension

Intensive Blood Pressure Treatment in Women

NHLBI's Systolic Blood Pressure Intervention Trial (SPRINT) found that compared to a standard blood pressure target of less than 140 mm Hg, more intensive treatment toward less than 120 mm Hg helped reduce deaths from heart attack and stroke, particularly among older, high-risk individuals with high blood pressure. When researchers analyzed changes in cardiovascular, renal, and overall serious adverse effects, they found no differences between men and women who received the intensive treatment. Both men and women in the intensive treatment group showed a reduction in adverse events compared to those in the standard treatment group, providing additional evidence to support intensive blood pressure management and control in women

Chronic Hypertension during Pregnancy

While there are established best practices for treating chronic hypertension in the general population, there is no consensus on whether to treat women for mild chronic hypertension during pregnancy. Although this condition carries risks for the mother and fetus, there are also concerns that lowering blood pressure could reduce blood flow to the fetus and impair fetal growth. The NHLBI-funded Chronic Hypertension and Pregnancy (CHAP) trial is designed to evaluate the efficacy and safety of treating pregnant women toward the same blood pressure target recommended for all reproductive-age adults (<140/90 mmHg). This intervention will be compared to usual care (no treatment unless blood pressure reaches ≥160/105 mmHg).

Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH) refers to high blood pressure in the lungs, caused by scarring and narrowing of the pulmonary arteries. It is 2-4 times more common in women than in men. The strong female sex predominance in PAH suggests that estrogens play a critical role in the pathophysiology of the disease. The main source of estrogens in post-menopausal women and in men is the metabolism of circulating androgens via aromatase. NHLBI is funding a placebo-controlled trial to determine if Anastrozole, a generic aromatase inhibitor which is FDA-approved for breast cancer, is a safe, effective treatment for PAH in postmenopausal women and in men.

While PAH is more common in women, women with PAH have better right ventricular (RV) function and survival as compared to men with PAH. Lower levels of a sex hormone called dehydroepiandrosterone (DHEA) increase the risk of PAH in men and women, and are associated with more severe pulmonary vascular disease, worse RV function, and mortality in PAH. An

NHLBI-funded trial will evaluate DHEA vs. placebo in both women and men with PAH and RV failure.

Chronic Obstructive Pulmonary Disease

Improving the quality of care for people with COPD, the Nation's fourth leading cause of death and a disease that is increasingly impacting women, is one of five goals established in the COPD National Action Plan, released by NHLBI and its partners in 2017.

Sex Differences in COPD

The NHLBI-supported COPDGene study has found a significantly higher symptom burden of COPD in women, especially younger women. Continuing analyses from the COPDGene study are seeking to understand the pathogenesis of increased severity of COPD in women and to develop gender-targeted clinical assessment and management approaches to improve outcomes for women and men with COPD at all ages.

Sex-Specific Genetic Risk in COPD

Women are more likely to die from COPD than men, and genetic factors may play a role in this. In an NHLBI-funded study, researchers analyzed genetic data from more than 10,000 current and former smokers with COPD and found that variations in a fetal lung development gene, CELSR1, were associated with COPD in women, but not men. Identification of further sex-specific risk factors and pathways may enable new interventions to reduce death and disability from COPD in women.

Interaction of Sex and Environmental Exposures

Another NHLBI-funded study found that household air pollution from biomass-fueled cooktops was associated with a higher prevalence of COPD, particularly in women. These exposures increased risk of COPD in women by 70% but in men by only 21%,making it likely a leading population-attributable risk factor for COPD in resource-poor settings.

Pregnancy and Maternal Health Outcomes

Preventing Preeclampsia

Preeclampsia affects 2-8% of pregnant women and is characterized by high blood pressure and elevated protein in urine. Preeclampsia usually develops after the 20th week of pregnancy and resolves after delivery. However, it can evolve into eclampsia—characterized by seizures or coma—which is a leading cause of maternal morbidity and mortality. Moreover, complications from preeclampsia, such as kidney failure, hemorrhage, and stroke, can lead to lasting health problems. NHLBI is funding a multicenter, randomized clinical trial of pravastatin – a common cholesterol-lowering drug – vs. placebo in 1500 women at risk of recurrent preeclampsia. The trial, Prevention of Preeclampsia in High Risk Women (PREP), is being conducted within NICHD's Maternal Fetal Medicine Units Network.

Pregnancy and Heart Health

NHLBI and NICHD support the nuMoM2b *(Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be)* Heart Health Study. This study follows women from the nuMoM2b cohort 2-5 years after delivery, to evaluate reported links between preeclampsia (and other adverse pregnancy outcomes), sleep and future maternal cardiovascular health. The goals are to identify future screening and preventive strategies.

Sleep Disorders

Sleep Problems and Blood Pressure

New findings reveal that poor sleep quality can increase blood pressure and the levels of a pro-inflammatory protein (NF-kappa B) implicated in the development of CVD, even in women who

slept 7-9 hours per night. Insomnia, which is 2-3 times more common in women than men, was also associated with activation of NFkB. The findings suggest that a portion of CVD risk might be mitigated by better management of insomnia and poor sleep quality.

Sleep Apnea during Pregnancy

The nuMoM2b Sleep-Disordered Breathing Study, funded by NHLBI and NICHD, found that sleep disorders and sleep-disordered breathing during pregnancy are linked to higher risk of gestational diabetes, preeclampsia, and preterm birth. Building on these findings, in 2018, NHLBI and NICHD launched a phase III clinical trial to determine whether treatment of sleep apnea during pregnancy reduces the risk of gestational hypertension, diabetes, and preeclampsia.

Women's Health Initiative (WHI)

NHLBI's Women's Health Initiative (WHI) is a major long-term research program designed to address the most frequent causes of death, disability, and diminished quality of life in postmenopausal women. Launched in 1991, this project originally recruited nearly 162,000 women aged 50-79, and was one of the most definitive, far-reaching clinical trials of women's health ever undertaken in the U.S. The WHI includes two major parts: an Observational Study and a Clinical Trial component.

The Observational Study is examining the relationship between lifestyle, health and risk factors and specific disease outcomes. Since recruitment was completed in 1998, the study has tracked the medical history and health habits of 93,676 women. The study has been renewed approximately every five years, and in fiscal year 2015, it was funded through fiscal year 2020.

The initial WHI Clinical Trials, now complete, enrolled 68,132 postmenopausal women ages of 50-79 into three trials testing unique prevention strategies. If eligible, women could choose to enroll in one, two, or all three of the trial components. The three components were:

- Hormone Therapy Trial (HT). This trial found that estrogen plus progestin hormone therapy after menopause increased the risk for heart disease, stroke, blood clots, breast cancer, and dementia. From the WHI, we now know that hormone therapy—estrogen plus progestin or estrogen alone—should not be used in postmenopausal women to prevent heart disease or to lower cholesterol levels.
- Dietary Modification Trial. This trial found that a low-fat diet did not reduce the risk of breast cancer, colorectal cancer, heart disease, or stroke, but did reduce the risk of ovarian cancer.
- Calcium/Vitamin D Trial. This trial showed that calcium and vitamin D supplements provide a modest benefit in preserving bone mass and preventing hip fractures in certain groups, including older women. The supplements did not prevent other types of fractures or colorectal cancer.

WHI researchers calculated the total net economic return of these trials, which cost $260 million in U.S. 2012 dollars, as $37.1 billion. This analysis reveals that large public research investments can yield considerable clinical and economic value.

Ongoing WHI Studies and Recent Findings

Women's Health Initiative Strong and Healthy (WHISH) Study

WHISH builds upon the Objective Physical Activity and Cardiovascular Health Study (OPACH), which included WHI participants, used wearable devices to measure the effect of physical activity on cardiovascular health in older women. The study has found that both light-

intensity and moderate-vigorous physical activity (PA) measured by accelerometer are associated with lower mortality among older women (aged 63-99). With each 30 additional minutes of light PA per day, the women had a 12% lower risk of death from any cause. And with each 30 minutes of moderate PA (brisk walking/bicycling), their risk was 39% lower. The WHI Strong and Healthy (WHISH) trial, involving some 50,000 women from the cohort, is now testing whether an intervention to increase their daily PA can reduce major cardiovascular events over four years of follow-up. WHISH is testing a centralized, public health intervention designed to improve physical activity levels and reduce CV events in older women. The study will also evaluate the safety of the intervention by examining risks of bone fractures, falls, and non-CVD mortality.

COcoa Supplement and Multivitamin Outcomes Study (COSMOS)

The COSMOS trial, which recruited from the WHI cohort, is testing whether cocoa flavonoids or multivitamins might reduce cancer and CVD among women aged 65 years and older and men aged 60 years and older. There is no previous large-scale randomized clinical trial in either men or women for cocoa flavonoids or in women for multivitamins. The number of WHI participants randomized into COSMOS was 4,611 women.

Risk Factors for Heart Failure

In a multiracial cohort of postmenopausal women from the WHI, risk factors for heart failure requiring hospitalization depended on the type of heart failure. Obesity, coronary heart disease, anemia, and atrial fibrillation were associated with preserved ejection fraction HF (HFpEF) but not with reduced ejection fraction HF (HFrEF). History of myocardial infarction was associated with HFrEF but not HFpEF. Obesity was a more potent risk factor for HFpEF among African American women than among white women. Another study using WHI data showed that dose-dependent increases in leisure-time physical activity and lower body mass index were both significantly associated with a decrease in risk for HFpEF.

Risk Factors for Cognitive Decline

The WHI Memory Study found that CVD, high blood pressure, and diabetes are associated with cognitive decline in older women. The study continues to investigate other risk factors and markers for cognitive decline including diet and medications.

WHI Sleep Hypoxia Effects on Resilience (WHISPER)

WHISPER will test the clinical relevance of a simple, home-based approach for identifying modifiable sleep characteristics with potentially powerful prognostic value regarding incident cardiovascular events and cancers, and cognitive decline and impairment.

Trans-Omics for Precision Medicine program (TOPMed)

TOPMed has genomic data from about 120,000 diverse individuals enrolled in more than 60 NHLBI-funded studies including the Women's Health Initiative (WHI). More than 11,000 whole genome sequences will be derived from WHI to explore genes that contribute to stroke, hypertension, and venous thromboembolism. These data will be analyzed along with data on sex, medical history, socioeconomic status, lifestyle and environmental factors, imaging, and biomarkers – with the goal of discovering new disease pathways and developing more personalized interventions.

NIH Strategic Plan for Women's Health Research

In line with the new Trans-NIH Strategic Plan for Women's Health Research, NHLBI's Strategic Vision, released in August 2016, sets the stage for supporting innovative approaches to addressing women's health across the Institute's broad research portfolio. Key in the

vision is the importance of investigating factors, such as age, sex, pharmacogenetic issues, and race that account for differences in health among populations and lead to individualized treatments or precision medicine. Accounting for sex differences is precision medicine at its most fundamental level and is a top NHLBI Strategic Plan priority. Other priorities include: understanding mechanisms of disease, trans-generational studies in women, more data about numbers of women in clinical trials, recruiting and retaining women scientists, awareness and education of CVD risk in women, and research into resilience including estrogen protection for PAH.

Scientific Workshops

Predicting, Preventing and Treating Preeclampsia

Currently, there are no effective treatments for preeclampsia aside from delivery. A workshop sponsored by NHLBI in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) on May 21 and 22, 2018 brought together 16 invited experts to discuss barriers and opportunities for predicting, preventing, and treating preeclampsia. The group recommended: (1) Research to understand the normal pregnancy physiology, mechanisms of resilience to preeclampsia, and the heterogeneity of mechanisms that result in preeclampsia; (2) Development of a risk score for younger women to assess for CVD risk and test new models of care to reduce risk of developing post-preeclampsia CVD; (3) Support for an observational study of pre-pregnancy and pregnancy that includes age-specific biosamples.

Female Sex and Gender in Lung/Sleep Health and Disease

To explore research needs and opportunities related to the impact of female sex and gender on lung health and management of lung disease, the NHLBI collaborated with the NIH Office of Research on Women's Health and the Office of Rare Diseases Research to hold a Sept 2017 workshop on "Female Sex and Gender in Lung/Sleep Health and Disease: Increased Understanding of Basic Biological, Pathophysiological and Behavioral Mechanisms Leading to Better Health for Female Patients with Lung Disease." NIH staff and investigators studying sleep disorders and lung diseases, including COPD and pulmonary hypertension, discussed the current understanding of sex differences influencing these conditions, as well as future research priorities and potential areas of collaboration.

Education and Engagement

NHLBI sponsors a national health education program, *The Heart Truth*®, to promote heart disease prevention among women.[27] It seeks to raise awareness that heart disease is the leading cause of death for women in the U.S., increase knowledge of the risk factors that render women susceptible to heart disease, and encourage women to talk to their doctors, learn their personal risk, and take action to reduce it. *The Heart Truth* collaborates closely with other components of the Department of Health and Human Services (HHS), including the HHS Office on Women's Health the NIH Office of Research on Women's Health, and the Centers for Disease Control and Prevention's Million Hearts® initiative.

The program uses the iconic *Red Dress*® to impart the awareness message. Awareness of the *Red Dress* symbol has grown considerably since its launch in 2002. In 2010, about 60% of women were aware of the Red Dress symbol, and those who reported awareness of the *Red Dress* or *The Heart Truth* campaign were more likely than other women to take at least one risk-reducing action as a result (up from 35% in 2008 to 57% in 2010).

Raising awareness about risk has done more than just inform women—it motivates them to act. Women who know that heart disease is their

27 *The Heart Truth*, its logo, *The Red Dress*, *Red Dress*, and Million Hearts are registered trademarks of HHS. National Wear Red Day is a registered trademark of HHS and the American Heart Association.

leading cause of death were 35% more likely to be physically active and 47% more likely to report weight loss than those who are unaware.

The Heart Truth's strategic framework is built on three pillars: national awareness-raising activities, community activation, and partnerships. National-level partnerships and activities, such as National Wear Red Day®, are designed to raise awareness of heart disease and its risk factors among American women. Each year, The Heart Truth implements an American Heart Month theme to increase awareness and burden of heart disease in women and all Americans. In 2017 and 2018, The Heart Truth implemented several social media activations in partnership with Women Heart Alliance and independently. All activations focused on empowering women by providing advice on eating healthy, being physically active, and controlling high blood pressure. These social media activities are accompanied by print and online resources for our community partners. Together, we reach women in all 50 states and the District of Columbia.

Partnerships with a wide variety of organizations—community, media, corporate, Government, nonprofit, and health professional—leverage *The Heart Truth's* outreach to its target audience, amplify the program's key evidence-based, public health messages, and support national activities and community programming. Over the past decade, the program has contributed to an increased awareness among women that heart disease is their leading cause of death—a recent American Heart Association survey showed that such awareness nearly doubled between 1997 and 2012, from 30% to 56%. Despite the increase of heart disease awareness in women, disparities remain in African-American women and Latinas. *The Heart Truth* continues to work to support outreach to these priority populations to reduce disparities and promote healthy behavior changes.

In developing the Strategic Vision, NHLBI engaged scientific, professional, and patient advocacy communities that align with our mission, including organizations that represent women's health issues (e.g. Women's Heart Alliance). To leverage the energy and wealth of ideas from these groups, in February 2017, NHLBI convened a "Champions Forum" involving representatives from patient advocacy organizations and research institutions. The aims were: (1) to assess the current state health promotion and education materials for women; (2) identify gaps in resources for women at risk for heart disease (3) to assess the effectiveness of current NHLBI materials in the field.

Another health education program sponsored by NHLBI is *COPD Learn More Breathe Better*®, which aims to raise awareness about chronic obstructive pulmonary disease (COPD) and encourage people and health care providers to discuss signs and symptoms to help diagnose the disease early. COPD is a debilitating lung disease and a leading cause of death in the U.S. Women are 30 percent more likely to have COPD and of the 16 million Americans diagnosed, 56 percent are women. The *Learn More Breathe Better* program addresses COPD's impact on women through a variety of educational activities throughout the year. For example, its social media messaging during National Women's Health Week, May 19-23, 2018 was focused on COPD's impact on women, and educational materials were shared with the program's Breathe Better Network—a formal partnership of COPD coalitions, organizations, and task forces that help integrate the *COPD Learn More Breathe Better*® program messaging and materials into outreach efforts across all 50 states and the District of Columbia.

Inclusion

Since its establishment in 1948, NHLBI has been a leader in improving inclusion of women

in research. For example, NHLBI's Framingham Heart Study, which was also launched in 1948, was one of the first epidemiological studies to address cardiovascular disease and was designed from the beginning to include women and men.

Having women well-represented in NHLBI-funded research studies, especially clinical trials, is critical for improving our understanding of how sex differences affect health and disease, and for development of safe and effective treatments and better health outcomes for everyone. As part of our continuing efforts to address cardiovascular disease in women, NHLBI monitors enrollment in the clinical research we fund. In fiscal years 2017 and 2018, females made up 54.4 and 56.5 percent of prospectively enrolled participants in NHLBI-funded studies.

Women's Health and Minority Health

Recent U.S. health statistics provide the following snapshot of racial/ethnic similarities and differences in the burden of leading causes of death relevant to the NHLBI mission.

- Diseases of the heart account for 22% of deaths (1st or 'leading' cause) in non-Hispanic white women, 23% (1st) in non-Hispanic black women, 20% (2nd) in Hispanic women, 20% (2nd) in non-Hispanic Asian or Pacific Islander women, and 17% (2nd) in non-Hispanic American Indian or Alaska Native women.
- Cerebrovascular disease (stroke) accounts for 6% of deaths (5th) in non-Hispanic white women, 7% (3rd) in non-Hispanic black women, 6% (3rd) in Hispanic women, 8% (3rd) in non-Hispanic Asian or Pacific Islander women, and 5% (7th) among non-Hispanic American Indian or Alaska Native women.
- Chronic lower respiratory diseases account for 7% of deaths (3rd) in non-Hispanic white women, 3% (7th) in non-Hispanic black women, 3% (7th) in Hispanic women, 2% (8th) in non-Hispanic Asian or Pacific Islander women, and 6% (4th) among non-Hispanic American Indian or Alaska Native women.

NHLBI supports an extensive portfolio of research focused on the health of racial and ethnic minorities, and on addressing health disparities that exist between these groups and the majority white population in the U.S. Of particular relevance are large epidemiological studies that enable detailed study of diseases and their associated risk factors in defined groups.

Initiated in 1985, the Atherosclerosis Risk in Communities (ARIC) study includes African Americans and whites living in four areas of the U.S.: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. A recent analysis of the ARIC cohort found that being an African American woman and having diabetes combine in a synergistic way to influence CVD risk. While previous studies had shown that diabetes is a stronger risk factor for white women than for white men, this analysis establishes the same pattern for African American women. This finding addresses an important gap in our understanding of African American women's health and has implications for screening and prevention of CVD in this population.

Since 2006, the Hispanic Community Health Study/Study of Latinos has monitored disease risk factors and outcomes in a Latino cohort that comprises self-identified Mexican Americans, Puerto Ricans, Cuban Americans, and Central/South Americans. Disease outcomes under study include CVD, stroke, asthma, COPD, sleep disorders, dental disease, hearing disorders, diabetes, kidney and liver disease, and cognitive impairment. Pregnancy-related complications (including preeclampsia, eclampsia, and gestational diabetes) were added as outcome measures in 2013. The study has found that CVD risk factors vary among distinct Latino groups. The prevalence of three or more CVD

risk factors is highest among participants with lower socioeconomic status, those with higher levels of acculturation to the U.S. (as determined by years of residence, generational status, and language preference), and those of Puerto Rican background. For example, 51% of Puerto Rican women in the study are obese, a higher rate than among Puerto Rican men or any other Latino group.

Other ongoing NHLBI-funded cohort studies include the Jackson Heart Study, which grew out of ARIC and launched in 1998, to address CVD prevalence, morbidity, and mortality among black women and men living in the Jackson area. The Multi-Ethnic Study of Atherosclerosis (MESA), launched in 1999, is investigating predictors and progression of subclinical CVD in a cohort that includes white, black, Hispanic, and Asian Americans living in six urban and suburban areas of the U.S. The Strong Heart Study began in 1988 and is designed to understand CVD mortality and risk factors among American Indians, with sites in Oklahoma, Arizona, and the Dakotas.

Women in Science

One of NHLBI's enduring principles is to enable and develop a diverse biomedical workforce. Increasing the representation of underrepresented groups, including women, in this pipeline is a top priority. NHLBI explicitly affirms our commitment to diversity of the scientific workforce in our Funding and Operating Guidelines. Among other things, workforce diversity—including representation of women—is one of the criteria considered for grants eligible for award through Selective Pay or Zone of Consideration funding strategies. The NHLBI Office of Science Policy, Engagement, Education, and Communications participated in the development of the Trans-NIH Strategic Plan for Women's Health Research, which includes the promotion of training a robust workforce that includes women.

Additionally, NHLBI celebrates the success of women in science and seeks opportunities for accomplished women scientists to inspire others. On May 3, 2018, NHLBI hosted Nanette Wenger, M.D. of Emory University as one of six thought leaders to speak as part of its 70th Anniversary lecture series. After graduating from Harvard Medical School in 1954, Dr. Wenger became one of the first physicians in the country to focus on heart disease in women and subsequently dedicated much of her career to reducing its toll. At a time when heart disease was considered a man's disease, she called attention to the fact that it was ubiquitous in women, but often overlooked and poorly managed. She continues to be a leader and champion for women's health. Dr. Wenger met with the NHLBI Women's Health Working Group and presented a public seminar on how changes in policy, research, and public and professional outreach have helped reduce the burden of heart disease in women since the 1960s.

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National Institute on Aging

I. Executive Summary

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer's disease (AD) and other dementias, implications of ovarian aging, menopause and menopausal hormone therapy, and other diseases and conditions. During FY 2017-2018, NIA-supported researchers made important progress in a number of women's health-related areas, including:

Alzheimer's disease and other dementias. Alzheimer's disease (AD) is more prevalent among women than men. NIA-supported investigators have identified important sex differences in genetic risk of the disease; AD biomarkers; and neuropsychiatric symptoms. In addition, investigators have made key discoveries regarding correlation between reproductive history, including use of hormone therapy, and cognitive health.

Reproductive health and menopause. Research continued through the Study of Women's Health Across the Nation (SWAN) and other studies on health across the menopausal transition. For example, SWAN investigators characterized women's hormonal trajectory as they approached the final menstrual period and determined that hormonal patterns characteristic of peak fertility may continue until the menopause itself. Elsewhere, investigators with the NIA-supported MsFLASH Network are currently conducting a large multicenter trial comparing two common treatments, a vaginal hormone pill and an over-the-counter gel, with placebo to evaluate their effects on bothersome vaginal symptoms and sexual function.

Bone health. SWAN investigators also found that chronic opioid use (e.g., five or more years continuous use) was associated with greater loss of bone mass than similar use of other analgesics among women.

Cardiovascular disease. In other news from SWAN, investigators found that a history of preterm birth (PTB) was associated with higher blood pressure and mean arterial pressure in late midlife, but PTB and other adverse birth outcomes were not associated with other forms of subclinical vascular disease outcomes among non-hypertensive women. In addition, SWAN participants who practice a healthy lifestyle—avoiding smoking, following a healthy diet, and engaging in regular physical activity—during the menopausal transition have lower levels of subclinical atherosclerosis later in their life.

Preventive healthcare. Elimination of cost-sharing—that is, requirement for a deductible or co-payment—under the Affordable Care Act increased screening mammography rates among women aged 65-74. However, all groups did not benefit equally; the rate of increase was smaller in areas with lower overall educational attainment and was negligible among Hispanic women.

Inclusion across the lifespan. An NIA analysis was completed in 2018 on the number of older adults included as participants in NIH-funded phase III clinical trials between 1965 and 2015. The data reflect a disproportionate underrepresentation of older adults in these clinical studies due to the use of both explicit and implicit exclusion criteria. Because older women outnumber older men by a significant margin, these results are particularly relevant to women. The analysis was a key factor in the establishment of NIH's 2019 Inclusion Across the Lifespan policy.

Ongoing research initiatives focusing on women's health and/or sex and gender differences include the Women's Health Initiative Memory Study (WHIMS) suite of studies assessing the effects of menopausal hormone therapy on memory, cognition, and mood in participants ages 65 and older, without dementia, who had been randomized to hormone therapy or placebo within the original Women's Health Initiative (WHI) trial; four Specialized Centers of Research Excellence (SCOREs) on Sex Differences, including Centers that explore sex difference in the context of Alzheimer's disease, influenza, and HIV infection; and an ongoing funding opportunity announcement **soliciting research** to increase our understanding of the impact of sex differences on the trajectories of brain aging and phenotypes of Alzheimer's disease risk and on the responsiveness to treatment. NIA's research portfolio aligns with the ORWH Strategic Plan. In addition, NIA supports communication and education activities related to women and aging, career development activities, and research on the specific health concerns of minority women.

II. Introduction

Older women outnumber older men in the United States, and the proportion of the population that is female increases with age. **In 2014, women accounted for 56 percent of the population ages 65 and older and for 66 percent of the population ages 85 and older**. Despite living longer, however, **older women are more likely to report depressive symptoms or limitations in physical function, are more likely to live alone** (a potential indicator or risk factor for isolation, lack of caregivers, or lack of support), and **live in poverty at a disproportionately high rate (**Federal Interagency Forum on Aging-Related Statistics, 2016). American women also lag significantly behind their counterparts in other higher income nations in terms of longevity, and since 1980, the pace of gains in life expectancy of older U.S. women has slowed markedly, compared to that in other industrialized countries (National Research Council, 2011). In fact, life expectancy has fallen 3 to 5 years behind other developed nations, including France, Italy, Spain, Switzerland, Australia, and Japan (National Research Council and Institute of Medicine, 2013).

NIA supports a diverse portfolio of research on older women's health, including studies on sex differences in the basic biology of aging; hormonal influences on cognitive health; women's health across the life course, with a particular emphasis on the menopausal transition; sex and gender-related demographic disparities in older age; economic implications of sex and gender at older ages; and age-related diseases and conditions that are unique to or more common in women, such as osteoporosis, breast and ovarian cancer, and urinary tract dysfunction.

Alignment with the NIH Strategic Plan for Research on Women's Health

Most NIA-supported research on women's health aligns closely with the NIH Strategic Plan for Research on Women's Health. For example, the Study of Women's Health across the Nation (SWAN), NIA's long-running multi-ethnic study of health around the menopausal transition, reflects Goal 3.1, *Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan*, as well as 3.9, *Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions*. The NIA Interventions Testing Program, in which compounds hypothesized to extend lifespan and health span are tested in male and female mice, exemplifies the Institute's commitment to Goal 1.4, *Include sex parameters in the design*

of experiments using animal models. And NIA's leadership within the NIH Women of Color (WOC) Committee of the trans-NIH Working Group on Women in Biomedical Careers has been instrumental to NIH's important work toward Goal 6, *Employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce*, in its entirety.

A Women's Health Liaison in the Office of Planning, Analysis, and Evaluation coordinates communication and reporting on NIA activities related to women's health and serves as liaison to the NIH Coordinating Committee on Research on Women's Health. Recent accomplishments in women's health, as well as ongoing and new research initiatives with a particular emphasis on women, are described below.

III. Accomplishments and Activities

Alzheimer's Disease and Related Forms of Dementia

Alzheimer's disease is the most common cause of dementia among people ages 65 and older, and it is a major public health issue for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. As many as 5.5 million people ages 65 and older in the United States are affected by Alzheimer's disease. Many more under age 65 are also affected. In addition, many thousands more have Alzheimer's disease-related dementias. Scientists agree that unless it can be effectively treated or prevented, the numbers will increase significantly if current population trends continue (Hebert et al., 2013).

The prevalence of Alzheimer's disease is significantly higher among women than among men. Recent estimates suggest that nearly two thirds of individuals diagnosed with the disease are female (Hebert et al., 2013), perhaps because women, on average, live longer than men. At the same time, most studies conducted in the United States have not observed sex differences in the incidence of Alzheimer's disease—that is, in the rate of developing the disease. However, several American studies, and most European and Asian studies on the subject, have shown a higher incidence of Alzheimer's disease among women after around age 80 (Mielke et al., 2014). The potential reasons for this are complex and may include differences in brain structure; differential effects of the APOE ε4 genotype, the most common genetic risk factor for late-onset disease (although this is being challenged; see Neu 2017 below); differences in education between men and women in the age cohorts currently at greatest risk (Mielke et al., 2014; Rocca et al., 2014); and effects of sex steroid hormones on the brain (Pike 2018).

NIA-supported investigators continue to study the mechanisms through which estrogen and related hormones work on the brain, as well as the effects of different forms of menopausal hormone therapy (MHT) on cognition. Initiatives exploring the effects of age-related hormone changes and MHT on the brain include:

- **The Women's Health Initiative Memory (WHIMS) Suite of Studies.** NIA intramural researchers conduct and manage the WHIMS suite of studies, which assess the effects of MHT on memory, cognition, and mood in participants ages 65 and older, without dementia, who had been randomized to hormone therapy or placebo within the original WHI trial.
- **Perimenopause in Brain Aging and Alzheimer's Disease.** The goal of this large, long-running Program Project, which was renewed in FY 2016, is to determine how the brain changes during the perimenopausal transition and how these changes can lead to development of early risk factors for developing Alzheimer's disease.

- **Estrogen and the Aging Brain at Midlife: The "Window of Opportunity" Hypothesis.** Administration of estrogens begun during a critical window near menopause is hypothesized to prevent or delay age-related cognitive decline and Alzheimer's disease and related dementias. However, due to potential health risks, women often limit use of estrogen therapy to a few years to treat menopausal symptoms. The long-term consequences for the brain, cognitive aging, and risk of dementia of short-term use of estrogens are unknown. NIA-supported investigators are currently using rodent models to determine the mechanism by which short-term use of estrogens near menopause could exert lasting benefits to women's cognitive health.
- **Endocrine Disruption and Risk of Alzheimer's Disease.** An NIA-supported Specialized Center of Research Excellence (SCORE) uses both humans and mice to establish the long-term hormonal effects of bilateral salpingo-oophorectomy (BSO), or surgical removal of the ovaries and fallopian tubes, which often takes place during a hysterectomy in order to decrease the risk of pathology and the need for future procedures and may be done to prevent breast and ovarian cancer in women at strong genetic risk. This research will enable us to develop a more complete understanding of the biological mechanisms involved, and to devise a targeted approach to identify and mitigate the adverse outcomes.

Advances

Hormone Therapy and Cognitive Health. Researchers with the NIA-supported Kronos Early Estrogen Prevention Study (KEEPS) found that use of menopausal hormone therapy was associated with a modest sustained increase middle cerebral artery velocity—a measure of cerebrovascular health—measured three years after cessation of hormone treatment. Additional studies are needed to explore mechanisms that may lead to the age-dependent responses to MHT, and to incorporate new interventions that improve and maintain cerebral blood flow regulation in women after menopause. (Barnes 2019) Elsewhere, investigators with the Early versus Late Intervention Trial with Estradiol (ELITE) found that hormone therapy may protect certain types of cognition in the presence of stress in postmenopausal women. Such estrogenic protection against stress hormone exposure may prove beneficial to both cognition and the neural circuitry that maintains and propagates cognitive faculties. (Herrera 2017) Finally, NIA-supported investigators found that in a rat model, rats who were ovariectomized at midlife and then given estradiol demonstrated cognitive benefits that persisted even after the treatment ended, suggesting that previous ongoing estradiol exposure, rather than cyclical, endogenous exposure, is necessary to enhance cognition long after termination of hormone exposure. (Black 2018)

Genotype and Sex Risk Factors for Alzheimer's Disease. Although the ε4 allele of the APOE gene is the main genetic risk factor for Alzheimer's disease (AD), the prevalent view among scientists has been that the presence of the ε4 allele affects women more strongly—that is, women who carry one or two copies of the allele have a greater risk of developing AD than men with the same number of copies. In a meta-analysis of 27 research studies in the Global Alzheimer's Association Interactive Network, NIA-supported investigators found that men and women with the APOE ε3/ε4 genotype have nearly the same odds of developing AD from age 55 to 85 years, but women have an increased risk at younger ages (e.g., between 55 and 70 years). Individuals with APOE ε4/ε4 showed increased risks versus individuals with ε3/ε4, as expected, but investigators saw no significant differences between men and women with ε4/ε4. (Neu 2017)

Sex Mediates the Association between Alzheimer's Biomarkers and Cognitive Decline. Alzheimer's disease is characterized by the presence of two pathological biomarkers—beta-amyloid and tau—in the brain and cerebrospinal fluid. Investigators used data from the NIA-supported Alzheimer's Disease Neuroimaging Initiative (ADNI) to correlate results of cognitive testing with tau and amyloid burden and atrophy of the hippocampus, a brain region important to learning and memory. Female sex was associated with greater hippocampal atrophy and longitudinal cognitive decline in the presence of enhanced AD biomarkers. The sex difference was particularly pronounced in women with low education and appeared to vary by *APOE* genotype. These results suggest that women may be more susceptible to the downstream effects of the AD neuropathological cascade. (Koran 2017) Elsewhere, investigators found that elevated vascular risk may influence tau burden when coupled with high beta-amyloid burden. These results suggest a potential link between vascular risk and tau pathology in preclinical AD—particularly among women, in whom the association was stronger overall. (Rabin 2018)

Sex Differences in the Neuropsychiatric Symptoms of Patients with Alzheimer's Disease. NIA-supported investigators analyzed data from a recent clinical trial of the antidepressant citalopram for the treatment of Alzheimer's-related agitation. They found that patients with AD with agitation were likely to exhibit other neuropsychiatric symptoms; also, women were more likely to exhibit a broader range of neuropsychiatric symptoms than men. These results suggest that the disease's clinical presentation may differ between men and women, and that potential treatment targets differ between the sexes. (Tao 2018)

Women's Aging and Health: Findings from the Study of Women's Health Across the Nation (SWAN)

NIA's flagship study of women's health is SWAN, an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from pre- to post menopause. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the pre- to peri- to postmenopausal transition in Caucasian, African-American, Chinese, Japanese, and Hispanic women. Initially funded in 1994, SWAN is a cooperative agreement consisting of seven clinical field sites, a central reproductive hormone laboratory, a coordinating center, an advisory panel, and a repository of blood, urine, and DNA specimens. The study is supported by NIA, the National Institute of Nursing Research, and the NIH Office of Research on Women's Health.

Findings from SWAN have greatly enhanced our understanding of women's health across the menopausal transition. For example, remarkably little is known about women's hormonal trajectory as they approach the final menstrual period (FMP). To characterize hormonal patterns in women approaching the menopause, SWAN investigators collected daily urine for one entire menstrual cycle or up to 50 days, whichever came first, annually, up to FMP or for up to 10 years in over 500 women. They determined that menstrual cycle hormone patterns in perimenopausal women resemble those of mid-reproductive-aged women until around five years before menopause. In addition, hormone patterns resembling those of women of peak fertility, though rare, can occur up to the very end of reproductive life in women, suggesting that women and their doctors should not minimize fertility or pregnancy risk until menopause is definitely established to have occurred (Santoro 2017).

Selected findings from SWAN in 2017–2018 include:

Bone Health. Investigators measured bone mineral density (BMD) among SWAN participants who were new users of acetaminophen, non-steroidal anti-inflammatory drugs, or opioids, and found that although the BMD decline over time was similar among the groups, five years of continuous opioid use may be associated with a greater BMD decline than five years on other analgesics. Further studies are needed to examine the relationship between very long-term, persistent opioid use and BMD. (Yoshida 2017)

Cardiovascular Disease. SWAN investigators found that a history of preterm birth (PTB) was associated with higher maternal blood pressure and mean arterial pressure in late midlife (average age was 60). PTB and other adverse birth outcomes (e.g., small for gestational age, stillbirth) were not associated with other forms of subclinical vascular disease outcomes among non-hypertensive women. (Cortes 2017) Elsewhere, SWAN investigators found that increased volume of fat around the heart was associated with coronary artery calcification in postmenopausal but not premenopausal women. Estradiol and hormone therapy appeared to attenuate these differences. (El Khoudary 2017) Finally, investigators reported that women who have a healthy lifestyle—avoiding smoking, following a healthy diet, and engaging in regular physical activity—during the menopausal transition have lower levels of subclinical atherosclerosis later in their life. These findings underscore the growing recognition of midlife as a critical window for prevention of cardiovascular disease in women. (Wang 2018)

Mental Health. Small clinical studies suggest depression is associated with alterations in adiponectin and leptin, adipocyte-derived secretory proteins involved in metabolic regulation; however, longitudinal data on these association are lacking. SWAN investigators found that in middle-aged women (mean age 45.6), depressive symptoms and history of major depressive disorder were unrelated to leptin. In women at midlife, depressive symptoms are associated with lower adiponectin, a critical anti-inflammatory biomarker involved in metabolic and cardiovascular conditions. (Everson-Rose 2018) Elsewhere, investigators analyzed the potential correlation between lifetime exposure to estrogen and depressive symptoms around and after the menopausal transition. They found that longer exposure to estrogen (e.g., a longer interval between the first menstrual period and the menopausal transition), including longer exposure to birth control pills, appeared to protect against development of depressive symptoms around and immediately after menopause. (Marsh 2017)

Physical Functioning in Older Age. SWAN investigators identified five distinct trajectories of physical activity in middle age (42-52 years): lowest, middle, and highest steady-state, as well as increasing and decreasing. They found that women in the middle and highest physical activity groups demonstrated better physical functioning than other women 15-17 years after baseline. (Gabriel 2017) Elsewhere, investigators found that visual impairment (defined as visual acuity worse than 20/40) correlates with reduced physical functioning in middle-aged women (ages 42-56). Routine eye testing and vision correction may help improve physical functioning in this population. (Chandrasekaran 2017)

Bone Health and Beyond: The Study of Osteoporotic Fractures (SOF)

The Study of Osteoporotic Fractures (SOF), the largest and best-characterized cohort of women in the 9th and 10th decades of life, used 22 years of repeated measurements to define age-related trajectories of cognitive, physical, and psychosocial parameters including cognitive function, physical performance, and bone mineral density. SOF also used Medicare claims data to examine whether trajectories within these parameters are associated with “optimal aging” as defined by longevity, active lifespan, exceptional

health span, and lower rates of inpatient and residential health care utilization. Findings published from this groundbreaking study in 2017-2018 include:

- Measures of mobility and cognition are associated with maintenance of independence and risks of hospitalization and mortality among late life women even after accounting for each other and other conventional predictors, suggesting that additive effects of reduced mobility and poorer cognition may be important to consider in medical decision making and health care policy planning for the growing population of adults aged 85 years and older. (Diem, 2018; Ensrud 2017)
- Older women with recent weight loss and those with sleep disturbances have higher subsequent health care utilization in large part due to greater burden of medical conditions and impairments in function among women with these conditions. (Schousboe 2018, Paudel 2017)
- Slow gait speed is associated with greater health care utilization in older women. (Cawthon 2017)
- Cumulative burden of depressive symptoms over nearly two decades was strongly associated with future likelihood of transitioning from community living to residence in a nursing home. (Byers 2018)
- Measurements of cognition, body weight and mobility and trajectories of these measures over time are important to consider when predicting risk of adverse outcomes in older adults including mortality, hip fracture, and dementia. (LeBlanc 2017; LeBlanc 2018)

Other Activities

Novel Treatments for Menopausal Symptoms: The MsFLASH Network. NIA continues to support the Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) Network, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition. MsFLASH investigators are currently conducting a large multicenter trial comparing two common treatments, a vaginal hormone pill and an over-the-counter gel, with placebo to evaluate their effects on bothersome vaginal symptoms and sexual function, and at the same time creating a biorepository of specimens for future research on the etiology of vaginal symptoms. As part of their project, the investigators are developing a set of comprehensive, evidence-based, user friendly and widely available multi-media materials to reach women and providers with the newest trial results evaluating the effectiveness of treatments ranging from hormones to complementary and alternative therapies to behavioral interventions for relief of hot flashes, vaginal, sleep, mood, and pain symptoms.

The Interventions Testing Program (ITP). This ongoing program, which began in 2003, supports testing of compounds with the potential to extend the lifespan and delay disease and dysfunction in a genetically heterogeneous mouse model of aging. Many interventions, including foods, diets, drugs, and hormones, are tested through the ITP. A key aspect of this program is that every compound is tested in both male and female animals. Six compounds have shown significant extension of median lifespan in animal studies, most in a sex-specific manner: aspirin, rapamycin, 17alpha-estradiol, acarbose, nordihydroguaiaretic acid, and Protandim©. In 2018, NIA expanded the program via two funding opportunity announcements under the SBIR/STTR program to support research and development of commercial pharmaceutical interventions that extend lifespan and/or health span, to prevent, treat, and/or slow the progression of symptoms associated with Alzheimer's disease or related forms of dementia in human cells and/or tissue, in-vitro models, and/or non-human animals.

Interventions may include, but are not limited to, those already studied in the ITP.

NIA Biobank Facilitates Research on Women's Health. In 2018, NIA established the Aging Research Biobank, a central biorepository to provide a state-of-the-art inventory system for the storage and distribution of specimen collections to the broader scientific community. The Biobank will accelerate science to help extend the healthy, active years of life for the world's fast-growing population of older adults. Currently, SWAN biospecimens and data collections are part of the biorepository and are available for sharing.

Other Advances

Genetic Variants Associated with Early Menopause Increase Risk of Cardiovascular Events in Women. Early menopause is associated with increased cardiovascular disease risk. However, the cause of this association is poorly understood. Previously, researchers have identified 56 alleles associated with lower age at natural menopause. NIA-supported investigators analyzed the correlation between presence of these alleles and age at first cardiac event in women, as well as in men who carried the same alleles. They found that genetic variants associated with earlier age-at-natural menopause are associated with increased cardiovascular disease risk in women, but not men, suggesting sex-specific genetic effects on cardiovascular disease risk. (Sarnowski 2018)

Group Class Reduces Urinary Incontinence Symptoms in Women. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that approximately half of women in the United States experience urinary incontinence (UI), which often impairs social, psychological, and physical well-being. NIA-supported investigators recently found that a two-hour group class at which women learned about bladder anatomy and function, types and causes of UI, bladder training, and behavioral strategies for bladder control was modestly effective in reducing frequency and severity of UI symptoms and improving quality of life as compared with a control group. Furthermore, the incremental cost per treatment success was less for the intervention group compared with the control group. This noninvasive, cost-effective intervention can be implemented in nonmedical settings and may offer a first-line approach that women can try before progressing to more intensive treatments. (Diokno 2018)

Elimination of Cost-Sharing Increases Screening Mammography Rates. An extensive body of evidence has shown that cost sharing — requiring people to pay for health care in the form of a deductible, copayment, or other out-of-pocket expense — reduces the use of health services, including lifesaving screening and prevention services. NIA-supported investigators used Medicare Advantage (MA) data to examine whether the elimination of cost-sharing for biennial screening mammography, as required under the 2010 Patient Protection and Affordable Care Act (ACA), increased screening rates in women aged 65 to 74. They found that the elimination of cost sharing for screening mammography under the ACA was associated with an increase in mammography rates among older women for whom screening is recommended. However, the increase was less pronounced among women living in areas with lower educational attainment. In addition, although mammography rates among Black and White women increased 8.4 and 6.5 percentage points, respectively, they remained essentially unchanged among Hispanic women. While this research shows the potential for increasing the use of preventive care, it also highlights the need for other levers to improve preventive care use. (Trivedi 2018)

IV. Sex and Gender Analyses

Sex is evaluated as a biological variable in NIA-supported research consistent with NIH policy.

Ongoing NIA-supported research specifically designed to identify and elucidate sex and gender differences in aging and age-related disease and dysfunction includes:

- Four Specialized Centers of Research Excellence (SCOREs) on Sex Differences, including Centers that explore sex difference in the context of Alzheimer's disease, influenza, and HIV infection.
- Studies of sex-specific genetic drivers of risk of and resilience to Alzheimer's disease.
- **A large program project grant that innovatively combines** informative animal models, high-quality human data, and sophisticated demographic analyses to generate a deeper understanding of the basis for sex differences in health and survival, as well as opportunities to reduce these differences.
- The Interventions Testing Program, which supports the testing of compounds with the potential to extend the lifespan and delay disease and dysfunction in a genetically heterogeneous mouse model of aging. All interventions are tested in both male and female animals, and sex differences in responses to several compounds have been identified.

V. Research on Health Disparities

Demographic projections predict a substantial change in the racial and ethnic makeup of the older population, heightening the need to examine and reduce differences in health and life expectancy. NIA is committed to addressing health disparities, with many initiatives supported in partnership with the National Institute on Minority Health and Health Disparities. Minority aging research is conducted throughout NIA's programs, and much of this research has relevance to the health needs of minority women, including the following current programs and projects:

- SWAN, which explores a number of health parameters among Caucasian, African-American, Chinese, Japanese, and Hispanic women.
- The MsFLASH initiative has successfully recruited sufficient numbers of African-American women to gather baseline data to analyze for differences by race and ethnicity in perimenopause/menopause characteristics.
- The Healthy Aging in Neighborhoods of Diversity across the Life Span study, a community-based research effort designed to focus on evaluating health disparities in minority and socioeconomically diverse populations.

Inclusion Efforts. NIA was instrumental in the development of the new NIH Inclusion Across the Life Span policy, which mandates that all applications for NIH-funded clinical studies received after January 25, 2019 include research participants across the lifespan, including children and older adults (unless there is a scientific justification to exclude them). The new policy also requires investigators to provide data on participant age at enrollment in progress reports. An NIA analysis that was foundational to the development of this policy was completed in 2018 on the number of older adults included as participants in NIH-funded phase III clinical trials between 1965 and 2015. The data reflect a disproportionate underrepresentation of older adults in these clinical studies due to the use of both explicit and implicit exclusion criteria. However, the authors suggest that outcomes of the trials may not be fully generalizable to the population of older adults. (Lockett 2019)

VI. Career Development

NIA actively encourages participation of women in its training and career development initiatives. The Institute supports a research study examining the barriers women face in careers in biomedical research in universities and research centers and also cofunds the University of Maryland Building Interdisciplinary Research Careers in Women's Health Program, which has a research emphasis on women and aging. The NIA Deputy Director also cochairs the NIH Women of Color (WOC) Committee of the trans-NIH Working Group on Women in Biomedical Careers. The WOC Committee sponsors the Women of Color Research Network LinkedIn site, which provides women of color and supporters of their advancement in the biomedical sciences information about the NIH grants process, advice on career development, and a forum for networking and sharing information.

VII. Communications and Education Initiatives

Many topics covered by NIA publications and online health information are of special interest to women. Recent communications activities include the following:

- Email, online, and social media outreach to promote NIA women's health research.
- NIA staff outreach to Federal and non-Federal organizations interested in caregiving and other women's issues.
- Development and distribution of evidence-based consumer publications on women's health topics, including the new tip sheet *Menopause: Treatments for Symptoms*.
- A feature article on menopause treatments for *Medline Plus* magazine (Winter 2017).
- Support for the Women of Color Research Network.
- Support for the U.S. Food and Drug Administration's Office of Women's Health Diverse Women in Clinical Trials campaign.
- Development and implementation of a national recruitment strategy for Alzheimer's disease and related dementias clinical studies.

Funding Initiatives, Workshops, and Conferences (2017-2018)

- **PAR 17-033: Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of Alzheimer's Disease Risk and Responsiveness to Treatment solicits research** to increase our understanding of the impact of sex differences on the trajectories of brain aging and phenotypes of Alzheimer's disease risk and on the responsiveness to pharmacologic and nonpharmacologic interventions. Six awards have been made to date under this FOA.
- **National Research Summit on Care, Services, and Supports for Persons with Dementia and their Caregivers – October 16-18, 2017.** This meeting focused on research that is needed to improve quality of care and outcomes across care settings, including quality of life and the lived experience of persons with dementia and their caregivers. Because a majority of both paid and informal caregivers are women, the Summit had special relevance to women's health.
- **Cellular and Molecular Aging of the Reproductive System – September 10-11, 2018. NIA's Division of Aging Biology h**eld this exploratory workshop to discuss cellular and molecular mechanisms that preserve function in organs of the male and female reproductive system that are critical to ensure healthy aging and prevent oncogenesis.

- **Organization for the Study of Sex Differences Annual Meetings. NIA provided partial support for the Organization for the Study of Sex Differences in 2017 and 2018 through an R13 grant. Of particular interest to NIA was the 2017 meeting entitled "Sex Differences Across the Lifespan," with a particular focus of the effect of sex on age-related diseases.**

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National Institute on Alcohol Abuse and Alcoholism (NIAAA)

I. Executive Summary

The mission of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is to generate and disseminate fundamental knowledge about the effects of alcohol on health and well-being and apply that knowledge to improve the diagnosis, prevention, and treatment of alcohol-related problems, including alcohol use disorder (AUD), across the lifespan.

NIAAA provides leadership in the national effort to reduce alcohol-related problems by:

- Conducting and supporting alcohol-related research in a wide range of scientific areas, including genetics, neuroscience, epidemiology, prevention, and treatment.
- Coordinating and collaborating with other research institutes and Federal programs on alcohol-related issues.
- Collaborating with international, national, state, and local institutions, organizations, agencies, and programs engaged in alcohol-related work.
- Translating and disseminating research findings to health care providers, researchers, policymakers, and the public.

Alcohol misuse refers to drinking in a manner, situation, amount, or frequency that could cause harm to an individual or those around them. It contributes to poor performance at school and work, family trouble, unprotected sex and sexually transmitted diseases, violence, memory blackouts, unintentional injuries, accidents, overdoses, and organ damage and disease. It also can lead to AUD, a serious condition that affects nearly 16 million people in the United States. The Centers for Disease Control and Prevention estimates that alcohol misuse costs the United States $249 billion per year due to health care expenses, lost workplace productivity, crime, property damage, and other adverse outcomes. An estimated 88,000 people (approximately 62,000 men and 26,000 women) die from alcohol-related causes annually, making alcohol the fourth leading preventable cause of death in the United States.

Studies indicate that women drink less often and less heavily than men but that the gaps have narrowed considerably. Among adults, alcohol use, including binge drinking, increased more steeply for women than men over the last few decades. Among adolescents, alcohol use declined but the decreases were bigger for males than females. As a result of these changes, once large differences in alcohol use and related harms between males and females are disappearing. These narrowing gender gaps in consumption are occurring amidst growing evidence that women are more susceptible than men to some of the physiological effects of alcohol, achieve higher blood alcohol concentrations, have a higher risk for the development of alcohol-related diseases, and show a higher vulnerability to alcohol use disorder.

NIAAA-funded preclinical studies in animal models have begun to reveal the mechanisms underlying sex/gender differences in drinking behaviors and related problems. In the past two fiscal years, scientific areas related to Goal 1 and Goal 2 of the NIH Strategic Plan for Women's Health Research have benefited from significant advances in knowledge.

NIAAA also maintains a strong program of research that examines how the presence of other medical conditions, along with environmental and social factors, can lead to different patterns of alcohol abuse and health vulnerabilities in girls and women throughout their lives. Scientists now recognize that human biology and behavior continue to change throughout life, which, in turn, affects individuals' drinking patterns and their decisions to alter drinking habits or to seek help for alcohol use problems. A lifespan perspective will allow researchers to identify how the emergence and progression of drinking behavior is influenced by changes in biology, psychology, and exposure to social and environmental inputs over a person's lifetime, and vice versa. This approach will help discover life-stage-appropriate strategies for developing individualized prevention and treatment programs for girls and women that fulfill Strategic Plan Goal 3.

This report highlights NIAAA's recent activities and accomplishments in biomedical and behavioral research related to women's health. The accomplishments fall into 10 research categories: (1) consortia; (2) prevention and treatment for women; (3) comorbidity of AUD and other psychiatric disorders; (4) alcohol, aggression, and violence; (5) precision medicine and novel therapy; (6) fetal alcohol exposure; (7) sex differences in basic research; (8) sleep; (9) women, alcohol use, and cardiac health; and (10) women, alcohol use, and HIV.

II. Accomplishments and Activities

Consortia

Adolescent Brain Cognitive Development (ABCD) Study (Objectives 1.8, 2.6 and 3.1). The ABCD Study is a nation-wide research consortium to investigate adolescent brain and behavior development and the effects of substance use on the normal developmental trajectory. The ABCD Study includes 21 research project sites and is funded by several NIH ICs including NIAAA. Starting at ages 9-10, over 10,000+ participants (males and females) are being studied in a longitudinal design into early adulthood on a variety of brain imaging, behavior/cognitive, and social and clinical measures. As of November, 2018, the ABCD study, successfully completed its baseline enrollment of 11,874 9 to 10-year-old participants and has begun follow-up assessments for the longitudinal study. The impact of sex and gender differences on the measures acquired will be evaluated at both the research project site and consortium-wide levels. The data acquired by the ABCD Study is made publicly available through the NIMH Data Archive.

National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) (Objectives 1.8, 2.6 and 3.1). NCANDA is a nation-wide effort to determine the effects of alcohol exposure on the developmental trajectory of the human adolescent brain, and to identify neurobehavioral vulnerabilities that may place an adolescent at risk for the subsequent development of alcohol use disorders. A community sample of 831 adolescents were enrolled in NCANDA and are now being followed in the cross sectional longitudinal design. The effect of sex and gender differences on the neuroimaging and behavioral/clinical measures acquired are being evaluated.

Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) (Objectives 3.1 and 3.3). Ongoing research within this consortium comprises multiple international sites with high incidence of FAS and FASD. Among the several projects that make up this consortium, work continues with a longitudinal cohort of moderate to heavy drinking women and controls in the Ukraine to help develop a panel of biomarkers along with a clinical prediction tool to improve the clinical case recognition of infants with FASD. Additional studies will evaluate the physical and mental health status of adults with FASD. Subsets of individuals will also undergo whole exome

sequencing to identify genetic factors that are associated with risk or resiliency for having a child with FASD. In addition, some consortium members are developing animal models of FAS and FASD with aims of clarifying mechanisms, improving diagnostic methods, and identifying genetic and molecular markers of these disorders. The long-term goals of this research consortium are to refine the diagnostic criteria for FAS/FASD, explore the underlying mechanisms of the disorder, and develop therapeutic interventions to provide relief to those affected with the most debilitating features of the disease (Chambers, U01 AA014835; Foroud, U01 AA026103; Mattson-Weller, U01 AA014834; Coles, U01 AA026108; Parnell, U01 AA021651).

Prevention and Treatment for Women

Age, Period, and Cohort Effects on Gender Differences in Alcohol Use and Alcohol Use Disorders in 47 National, Longitudinally-Followed Cohorts (Objective 1.8). Gender differences in alcohol consumption are changing in the U.S. Adolescent girls are now more likely to initiate alcohol consumption and binge drinking than boys. Existing evidence points to cohort effects on gender differences in alcohol consumption as well, but available data are not sufficient for public health action. First, there is insufficient information on whether changing gender differences are affecting all age groups or are particularly salient for specific developmental time periods, or what future public health burden will result from inaction. Second there are almost no data on why gender differences are converging. However, this project, a secondary analysis of data collected on 47 longitudinal cohorts, will provide evidence on when historically and developmentally gender convergences have occurred. It will also forecast future trends based on that evidence (Keyes, R01 AA026861).

Outcomes of Recurrent DUI-Moms and Their Children (Objective 1.8). This is a study of the intergenerational transmission of problems related to alcohol use. A good source of subjects with severe alcohol use disorders is the pool of women whose records show multiple convictions for Driving Under the Influence (DUI). The investigators have access to the administrative date on DUIs that can be matched with longitudinal data gathered on a cohort of women and their adolescent children (collected in earlier studies by the investigators). By combining these data sources, the investigators aim to examine the course of alcohol use disorders among the mothers over time and to determine whether this is associated with differences among their 15 year old children in early drinking, early tobacco and drug use, early sexual experience, and childhood trauma (Bucholz, R21 AA025420).

Sex Differences in the Response to Abstinence from Alcohol (Objectives 1.5 and 1.8). This study is designed to investigate the post-abstinence response to alcohol in men and women. Previous research from these investigators found that after a period of abstinence women would work harder for alcohol than men in a progressive-ratio paradigm. Following a two-week monitored abstinence period, sex differences in free-access alcohol self-administration and changes in alcohol elimination rates will be studied. Differences in the post-abstinence response to alcohol may help to provide an explanation why some women progress faster to the onset of an alcohol use disorder than men (Plawecki & Cyders, R01 AA027236).

Neurobiological Factors Underlying Sex Differences in Risk for Alcohol Abuse (Objective 1.5). This career development award addresses neural and hormonal differences between sexes that contribute to the differential risk for alcohol-related problems. The focus of the research project is on the role of ovarian hormones during response inhibition, a behavior strongly linked to alcohol use disorder. An innovative aspect of the application is the combined emphasis on both hormonal and neural

factors that may contribute to the differential response of males and females. Findings from this study should help in understanding how deficits in inhibitory control affect women differently than men in response to drinking (Weafer, K01 AA024519).

Alcoholics Anonymous (AA) Linkage for Alcohol Abusing Women Leaving Jail (Objective 2.5). This research group has found that those who attend weekly AA, there is an association with improvements in alcohol use and alcohol-related consequences post-incarceration. Because regular AA attendance is associated with improvements in alcohol-related consequences, investigators in this study will conduct a randomized clinical trial (n=400) evaluating the effectiveness of an innovative method to enhance the linkage between jailed alcohol abusing women who are returning to the community and AA resources. AA meetings are widely available and free which enhances post-incarcerated women to attend AA. Therefore, AA meetings are a cost-effective way to reach the vulnerable population which may dramatically impact the care of post-incarcerated women nationwide (Stein, R01 AA021732).

Comorbidity: AUD and Other Psychiatric Disorders

A Controlled Test of Interpersonal Rejection, Social Anxiety, and Alcohol Use Among Female Adolescents (Objective 1.5). This study is designed to understand the causal relationships between social anxiety, rejection, and alcohol use among teenage girls. The central hypothesis of the study is that acute social rejection, a common social stress factor for female adolescents, elicits greater sensitivity to alcohol-related cues and a desire to drink. The proposed research on alcohol use in teenage girls (for this project: age 14-17) is vastly understudied. It is expected that this project will provide evidence regarding the role of social anxiety in problematic alcohol use among female adolescents and help establish coping strategies as a key intervention target in reducing risky drinking among socially anxious girls (Blumenthal, R15 AA026079).

Developing a Brief Early Cognitive Intervention for PTSD and Alcohol Misuse (Objective 2.5). Sexual assault is a substantial problem in the US and leads to devastating health consequences and public health costs. Intervening early after sexual assault may help decrease the development of chronic psychopathology, particularly PTSD and alcohol misuse. The purpose of this study is to develop and evaluate an intervention for victims of sexual assault based on empirically supported cognitive treatment principles for both PTSD and AUD symptoms to be delivered in a brief one session format in the 6 weeks following sexual assault. The brief intervention group will be compared to a group of women who receive weekly symptom monitoring only to provide information on the efficacy of the intervention compared to the natural recovery process (Bedard-Gilligan, R34 AA022966).

Alcohol, Aggression and Violence

A Multi-component Alcohol and Sex Risk Intervention for College Students (Objective 1.8). Risky alcohol use, sexually transmitted infections, and sexual violence constitute highly prevalent and interrelated public health concerns in the lives of college students. College women are particularly vulnerable, with 18% reporting sexual victimization over a two-year period. This project is designed to test a tri-pronged sex-positive intervention involving: normative re-education to modify peer misperceptions, protective behavioral skills training to increase drinking-related and sexual-risk protective behaviors, and bystander intervention training to reduce alcohol problems and sexual violence (Napper, R34 AA026032).

Integrating Alcohol Myopia and Objectification to Understand Sexual Assault (Objective 1.8). The goal of this project is to identify the processes that occur between

potential perpetrators and victims following intoxication. Two complimentary sub-studies are being conducted. The first is designed to evaluate a novel, process-oriented model that addresses when, why, and for whom alcohol-involved sexual assault occurs. The second sub-study is designed to examine the reduced attentional capacity resulting from intoxication that increases self-objectification in women, putting them at greater risk for victimization. By integrating both approaches, the work will advance our knowledge of how key dispositional risk factors interact with hypothesized mechanisms of sexual and self-objectification to increase risk for sexual assault (Gervais, R01 AA025090).

Alcohol Involved Sexual Assault Risk in the Routines of Daily Life: A Social Goal Perspective (Objective 1.8). This study will use a longitudinal community sample of young adult women first recruited at ages 11-12 (Colder & Read, R01 DA020171). Short term (collected weekly) data will examine how interpersonal goal orientations in young adulthood contribute dynamically to engagement in routine activities that carry risk for sexual assault and in protective behaviors that reduce such risk. Using previously collected data from the subjects, a longer-term analysis will examine how the development of interpersonal goals across adolescence may portend engagement in risky activities or in protective behaviors in young adulthood, and how individual (self-regulation) and environmental (peer affiliation) factors may moderate this developmental pathway. Finally, an analysis that combines the short term and long-term data will examine reciprocal processes between risk activities and interpersonal goals and whether these reciprocal pathways are moderated by earlier adolescent interpersonal goal development (Read, R01 AA026105).

Precision Medicine and Novel Therapy

Sex-appropriate Treatment Development for Alcohol Use Disorders (Objective 1.5). This program project is designed to evaluate the role of the noradrenergic system to target sex-dependent factors known to maintain alcohol use in women (including stress reactivity and associated neurodegeneration) versus men (alcohol-related positive reinforcement). It also will evaluate guanfacine as a prototypical medication to preferentially target these sex-dependent factors to improve AUD treatment outcomes (McKee, P01 AA027473-06).

Positron Emission Tomography (PET) Imaging of Naltrexone Occupancy of Kappa Receptors in Heavy Drinkers (Objectives 1.5 and 2.6). This grant is using PET to measure binding potential of kappa opioid receptors in the brain of men and women with and without abusive alcohol use. Kappa receptor occupancy is also measured during use of the opioid antagonist naltrexone for treatment of alcohol use disorder. A preliminary study recently published (Vijay et al., 2016; PMID: 27648372) was first to report a sex difference in the brain kappa opioid receptor system with men having higher receptor availability than women (Morris & Krishnan-Sarin, R01 AA021818).

Oxytocin to Enhance Alcohol Behavioral Couple Therapy (Objective 1.5). This study is designed to investigate if intranasal oxytocin administration can enhance the value of Alcohol Behavioral Couples Therapy (a structured cognitive-behavioral treatment program). The effectiveness of the combined treatments on reducing alcohol consumption, improving couple relationship functioning, and the neural response to alcohol and relationship conflict cues will be investigated (Flanagan, R01 AA027212-01).

Fetal Alcohol Exposure

Determination of Non-hormonal Effects of Sex Influence After Alcohol Exposure During Early Development (Objectives 1.1. and 1.5). This project is designed to test the hypothesis that sex is an important variable in mediating the effects of ethanol exposure on the CNS just after neural tube closure, an early stage

of CNS development. The project examines changes in DNA methylation in the telencephalon (primordial forebrain) of the developing neural tube because ethanol has been shown to alter DNA methylation and a wide literature supports sex-specific differences in DNA methylation. The ability to understand sex and sex-by-genotype differences in DNA methylation, particularly early in brain development, will likely improve our understanding of how sex differences in brain function occur and potentially identify molecular pathways that mediate this difference (Hamre & Goldowitz, R01 AA023508).

Sexually Dimorphic Effects of Maternal Ethanol Exposure on Melanin-concentrating Hormone (MCH) and Behavior in Adolescent Offspring (Objective 1.5). The effects of prenatal alcohol exposure and role of neuroimmune systems are unknown *in utero*, during exposure, and afterwards during the adolescent and adult stages. A specific population of neurons in the rodent lateral hypothalamus expresses an inflammatory chemokine ligand and the orexigenic neuropeptide MCH, that promotes drinking behavior. Maternal ethanol consumption increases the density of these neurons and in the adolescent stimulates ethanol drinking and anxiety. The anatomical and behavioral changes are sexually dimorphic and consistently stronger in females. The results will help to explain the underlying cellular mechanisms that mediate the effects of prenatal alcohol exposure on adolescent behavior and the higher level of risk factors reported in women (Chang et al., 2018; PMID:30201767; Barson & Leibowitz, 2017; PMID:29056152) (Leibowitz, R01AA024798).

Undernutrition-Helminth-Alcohol Interactions, Placental Mechanisms, and FASD Risk (Objective 3.4). This consortium grant is in collaboration with international investigators at Research Institute for Tropical Medicine (RITM) in Manila, the Philippines. In the proposed studies, investigators will recruit 400 women at 10-16 weeks gestation residing in Leyte, the Philippines, a low/middle income country where 75% of subjects reported continued alcohol consumption at 12-16 weeks gestation. They will examine whether alcohol consumption during pregnancy exacerbates the risk of co-morbidities common among women in the Philippines (helminthiasis, undernutrition, and microbial translocation) resulting in an increased risk of fetal growth retardation and adverse infant outcomes. Given that prenatal deaths rank among the highest reason for mortality in low and middle income countries, findings from this study will be highly significant as they will inform prenatal interventions to reduce these risks (Friedman & Gundogan, U01 AA024092).

Assessing Stable Characteristics of Endocrine Function Among Boys and Girls with Prenatal Alcohol Exposure as a Novel Clinical Tool (Objective 3.1). This study is designed to investigate endocrine hormone dysregulation as an underlying mechanism for mental health outcomes in individuals with FASD. These studies build upon extensive animal work that prenatal alcohol exposure impacts the fetal programming of the developing endocrine system. The current project will leverage resources and data collected by two NIH-funded research programs: Adolescent Brain Cognitive Development (ABCD) study in the United States and the Prenatal Alcohol Sudden Infant Death Syndrome and Stillbirth (PASS) birth cohort in South Africa (Uban, K01 AA026889).

Sex Differences in Basic Research

Sex Hormones Render the Female Brain More Vulnerable to Binge Alcohol Damage via the Glucocorticoid System and Mediates Exercise-driven Repair (Objective 1.5). The overall objective of this study is to determine mechanisms underlying female brain susceptibility to alcohol damage and those underlying exercise-driven repair. The investigators hypothesize that early organizational effects of sex hormones, and not activational effects, contribute to female brain susceptibility to binge alcohol. In contrast,

the activational effects of stress hormones in the female hippocampus are hypothesized to mediate exercise-driven repair of binge alcohol damage. The findings from this study will identify mechanisms contributing to the susceptibility of female brain to binge alcohol utilizing a novel model and exercise-driven repair (Leasure, R01 AA025380).

Sex Differences in the Effects of AUD on Brain Circuitry Using Existing Data (Objectives 1.5 and 2.6). The main goal of the study is to apply a novel network-based neurobiological model of Theory of Mind (ToM) to investigate sex differences in functional and effective connectivity and the underlying structure of the default mode network (DMN) in AUD. As part of the objective, the study aims to provide insights into the nature of ToM-related brain circuit dysregulation in AUD and sex differences that may play a key role in alcohol misuse and AUD progression. The study will identify 140 matched-sample resting-state functional Mass Resonance Imaging (fMRI) data sets from the existing NIH Human Connectome Project (HCP) database and apply a new technique for analyzing brain network activation developed and implemented for functional connectivity analysis. The preliminary results showed significant sex differences of brain activation and functional connectivity in several brain regions including the anterior DMN (aDMN) and the dorsal attention network (DAN) (Nickerson, R21 AA024565).

Cerebral White Matter Sex Dimorphism in Alcoholism: A Diffusion Tensor Imaging Study (Objectives 1.5 and 2.6). This study is designed to investigate possible structural differences in white matter tracts in the brain of males and females with alcohol use disorder and unaffected male and female controls. The findings demonstrated that men with alcohol use disorder had lower fractional anisotropy (FA), a summary measure of white matter microstructural integrity, within three white matter tracts than unaffected male controls. The females with alcohol use disorder showed the reverse pattern from males in that they had higher FA values in the three tracts than unaffected female controls. These results suggest sex-related abnormalities in the white matter tracts that could be related to a history of alcohol abuse. Understanding what functions are negatively affected by alcohol and which functions are spared could lead to tailored interventions for alcohol use disorders that consider the important role that sex differences may play (Sawyer et al., 2018; PMID 29795404) (Oscar-Berman, R01 AA07112).

Adolescent Alcohol and Anxiety (Objectives 1.4 and 1.5). The focus of this project is to understand how interactions of sex, age, and alcohol drinking history may impact affective behaviors as consequences of excessive voluntary binge alcohol intake. Recent findings suggest that sex, prior stressor history, and prior binge-drinking history interact in complex ways in mice to impact sensitivity to alcohol's motor-stimulating, -coordinating and intoxicating effects, as well as to influence subsequent heavy drinking. Unpredictable, chronic, mild stress history potentiated subsequent binge-drinking in male mice; whereas a prior binge-drinking history increased subsequent ethanol intake in females only, irrespective of prior mild stress history (Quadir et al., 2017; PMID: 28803118) (Szumlinski, R01 AA024044).

Sleep

Sex Differences in Autonomic Nervous System Function and Depression Across Adolescence (Objective 1.5). The administrative supplement project recently funded by ORWH will investigate sex differences in the developmental trajectory of autonomic nervous system (ANS) function and the association with symptoms of depression during adolescence. Data come from a total of 150 adolescent boys and girls (12-21 years old) being followed longitudinally by the National Consortium on Alcohol and Neurodevelopment in Adolescence. The adolescent girls and boys participated in an

overnight sleep study where polysomnography recordings and ANS function (electrocardiograph recordings)) were measured during a prolonged period of sleep without waking-related confounds. The ANS controls many physiological functions and ANS alterations have been implicated in the development of depressive disorders. Understanding the developmental trajectory of ANS development in adolescent girls and boys may provide clues for a causal pathway for the higher incidence of vulnerability to depressive symptoms in girls (Baker, U01 AA021696).

Women, Alcohol Use, and Cardiac Health

Sex/Estrogen-Dependent Vulnerability to Alcohol-Evoked Cardiotoxicity: Role of Circadian Rhythm-Regulated Enzymes (Objectives 3.1 and 3.6). Moderate alcohol consumption provides a cardioprotective effect in men, but surprisingly may cause cardiotoxicity in women. The underlying mechanism of this phenomenon is not well understood. This study is designed to investigate the role of circadian effects and differences in alcohol effects on circadian balance downstream of the previously demonstrated modulation of estrogen receptor activity by alcohol. This investigation is clinically relevant in view of the rise in acute alcohol consumption especially by young women (Abdel-Rahman, R01 AA014441). A recent review by Abdel-Rahman reported that anatomical differences and the dampening effects of estrogen on systemic signaling systems contribute to greater toxicity in women of cardiovascular drugs (Abdel-Rahman, 2017; PMID: 28340373).

Women, Alcohol Use, and HIV

Reducing Alcohol-related HIV/STI Risk for Women in Reproductive Health Clinics (Objective 2.5). Alcohol use increases risk for HIV/STI acquisition, especially among young women. Investigators in this study will develop and pilot test an integrated alcohol and sexual risk reduction intervention for use in reproductive health and family planning (RHFP) settings where many young at-risk women can be found. This individually-delivered Brief Intervention (BI) will incorporate proven strategies (e.g., personalized feedback, normative comparisons, goal setting) to promote alcohol and sexual risk reduction. It will also include novel components that address sexual behavior as both a cause and consequence of alcohol intoxication, and that address partner type as a contextual determinant of both alcohol use and sexual risk behavior. The investigators will also develop a user-friendly website to enhance behavioral skills development and maintenance of initial intervention gains. They are planning a fully-powered, R01-supported, randomized controlled trial to test the longer-term effects of the integrated alcohol and sexual risk reduction intervention (Carey, R34 AA023158).

Using Community Based Participatory Research to Engage Hazardous Drinking Women in the HIV Prevention and Care Continuum (Objectives 2.5, 4.3 and 4.4). This team has demonstrated a strong association between alcohol misuse and HIV risk behaviors among at risk and women living with HIV (WLWH), poorer retention in HIV care and lower use of and adherence to antiretroviral therapy (ART). They have developed theory-based, in-person and computer-delivered brief interventions (CBI) for at risk and WLWH with alcohol misuse, demonstrating drinking reductions in recent randomized control trials. However, behavioral and structural barriers to optimal uptake of alcohol interventions and engagement in the HIV Prevention and Care Continuum remain. Working in partnership with community stakeholders, including at risk and WLWH, these investigators will determine how best to expand current alcohol interventions to address these barriers, and how to best implement alcohol interventions in the community. Among other activities, they will conduct a pilot trial to determine whether the addition of peer navigator support related to comorbid mental health and HIV prevention practices can enhance CBI and improve alcohol

and HIV prevention and care outcomes among women at risk and living with HIV/AIDS (Chander, U34 AA026220).

III. Health Disparities

Creating Support for Reservation-Based and Urban American Indian Alaska Native Families Dealing with FASD (Objectives 3.9, 5.1 and 5.2). *Healthy Native Nation* –This is an ongoing NIH/ Native American Research Centers for Health funded study initiated in 2014. Healthy Native Nation provided targeted support for individuals and families living with FASD by developing a model National Organization on Fetal Alcohol Syndrome (NOFAS) affiliate with one reservation-based location and one urban location. The research team described the modification of an existing web-based screening, brief intervention, and referral to treatment intervention to reduce risky drinking among American Indian Alaska Native (AIAN) women of childbearing age in Southern California into a peer-to-peer-based intervention using motivational interviewing. There are 566 federally recognized AIAN tribes across the United States of which 109 are in California (Montag et al., 2017; PMID: 28833270; Chambers, S06 GM106376/ U261IHS0081).

Preventing Alcohol Exposed Pregnancy among Urban Native Young Women: Mobile CHOICES (Objectives 3.3 and 5.2). Fetal alcohol spectrum disorders (FASD) result in neurodevelopmental deficits and lifelong disability; they are a leading cause of preventable birth defects in the U.S. American Indian and Alaska Native (AIAN) young women are especially vulnerable. The goal of this project is to expand the reach of services to urban AIAN young women through mHealth technology to prevent alcohol exposed pregnancy and FASD. Building upon a previous R21 project, the current efforts of the investigators use community-based participatory research methods to develop and test a motivational interviewing intervention designed to increase contraceptive use and decrease drinking among women at risk in an Ojibwe community (Kaufman, R01 AA025603).

Factors Responsible for Racial-Gender Disparities in Alcohol Services Use (Objective 3.9). Racial/ethnic minorities appear less likely than Whites to obtain any help for problem drinking, receive specialty alcohol treatment, or attend 12-step groups. Among those with AUD, women are less likely to obtain treatment, more likely to present with comorbid conditions, and remain in treatment for shorter durations than men. Furthermore, gender may exacerbate racial/ethnic disparities. Among men, Latinos are less likely, and Blacks are equally likely, to receive alcohol services as Whites; however, both Black and Latina women have approximately one-quarter the odds of obtaining alcohol services as White women. The purpose of this study is to extend current knowledge about the mechanisms responsible for racial/ethnic and gender disparities in access to alcohol services using longitudinal data obtained in the National Epidemiological Survey of Alcohol and Related Conditions (NESARC). By focusing on the combined effects of race/ethnicity and gender, the study will provide further information about sub-groups for whom risk of unmet alcohol treatment need is greatest and will help to identify the most efficient intervention points to increase the use of alcohol services (Gilbert, R21 AA023878).

IV. Science, Technology, Engineering, and Mathematics Efforts

Building Interdisciplinary Women's Health at Medical University of South Carolina (MUSC) (Objective 6.2). This grant is from the (MUSC is supported by the Building Interdisciplinary Research Careers in Women's Health (BIRCWH)) K12 Scholars Program. The overall objective of MUSC's BIRCWH program is to attract translational scientists in the neuroscience

arena to broaden interdisciplinary research related to women's health in South Carolina and throughout the U.S. This program reaches across professional and scientific boundaries to transform women's health outcomes by developing a cadre of highly trained early career scientists committed to interdisciplinary research to benefit the health of women, advance research on sex/gender influences on health, encourage interdisciplinary research methodology, and advance knowledge in the treatment of women's health issues related to brain and behavior across the lifespan (McGinty, K12 HD055885).

NIAAA-Supported Research: A Grantsmanship Workshop at Research Society on Alcoholism (RSA) (Objective 4.5). This workshop, organized by RSA Education Committee, provides young investigators with up-to-date information about NIAAA grant funding opportunities and the opportunity to participate in break-out sessions on select topics with NIAAA program staff and experienced investigators. The main goal of the workshop is to provide the attendees with the tools and resources necessary to become successful alcohol researchers. In 2017 and 2018, more than 50 percent of the attendees were women.

NIAAA Summer Research Internship Program. This program provides research internships for high school and undergraduate students with a goal of recruiting underrepresented racial/ethnic students into research. This 8-week paid program exposes students to alcohol abuse research and encourages them to pursue careers in biomedical and behavioral research. Students' activities include but are not limited to laboratory experiments, data collection activities, data analysis, patient recruitment, manuscript preparation, literature reviews, and library research. In 2017, NIAAA awarded 20 internships, of which 13 were to women (65 percent). In 2018, 23 internships were awarded, of which 15 were to women (65 percent).

Diversity Administrative Supplements. This program provides support to existing NIH grants for the purpose of supporting pre- and post-doctoral students and eligible investigators from groups underrepresented in health-related research. In 2017, NIAAA awarded 13 of the 21 applications submitted for funding. Fifty-four percent represented women from Hispanic (4) and African-American (3) origin. NIAAA also jointly hosted a Diversity Scholars Workshop with NIDA which featured speakers with past Diversity Supplement awards, interactions with NIDA and NIAAA Program Staff and talks from Training (T32) Directors from both NIDA and NIAAA. In 2018, NIAAA awarded 12 of the 18 applications submitted for funding. Sixty-seven percent represented women from Hispanic (3), African American (4), and disability status (1) groups. NIAAA jointly sponsored a Diversity Scholars Workshop with NIDA. Nine of the 10 attendees invited to participate were women with previous diversity supplement awards. NIAAA also featured a prominent female T32 Research Investigator to speak to the students about training opportunities.

V. Funding Initiatives

Effects of In Utero Alcohol Exposure on Adult Health and Disease (R21 Clinical Trial Optional (R01 and R21) (PA-18-507 and PA-18-508). This Funding Opportunity Announcement (FOA) is intended to support novel research on how prenatal alcohol exposure may contribute to the etiology of chronic diseases and health conditions later in life. Central to this theme is the developmental origins of health and disease (DOHaD) concept which suggests that fetal adaptations in response to adverse intrauterine conditions may increase the risk for childhood and adulthood disease. The goal of this FOA is to stimulate a broad range of research to: 1) leverage existing prospective birth cohorts to define the role of maternal alcohol consumption in the DOHaD process; 2) investigate the biological,

cellular, and molecular mechanisms by which prenatal alcohol exposure may impact disease outcomes later in life; and 3) identify biomarkers associated with gestational alcohol exposure that may predict adult disease susceptibility in exposed offspring. Studies supported by this FOA will provide fundamental insights into a possible fetal-basis to adult disease that is influenced by maternal alcohol use.

Model Continuums of Care Initiative (MCCI) for Women and Girls at Risk and Living with HIV/AIDS and Harmful Alcohol and Associated Comorbidities Planning Cooperative Agreement (U34) (RFA-AA-17-013). NIAAA participate with ORWH and NIDA in this initiative which promotes the development and evaluation of integrated multilevel interventions to reduce alcohol consumption as a key approach to preventing new infections and enhancing treatment adherence in communities in the U.S. where racial and ethnic minority women bear a disproportionate share of the HIV/AIDS disease burden. Two U34 planning grants were awarded in 2017 (Johns Hopkins; Florida International University) under this RFA. Results of this research will provide the evidence base for the development of more effective systems of care for women and girls at risk and living with HIV, including pregnant mothers who engage in risky drinking and other substance use.

Women & Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R03, R21, R01 Clinical Trial Optional) (PA-18-601, PA-18-602, PA-18-603). NIAAA continues to participate with NIDA in an initiative to promote research on women and sex/gender differences in drug/alcohol abuse and dependence. The purpose of this FOA is two-fold: (1) to advance identification of male-female differences in drug and alcohol research outcomes, to uncover the mechanisms of those differences, and to conduct translational research on those differences, and (2) to advance research specific to women or highly relevant to women. Both preclinical and clinical studies are sought across all areas of drug and alcohol research.

Workshops and Meetings

2017 National Conference on Harmful Alcohol and Opioid Use Among Women and Girls (Objectives 1.9 and 4.5). NIAAA hosted the conference in partnership with the Women, Drinking, and Pregnancy Work Group of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders, the National Institute on Drug Abuse/NIH, the Office of AIDS Research/NIH, the Office of Research on Women's Health/NIH, and the Substance Abuse and Mental Health Services Administration. The conference reviewed key findings from current research on the causes, consequences, prevention, and treatment of harmful alcohol, opioid, and other substance use among women and girls, and the best approaches for sustaining recovery. Key objectives were to identify important directions for future research and to provide a platform for developing coordinated approaches for addressing epidemic substance misuse among women. Conference highlights included a keynote address, "Alcohol and the Female Brain," by NIAAA Director as well as presentations and group discussions of diverse areas of addiction prevention and treatment (Washington, DC, October 26-27, 2017).

Conference on Sleep and Women's Health (Objective 4.5). The National Center on Sleep Disorders Research, in partnership with the Office of Research on Women's Health, and the HHS Office of Women's Health organized a conference entitled "Sounding a Wake-Up Call: Sleep and Women's Health". NIAAA sponsored a session in this conference with three speakers who highlighted the gender specific effects of alcohol in regulating sleep and circadian changes (NIH, Bethesda, MD, October 16-17, 2018).

2018 Quarterly Webinars on Substance Use Among Women and Girls. Starting in 2018, NIAAA's Interagency Work Group on Drinking and Drug Use in Women and Girls began hosting a series of quarterly webinars on harmful substance use among women and girls with some of the nation's leading experts in this area. Topics addressed thus far include: 1) Substance Use Among Hispanic Women and Girls (3-18); 2) FASD Prevalence (6-18); and 3) Gender differences and generational trends in alcohol use and mental health among U.S. adolescents and adults (11-18).

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National Institute of Allergy and Infectious Diseases (NIAID)

I. Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to understand, diagnose, prevent, treat, and, ultimately cure infectious and immune-mediated diseases, including diseases that affect the health of women and girls. NIAID involves women in many of its clinical studies on treatment and prevention of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), autoimmune diseases, and other infectious diseases. NIAID also collaborates with other organizations on research initiatives within NIAID's mission areas that aim to improve women's health.

This biennial report provides an overview of selected NIAID-sponsored women's health activities. The first section describes scientific accomplishments and activities in research on HIV/AIDS; non-HIV infectious diseases including sexually transmitted infections (STIs), malaria, influenza, and Zika virus infection; and immunology and immune-mediated diseases. Accomplishments in HIV/AIDS include development and testing of intravaginal rings containing antiretroviral drugs, vaccine research that evaluates the safety and efficacy of a broadly neutralizing monoclonal antibody in reducing incidence of HIV/AIDS infection in African women, and therapeutic research studies analyzing possible adverse pregnancy outcomes of antiretroviral therapy (ART). Also noted is a clinical trial demonstrating the effectiveness of an ART regimen to minimize the risk of mother-to-child transmission of HIV for the duration of breastfeeding. Other highlights include an investigation into a potential therapy for Zika virus infection and studies examining hormonal influences on influenza infection. This report includes basic research findings that could lead to an improved understanding of the inflammation response that occurs in autoimmune diseases that disproportionately affect women, such as systemic lupus erythematosus (SLE); and insights into immunological changes during pregnancy.

An overview of NIAID activities that address the objectives of the NIH Strategic Plan for Women's Health Research includes a description of the NIAID Women's Health Research Working Group. Additional sections provide overviews of NIAID activities to increase the enrollment of pregnant women in ethically appropriate clinical research; career development activities; research initiatives; conferences and publications; and research on health disparities in women and special populations.

II. Accomplishments and Activities

HIV/AIDS

Working Toward a Safe, Effective, and Acceptable Microbicide for HIV

Women face a greater risk of acquiring HIV than men in part because of substantial exposure to semen at mucosal membrane sites, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners, such as injection drug use or having sex with men. The Microbicide Trials Network (MTN) was formed by NIAID and NIH partners in 2006 as an international

collaborative clinical trials network to develop and evaluate microbicide products aimed at reducing the sexual transmission of HIV. MTN consists of a robust network of expert scientists and investigators, with US and international clinical research sites. The network uses a focused research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission. NIAID-sponsored research focuses on the development of topical microbicides that: (1) prevent HIV infection and/or viral replication, (2) are safe and do not irritate vaginal, cervical, urethral, or rectal tissues, and (3) reduce HIV transmission and acquisition, even in the presence of other STIs, which increase the risk of acquiring HIV. MTN is enrolling and/or conducting several studies evaluating the safety and adherence to use of a vaginal ring containing the antiretroviral drug dapivirine, including the following:

- MTN-044/IPM 053/CCN019: This Phase I study will assess the pharmacokinetics and safety of a vaginal ring containing dapivirine and levonorgestrel used for 90 days. The study will also investigate the acceptability of and adherence to this HIV prevention-plus-contraception method.
- MTN 034 (REACH study): In 2019, NIAID will begin enrolling participants in a Phase IIa study to assess the safety of and adherence to the dapivirine vaginal ring and oral pre-exposure prophylaxis (PrEP) in adolescent girls and young women in sub-Saharan Africa. PrEP is a strategy in which healthy people routinely take one or more antiretroviral drugs to reduce their risk of getting HIV. The trial will collect safety and adherence data over the course of study product use to more fully understand issues that affect product uptake.
- MTN 029, MTN-029/IPM 039: This Phase I study is designed to assess the presence of dapivirine in breast milk when the drug is delivered via vaginal ring. The primary objective of this trial is to assess the pharmacokinetics as well as safety, tolerability, and adherence to the ring, when used for 14 consecutive days by lactating women.

Evaluating the Efficacy of Long-Acting HIV Pre-Exposure Prophylaxis (PrEP)

The NIAID HIV Prevention Trials Network (HPTN) was established in 2000 as an international collaborative clinical trials network to develop and test the safety and efficacy of primarily non-vaccine prevention strategies such as PrEP. The one currently validated PrEP method involves taking a daily dose of two antiretrovirals, tenofovir and emtricitabine, in a single pill marketed as Truvada®. NIAID supports research to develop longer-acting forms of HIV prevention. In 2017, the HPTN announced the initiation of the first large-scale study in women of a long-acting injectable drug to prevent HIV, called cabotegravir (CAB). The study, HPTN 084 is a Phase III study comparing long-acting injectable CAB to a combination of daily oral PrEP in 3,200 HIV-uninfected, sexually active women in sub-Saharan Africa. The HPTN is also currently conducting a Phase III study (HPTN 083) to evaluate CAB versus daily oral PrEP in populations of men who have sex with men and transgender women who have sex with men. If found to be safe and effective for HIV PrEP, injectable CAB may be an easier, more desirable, and discreet alternative to daily oral PrEP for some women.

Risk Factors Identified for Cytomegalovirus Infection of Infants Born to HIV-Infected Women

Cytomegalovirus (CMV)—a common virus that infects people of all ages—can infect infants at birth, which may lead to developmental delays and hearing loss. Once CMV is in a person's body, it stays there for life and can reactivate. People infected with CMV can shed the virus through bodily fluids such as urine, saliva, or breast milk, but little is known about the

relevance of CMV shedding in urine and cervical specimens, especially in the context of persons infected with HIV. As part of the NIAID-funded HPTN network, investigators examined whether pregnant, HIV-positive women had detectable CMV in their urine at time of birth and whether that could increase the chances of transmitting CMV to their infant. The researchers evaluated a subset of the mother-infant pairs in the perinatal HPTN 040 study, which enrolled women who were identified as HIV-infected around the time they gave birth, and who therefore had not received ART before labor. Women with CMV in their urine during labor were 30 times more likely to have infants with congenital CMV than those without, and 5 times more likely to transmit HIV to their infants, suggesting that maternal CMV urinary shedding at the time of birth is a significant risk factor for both CMV and HIV transmission to infants born to women who did not receive ART during pregnancy (Adachi K et al, 2017. PMID 8369278).

Continuing Anti-HIV Therapy After Pregnancy in Non-Breastfeeding Women Provides Benefits

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), sponsored by NIAID and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), develops and evaluates safe, cost-effective approaches for interrupting mother-to-infant HIV transmission; evaluates treatments for HIV-infected children, adolescents, and pregnant women; investigates strategies for treating and preventing co-infections and illnesses associated with HIV; and evaluates vaccines for preventing HIV sexual transmission among adolescents. As part of the NIAID-funded Promoting Maternal and Infant Survival Everywhere (PROMISE) study, researchers found that maternal and infant ART strategies were equally safe and effective at preventing transmission of HIV to the infant for up to 24 months of breastfeeding. These results show that while the preferred strategy of treating the mother as part of lifelong ART is highly effective at reducing mother-to-child HIV transmission, infant ART is an effective and safe alternative (Flynn et al 2018. PMID 29239901). To further understanding of the benefits of continuing anti-HIV therapy for postpartum women, another component of the PROMISE study (the "HAART Standard") was designed to assess the risks and benefits of continued ART compared with stopping ART after delivery and restarting when clinically indicated by a drop in CD4 T-cell counts below a certain level, or by other factors. Findings from this study provided further evidence that ART benefits women with early-stage HIV infection (Currier JS et al., 2017. PMID 28489856).

Composition of Female Genital Tract Microbiome May Affect Risk of HIV Infection

HIV prevalence in young African women is up to eight-fold higher than in young African men, suggesting that biological factors in the female genital tract may increase susceptibility to infection. Scientists previously hypothesized that certain types of bacteria that naturally colonize the female genital tract may be linked to decreased rates of HIV infection. To test this hypothesis, NIAID-funded researchers turned to Females Rising through Education, Support and Health (FRESH), an ongoing trial funded by the Bill & Melinda Gates Foundation, that comprises healthy, HIV-uninfected 18- to 23-year-old black South African women who are provided with intensive HIV prevention counseling and HIV testing. Researchers found that distinct bacterial types and communities are associated with an increased risk of HIV infection. The results suggest that South African women may be at increased risk of HIV infection based on their reproductive tract microbiota and emphasize the importance of considering the microbiome when developing new approaches to reduce HIV infection (Gosmann C et al., 2017. PMID 28087240).

Evaluating Promising HIV Vaccine Candidates

The HIV Vaccine Trials Network (HVTN) is an international collaboration of scientists searching for an effective and safe HIV vaccine. The purpose of the HVTN is to facilitate the process of testing preventive vaccines against HIV/AIDS, conducting all phases of clinical trials, from evaluating experimental vaccines for safety and the ability to stimulate immune responses to testing vaccine efficacy. Studies conducted by HVTN enroll both men and women, and data are analyzed for gender differences regarding safety, tolerability, and immune responses. Two ongoing HVTN studies are evaluating the safety and efficacy of promising HIV vaccine candidates:

- HVTN 705, (Imbokodo study): A large Phase IIb proof-of-concept study will evaluate the safety, tolerability, and efficacy of a prime/boost vaccine regimen among women in sub-Saharan Africa. The study will enroll an estimated 2,600 participants and will evaluate two vaccines, called Ad26.Mos4.HIV (Ad26 vaccine) and Clade C gp140 (protein vaccine).
- HVTN 703/HPTN 081: A Phase IIb study is evaluating the safety and efficacy of VRC01, a broadly neutralizing monoclonal antibody developed by NIAID, in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa. Full enrollment was reached in September 2018, and 1,885 participants are now in follow-up study.

Characterizing Health Disparities Among Women Living with HIV

The Women's Interagency HIV Study (WIHS) is the largest observational study of HIV-infected women and includes participants living in ten US metropolitan areas. WIHS has an active research program investigating health disparities among HIV-positive women, particularly in the Southern United States. WIHS investigators published a study showing that the prevalence of sexually transmitted infections was inversely correlated with voter turnout and positively associated with felony voter disenfranchisement (Haley et al., 2018. PMID 30442564). An analysis of WIHS data showed a significant association between sustained perceived social support and increased ART adherence in the WIHS (Chandran et al., 2018. PMID 30311104). WIHS data also demonstrated that food insecurity is associated with elevated levels of inflammation among HIV-positive women regardless of HIV control (Leddy et al., 2018. PMID 30165648), and unstable housing reduces the likelihood of viral suppression by 51% and the probability of having adequate white blood cell count by 53% (Galárraga et al., 2018. PMID 30153546).

Chronic Hepatitis C Infection in Women May Affect Response to Anti-HIV Therapy

In the United States, one in four people living with HIV are also infected with hepatitis C virus (HCV). Suppressing HIV levels through ART improves long-term health and reduces transmission of HIV to uninfected sexual partners. Yet the effects of chronic HCV co-infection on the effectiveness of ART for HIV infection are unclear, especially among women. To estimate the effects of chronic HCV on the ability of ART to control HIV in women for up to 15 years, researchers analyzed WIHS data and found that chronic HCV infection may negatively affect early HIV viral response to ART, highlighting the need to carefully monitor HIV care and facilitate access to HCV treatment among people with HIV/HCV co-infection (Willis SJ et al., 2018. PMID 29334550).

Sex-Based Differences in ART Initiation, Switching, and Treatment Interruptions

The International Epidemiology Databases to Evaluate AIDS (IeDEA) was established by NIAID in 2006 to bring together HIV clinical data collected as part of research initiatives and diverse care programs. Seven global regions have enrolled nearly 1 million patients who are

representative of the HIV epidemic within their region. The North American AIDS Collaboration of Observational Research Databases includes data from more than 7,800 women living in the United States or Canada. In 2018, researchers published a collaborative analysis of IeDEA cohort data evaluating sex-based differences in HIV treatment patterns among more than 700,000 participants in six regions across the Americas, Asia, and Africa. Results from the study suggest that women from North America and southern Africa regions were significantly more likely than men to switch their first-line regimen, and that only in North America were women more likely to have treatment interruptions than men. Future studies to define possible reasons for switching (toxicity, pregnancy, drug interactions or resistance) are essential to understanding the sex differences observed in treatment changes and interruption (Giles ML et al., 2018. PMID 29956882).

Correlation Between ART Program Attrition and Pregnancy in East Africa

Investigators used data from the IeDEA-East Africa collaboration to examine the impact of pregnancy on treatment and found that pregnant women constituted an increasing proportion of individuals initiating ART (5.3% in 2004, 12.2% in 2014) (Holmes CB, et al., 2018. PMID 29342180). Pregnant women were at higher risk of loss-to-follow-up (LTFU) care than males; however, older adolescents had higher rates of LTFU compared with adults or younger adolescents, primarily driven by both pregnant and non-pregnant females. These data can help programs identify those at greatest risk for LTFU and address efforts to support and retain this population (Nuwaaba-Biribonwoha, et al., 2018. PMID 30225908).

Adverse Pregnancy Outcomes of Antiretroviral Therapy

The Centers for AIDS Research (CFAR) is a unique trans-NIH program that provides infrastructure to support interdisciplinary, peer-reviewed HIV/AIDS research. There are currently 19 CFARs at academic and research institutions throughout the United States. In 2017–2018, CFARs supported more than 30 women's health pilot projects through the CFAR Developmental Cores.

Women with HIV are at risk of infecting their children during pregnancy, during birth, or shortly thereafter. NIAID-funded researchers analyzed data on pregnant HIV-infected women collected from two US-based studies. The women received one of three common three-drug ART regimens. Overall, women in the three groups had similar risks of having infants born prematurely or with low birth weight. An analysis of the women who started treatment before conception suggested that those treated with tenofovir, emtricitabine, and lopinavir/ritonavir had an increased risk of preterm birth compared to those receiving the two other ART regimens (Hoffman RN et al., 2019. PMID 29868833). In a separate study, NIAID-supported investigators reviewed data from a large clinical trial in which HIV-infected women who were treated during pregnancy were randomly assigned to either continue or stop ART after giving birth. The investigators examined the effects on the outcomes of a subsequent pregnancy, including spontaneous abortion and stillbirth, but the results were inconclusive, as not all women adhered to the prescribed ART regimen. Further studies are needed to inform decisions on how to balance the relatively low risks of adverse pregnancy outcomes against the benefits of lifelong, uninterrupted ART (Rough K et al., 2018. PMID 29694825).

Risk of Acquiring HIV Increases During and After Pregnancy

Previous studies have suggested that pregnant women may have a higher risk of HIV infection compared to non-pregnant women. NIAID-supported researchers compared the probabilities of male-to-female HIV transmission per sex act

among non-pregnant, pregnant, and postpartum women. Researchers found that a woman's risk of acquiring HIV through sex with a male partner living with HIV increases during pregnancy and is highest during the first 6 months after childbirth, even after considering behavioral factors, such as use of condoms or PrEP. The findings underscore the importance of expanding HIV prevention and testing services for pregnant and postpartum women living in areas with high HIV prevalence and suggest that the physiological changes that a woman's body undergoes during and after pregnancy contribute to an increased risk of acquiring HIV (Thomson KA et al., 2018. PMID 29514254).

High Doses of Anti-HIV Drug Tenofovir Inhibit Wound Healing in Cells of Female Reproductive Tract

Low effectiveness of PrEP approaches in women, such as intravaginal application of the anti-HIV drug tenofovir, is partially attributed to lack of adherence to the treatment regimen, but other biological or physiological factors may also play a role. For example, the integrity of physical barriers such as the mucous membranes lining the female genital tract plays a significant role in HIV prevention, and little is known about the process by which the body repairs these tissues and how anti-HIV drugs may affect this process. NIAID-supported investigators assessed whether two related antiretroviral drugs used in PrEP, tenofovir disoproxil fumarate (TFV) and tenofovir alafenamide (TAF), affect wound repair of female reproductive tract tissue from the outermost layer (epithelium) and inner layers (stroma) of the mucosal lining. The results suggest that researchers may wish to consider effects of antiretroviral drugs on wound healing processes in physical barriers to HIV transmission, including the mucosal lining of the female reproductive tract, in future PrEP clinical trials (Rodriguez-Garcia et al., 2017. PMID 28368028).

Infectious Diseases other than HIV/AIDS

Inflammation Plays Role in Malaria-Related Pregnancy Loss and Premature Delivery

The parasite *Plasmodium falciparum* is the deadliest and most common malaria-causing species in Africa. Malaria infection during pregnancy has substantial risks for the pregnant woman, her fetus, and the newborn child. In a study published in 2017, NIAID scientists and their colleagues measured the blood levels of six different cytokines or chemokines—small proteins that are secreted by immune cells and either stimulate or reduce inflammation—from 638 malaria-infected and uninfected pregnant women in Mali. The researchers found that maternal inflammatory immune responses to malaria infection during pregnancy predicted an increased risk of pregnancy loss and preterm delivery. The results emphasize the role of the maternal immune system in influencing pregnancy outcomes during malaria infection and suggest that it may be possible to use blood tests to predict the risk of malaria-associated pregnancy complications (Fried M et al., 2017. PMID 29020221).

Anti-Malaria Antibodies from Mother Protects Infants from Severe Malaria

Researchers have known for decades that newborns and young infants in sub-Saharan Africa are relatively resistant to malaria infection and severe malaria. Following up on earlier findings, NIAID-funded researchers and their colleagues in NIAID's Laboratory of Malaria Immunology and Vaccinology investigated whether antibodies that target a *P. falciparum* protein called PfSEA-1 are transferred from mother to child during pregnancy, and whether these antibodies are associated with a reduced severity of malaria in the infants. Researchers found that antibodies to a malaria protein, SEA-1, from the mother can confer resistance to severe malaria or death in the offspring. The results also

suggest that vaccinating pregnant women with PfSEA-1 could help their infants survive malaria infection (Kurtis JD et al. 2018. PMID 30165569).

Antibody Protects Against Fetal Abnormalities in Mouse Model of Zika Virus Infection

Zika virus is a mosquito-borne virus that can be sexually transmitted and may cause serious birth defects, including microcephaly, in babies born to mothers infected with the virus during pregnancy. Microcephaly is a condition marked by an unusually small head, brain damage, and developmental delays. Zika virus infection has been associated with other fetal development problems, including eye defects, hearing loss, and impaired growth. There is no drug or vaccine to treat or prevent Zika virus infection. To develop possible therapies for Zika virus infection, NIAID-supported researchers isolated distinct antibodies from immune cells of three people who were previously infected with Zika virus. They found one antibody, ZIKV-117, that neutralized all types of Zika virus tested, including African, Asian, and American strains. Giving a single dose of ZIKV-117 to Zika virus-infected male mice with weakened immune systems up to five days after infection protected the mice from death. Additionally, treating pregnant mice with ZIKV-117 before or immediately after infection with Zika virus reduced virus levels in the placenta and in the fetal brain and improved fetal survival and health. This study suggests that ZIKV-117 treatment can reduce transmission of Zika virus from mother to fetus, treat active Zika virus infection, and improve pregnancy outcomes in Zika-infected mice (Sapparapu G et al. 2016. PMID 27819683).

Pregnancy Loss Associated with Zika Virus Infection May Be More Common than Thought

In a recent analysis, a large team of experts funded in part by NIAID found that fetal death associated with Zika virus occurred in 13 of 50 (26 percent) of the animals studied. Macaques infected early in pregnancy had significantly higher rates of fetal death than those infected after 55 days of pregnancy. The results track with human data showing more severe fetal outcomes in women infected with Zika in their first trimester compared to those infected later in pregnancy. These findings raise the concern that Zika virus-associated pregnancy loss in humans may be more common than currently thought (Dudley DM et al. 2018. PMID 29967348).

New Clues to Why Influenza Illness Is More Severe in Women than Men

Influenza virus causes an acute respiratory infection in humans by entering and replicating in lung cells. Each year, seasonal influenza kills between 12,000 and 56,000 Americans and leads to between 140,000 and 710,000 hospitalizations. Pandemic influenza can produce even greater devastation. Studies have shown that females have more inflammation in the lungs in response to influenza infection and overall have a more severe outcome compared to males, despite having comparable levels of influenza virus in the body. This suggests that the worse outcome in females may result from an inability to resolve inflammation rather than a failure in controlling viral replication. To help understand these differences, NIAID-funded researchers evaluated possible sex-based differences in production of a growth factor called amphiregulin (AREG), one of many factors that helps repair and restore the integrity of tissues damaged from inflammation during infection. The researchers found that AREG production was greater in lung tissue and laboratory-grown cells derived from males (both human and mouse) than from females. They further showed that the presence of the male sex hormone testosterone also contributed to the faster recovery of males as compared to females following influenza infection. These findings suggest that AREG and testosterone both contribute to limiting tissue damage from inflammation and mediate faster repair of damaged lung tissue (Vermillion MS et al., 2018. PMID 30012205).

Estrogen Reduces Lung Inflammation and Protects Female Mice from Severe Influenza

Estriol (E3) is a form of estrogen known to have anti-inflammatory effects. In an effort to understand the effects of this hormone on influenza-mediated inflammation, NIAID-funded researchers investigated the effects of E3 treatment on influenza infection in mice. They found that treating female mice with E3 reduced total lung inflammation and improved disease outcome following infection with nonlethal doses of influenza A virus. These findings suggest that, although the mechanisms of estrogen-modulated impacts on the course of disease are complex and vary between tissues, overall evidence indicates that estrogen-dependent effects may impact immune responses and provide protective effects during influenza A virus infection (Vermillion MS et al., 2018. PMID 30032246).

Novel Mechanism Identified for Cancer-Promoting Effects of Human Papillomavirus (HPV) Infection

HPV is the most common sexually transmitted infection and occurs most frequently in resource-limited settings, particularly among those who are younger, female, and infected with HIV. HPV can cause genital warts and other skin warts and benign tumors of the respiratory tract. These lesions can be especially problematic in individuals whose immune systems are compromised by HIV infection or by drugs given after organ transplantation. Certain types of sexually transmitted HPVs, known as high-risk HPVs, cause virtually all cases of cervical cancer and can also cause several other cancers, including anal, head and neck, vaginal, and vulvar cancers. Two of these high-risk viruses, HPV16 and HPV18, are responsible for most HPV-caused cancers. NIAID-supported researchers found that a combination of viral and host-cell DNA sequences drives increased expression of proteins that promote uncontrolled cell division and an accumulation of mutations in infected cells, ultimately leading to cancer. These findings suggest that cancer cells that harbor integrated HPV could ultimately be targeted by therapies that disrupt these host-cell DNA sequences (Warburton A et al., 2018. PMID 29364907).

Brd4 Protein May Be Therapeutic Target for Human Papillomavirus

HPV replication is complex, involving successive phases in different layers of skin, making it difficult to reproduce and study in the laboratory. To circumvent this problem, NIAID researchers manufactured HPV-like particles, called HPV quasiviruses, which contain the HPV genome packaged inside a viral shell similar to true HPVs. The researchers then used these HPV quasiviruses to study the importance of the human cell protein Brd4 in the early stages of HPV infection. They infected cells with HPV quasiviruses and found that loss of Brd4 reduced the production of HPV genes and proteins. These results indicate that Brd4 is integral early in the HPV life cycle and may be a promising therapeutic target for developing measures against HPV infection (McKinney CC et al., 2016. PMID 27879331).

Newly Identified Virulence Factor Helps *Listeria monocytogenes* Bacteria Infect the Placenta

The bacterium *Listeria monocytogenes* (Lm) causes a wide variety of diseases that range from a mild infection of the digestive tract that causes gastrointestinal distress in healthy people to bacterial meningitis, a life-threatening disease that causes swelling of tissues surrounding the brain and spinal cord, in people who have weakened immune systems. Lm is a significant health threat to pregnant women and their unborn children, as infection with this microbe during pregnancy frequently leads to premature delivery and stillbirth. As part of an effort to understand how Lm bacteria overcome the relatively high resistance of the placenta to infection by microbes, NIAID-funded researchers identified the virulence factor InlP, which promoted Lm infection of the placenta in mouse and guinea

pig models. Based on these results, InlP may provide a new tool for further study of microbial interactions with the maternal immune system and placenta and could eventually lead to new interventions for the prevention or treatment of infection-related complications in pregnancy (Faralla C et al., 2016. PMID 27736782).

Researchers Characterize Chlamydia Disease Characteristics and Outcomes in Women

Chlamydia is a common STI caused by infection with *Chlamydia trachomatis* (*C. trachomatis*) bacteria. Chlamydia can have serious consequences in women, including chronic pelvic pain, ectopic pregnancy (pregnancy outside the uterus), and infertility. Researchers commonly use a mouse model to study chlamydia infection of the female urogenital tract and to research potential treatments and vaccines. However, this model exhibits different characteristics depending on which strain of chlamydia is used—*C. trachomatis* or the related mouse strain *Chlamydia muridarum* (*C. muridarum*)—due to differences in factors such as replication, immune response, and protective immunity. In a study published in 2017, NIAID researchers examined *C. trachomatis* and *C. muridarum* infections in mice following surgical removal of their uterus. By studying the different disease characteristics of these strains, researchers may be able to better understand the chlamydia infection process and subsequent outcomes in women and thereby aid the development of treatments and vaccines (Yang C et al., 2017. PMID 28461392).

Immunology and Immune-Mediated Diseases

Immune Responses at the Maternal-Fetal Interface

NIAID supports research on immunology and immune-mediated diseases and their effects on women's health. The goal of this research is to increase the health and well-being of women by developing new methods to prevent and treat autoimmune and other immune-related problems specific to women, including the impact of pregnancy.

In a healthy pregnancy, the mother's immune system accepts, or tolerates, the presence of the developing fetus. Similarly, the fetal immune system does not react against cells from the mother that cross the placenta. Premature or preterm birth can be a sign that there is a breakdown in the maternal-fetal tolerance. While research has shown that maternal immune responses against the fetus can lead to pregnancy complications, not much is known about the role of the fetal immune system in causing complications. To investigate the potential role of the fetal immune system in premature birth, NIAID-funded researchers compared the characteristics of cord blood from preterm and full-term infants. Cord blood from premature infants had elevated levels of inflammation-promoting molecules and a greater activation of immune response-boosting cells called dendritic cells. It also contained immune cells known as T-helper cells, primed to react against molecules from the mother. Finally, cord blood from premature infants also contained many more maternal cells than cord blood from infants not born prematurely. The study findings suggest that an interplay between inflammation, maternal cells that cross the placenta, and aberrant activation of the fetal immune system may play a role in some preterm births (Frascoli et al., 2018. PMID 29695455).

Influenza Vaccine Responses Decline When Administered During Later Stages of Pregnancy

During pregnancy, the placenta performs many critical functions, including protecting the fetus from infection. Researchers are trying to develop new technologies to understand how the placenta functions and how to better protect the fetus against infection. To better understand influenza vaccine responsiveness during pregnancy, NIAID-funded researchers evaluated serum

obtained both before and after vaccination from pregnant and nonpregnant women They showed that the levels of antibody subtypes declined as pregnancy progressed and vaccine responses declined when vaccination occurred later in pregnancy. These results may have implications regarding the optimal timeframe for influenza vaccination of pregnant women (Schlaudecker et al., 2018. PMID 29941326).

Researchers Identify Key Mediators Responsible for Suppressing the Immune Response

Systemic lupus erythematosus (SLE, or lupus) is a chronic autoimmune disorder that can affect multiple organs and often causes skin rashes, joint inflammation, and pain. Women, particularly women of color and women of child-bearing age, are much more likely than men to develop lupus. Although the causes of lupus are complex and only partially understood, abnormalities in the clearance of apoptotic cells (cells that undergo a programmed cell death process) are thought to be key contributors. Immune cells called macrophages are responsible for safely eliminating apoptotic cells and preventing tissue damage by silencing their inflammatory signals. NIAID-funded researchers recently identified and characterized tissue-specific macrophages that were responsible for removing apoptotic cells and identified the mediators that are essential in silencing the inflammatory response (Roberts et al., 2017. PMID 29150239).

Ritixumab Treatment Affects Replenishment of the B-Cell Repertoire

Systemic sclerosis (SSc), also known as scleroderma, is a severe and often fatal autoimmune disease marked by hardening of the skin and the connective tissue of internal organs. Women are about four times more likely than men to develop the disease. Patients with SSc often develop difficult-to-treat complications such as a type of increased blood pressure in the lungs known as pulmonary arterial hypertension (PAH). NIAID-supported researchers analyzed blood samples from women receiving rituximab, a synthetic antibody that selectively reduces the number of B cells circulating in the blood, as part of a clinical trial. The researchers found that systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) is associated with abnormalities in B-cell development, particularly in the diversity of antibodies and in the proportions of specific B-cell subtypes. When the researchers examined the dynamics of B-cell depletion during and after rituximab treatment, they found differences among participants in the pattern of B-cell replenishment. They also concluded that the time to repletion after treatment may be a predictable outcome, which could help identify patients who would benefit most from rituximab treatment (de Bourcy et al., 2017. PMID 28963118).

III. NIH Strategic Plan for Women's Health Research

The research findings described in this report (see Accomplishments and Activities) support many ORWH Strategic Plan Goals and Objectives, including:

Goal 1.2: Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

Goal 1.6: Increase basic and translational research on sex/ gender differences in the pathobiology, prevention, and treatment of diseases including HIV/AIDS, urinary tract and sexually transmitted infections.

Goal 1.8: Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being.

Goal 3.3: Encourage research on safe and effective interventions for conditions affecting pregnant women.

Goal 3.4: Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.

Goal 3.9: Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.

Goal 4.2: Establish new ventures and initiatives with a wide cross-section of partners, including NIH institutes, centers, and offices; academia; other Federal agencies; international organizations; private foundations; and industry

The **Trans-NIAID Women's Health Research Work Group** focuses on women's health and gender-based research activities that advance the mission and research priorities of NIAID and provides recommendations for future women's health research opportunities. The work group performs the following functions:

- Heightens awareness across NIAID of the importance and substance of women's health research
- Develops a common framework for identifying and assessing gender-based and women's health research
- Encourages trans-NIAID and trans-NIH collaborations on women's health research activities
- Coordinates various NIAID-wide presentations on topics such as on safety and effectiveness of hormonal contraceptives in women on ART, malaria vaccine research, and altered immune function during pregnancy.

IV. Inclusion

Inclusion of pregnant women in clinical research has been a major ethical and practical challenge, and few drug development portfolios include labeling information for use of drugs in pregnant women. The evidence base for clinical practice involving treatment of pregnant women suffers because inadequate safety, dosing, and efficacy studies are conducted in this population. Many pregnant women are undertreated for serious illnesses due to clinician uncertainty about safety of standard regimens. In the HIV context, clinical trials of biomedical prevention options have historically not included pregnant women, even though pregnancy is a critical time of vulnerability to HIV acquisition. HIV comorbidities such as tuberculosis may be undertreated during pregnancy due to concerns about safety of drug regimens. Despite a long history of using HIV antiretrovirals in pregnancy for interruption of mother-to-child transmission of HIV, newer HIV treatment regimens may also raise safety concerns during pregnancy, as evidenced by recent findings regarding a possible increase in the rate of congenital malformations with the use of the drug dolutegravir.

To address the gaps in inclusion of pregnant women, a NIAID-funded bioethics team is developing ethics guidance for investigators and review bodies to enable responsible and ethical inclusion of pregnant women in research related to HIV/AIDS. As the team develops the guidance, they have conducted critical formative research to understand attitudes, practices, and legal barriers related to inclusion of pregnant women in HIV research. Publications are included in the References, and the guidelines for inclusion of pregnant women are nearing completion, with release anticipated in 2019.

V. IC STEM Efforts

NIAID supports efforts that align with Goal 6.2, *Lead the way in encouraging institutions to*

recognize mentoring as an essential component of building career success in their training programs. NIAID recently established the AIDS Clinical Trials Group (ACTG) Minority HIV Investigator Mentoring Program (MHIMP) Award to encourage more minority investigators to participate in ACTG research activities. It provides an opportunity for the ACTG network– affiliated clinical research sites to mentor minority junior investigators interested in conducting advanced clinical research in virology, immunology, pharmacology, or other aspects of HIV/AIDS. The goal of the program is to equip the minority investigators to advance to the next level in HIV/AIDS clinical investigation following program completion. NIAID continues to cosponsor the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) mentored career development awards (RFA-OD-09-006), which support the development of women's health researchers.

NIAID also cosponsors the Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (PA-18-592), which aims to encourage individuals to re-enter an active research career after an interruption for family responsibilities.

VI. Funding Initiatives, Workshops and Conferences

NIAID sponsored a workshop entitled "Multipurpose Prevention Technology Development: Strategies for Addressing the Biomedical, Behavioral, and Regulatory Challenges." Multipurpose prevention technologies (MPTs) combining contraception and HIV infection have recently emerged as promising next-generation HIV prevention products. Interest in the MPT concept derives from women's desire to have a single product that would confer both prevention of unintended pregnancies and protection from HIV infection, thus potentially increasing product uptake and adherence. This two-day workshop addressed the complexity of MPT development and proposed a strategy for optimizing the movement of MPTs along a product development pathway that integrates behavioral, social, and regulatory science at the earliest stages to increase the likelihood of moving viable MPTs to market. NIAID also supports an MPT-focused funding opportunity announcement, "Development of Multipurpose Prevention Technologies: A Strategy for the Prevention of Sexually Transmitted Infections (STIs) (R61/R33)" (RFA-AI-16-085), and made three awards in FY 2018.

In 2018, NIAID announced the funding opportunity entitled "Immune Mechanisms at the Maternal-Fetal Interface (R01 Clinical Trial Optional)" (RFA-AI-18-023), which solicits research to determine the roles and interactions of immune cells at the maternal-fetal interface throughout pregnancy, including mechanisms of responses to vaccination and infection, that protect or impact the fetus and that may influence fetal immune system development.

In December 2016, the Inter-CFAR Collaboration on HIV Research in Women held a symposium hosted by the University of Alabama at Birmingham CFAR, which focused on research in the area of vulnerable populations, microbiome in HIV-infected women and its impact on health outcomes, and the HIV continuum of care across the lifespan of women.

NIAID continues to participate in several funding opportunities relevant to women's health and the influence of sex on health and disease. The **Administrative Supplements for Research on Sex/Gender Influences** provides funding for research highlighting the impact of sex/gender in human health and illness. The **U3 Administrative Supplement – Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations** supports research that examines clinical differences among women of diverse racial and ethnic backgrounds,

sexual and gender minority women, and women with physical, intellectual and developmental, and/or sensory disabilities. NIAID also participates in **Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations** that support research focused on health issues affecting SGM populations, such as lesbian, gay, bisexual, and transgender people, and individuals with differences or disorders of sexual development (sometimes referred to as "intersex" or as specific diagnoses). The research addresses areas beyond HIV/AIDS, including studies on increased disease risk, behavioral and social health, approaches to personalized medicine, access to care, reproductive and sexual development, and resilience.

VII. Health Disparities

NIAID supports research to understand and eliminate health disparities among women and special populations, including racial and ethnic minorities, sexual and gender minorities, rural women, women of lower socioeconomic status, and women with disabilities. The following scientific programs, activities, and advances are highlighted in this report:

- Microbicide Trials Network (MTN)
- HIV Prevention Trials Network (HPTN)
- IMPAACT
- WIHS
- IeDEA
- Inter-CFAR Collaboration on HIV Research in Women
- Sex differences in influenza infection
- Research on STIs including HPV, and chlamydia

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

I. Executive Summary

Overview

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports a broad range of research, research training and career development activities, and health information programs for many debilitating diseases affecting Americans. NIAMS funds studies on a number of diseases that disproportionately affect women, including fibromyalgia, osteoarthritis (OA), osteoporosis, rheumatoid arthritis (RA), scleroderma/systemic sclerosis, systemic lupus erythematosus (lupus), and juvenile idiopathic arthritis (JIA).

Program Highlights

The anticipated increase in the U.S. elderly population will be accompanied by an increased number of women who are at risk of fragility fractures. Effective osteoporosis medications are available, but treatment rates and adherence rates are low. Most data regarding the benefits and risks of pharmacologic fracture prevention interventions come from the clinical trials that led to the drugs' regulatory approval, generally with treatment duration of 3-5 years. Thus, healthcare providers lack clear guidance regarding which patients will benefit or may be harmed from continued drug intervention beyond the original trial period. These and other issues related to bone-preserving medications have prompted NIAMS, the National Institute on Aging (NIA), the NIH Office of Disease Prevention, and several other NIH components (including ORWH) to launch a Pathways to Prevention effort on Appropriate Use of Pharmacologic Therapies for Osteoporotic Fracture Prevention. The resulting workshop, to be held in early FY 2019, will assess the scientific evidence regarding the risks and benefits of short- and long-term use of osteoporosis medications and the patient and clinician factors that influence the use of these drugs.

NIAMS, in partnership with the National Institute of Allergy and Infectious Diseases (NIAID), also manages the Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus (AMP RA/Lupus) Program for NIH. The program began in FY 2014 as a 5-year, $41 million effort to generate a comprehensive understanding of the mechanisms of tissue damage in RA and lupus. Partners include AbbVie, Bristol-Myers Squibb, Janssen, Merck, Pfizer, Sanofi, Takeda, the Arthritis Foundation, the Lupus Foundation of America, the Lupus Research Alliance, the Rheumatology Research Foundation, and the Foundation for the National Institutes of Health. In 2018, the partner organizations agreed to provide approximately $8.9 million in additional funding for a sixth year to deploy and test emerging molecular technologies that will increase the information obtained from kidney and synovial tissues collected by the program. To date, the network of clinicians, translational researchers, and bioinformaticians have developed novel tools and techniques that have transformed the way researchers are approaching autoimmune disease. With phase 1 of the initiative complete and phase 2 ongoing, data generated from cutting-edge technologies are being made publicly available for other researchers to interrogate. In fact, phase 1 research data available through the NIAID ImmPort database already have been shared over 1,300 times. At the same time, the network has implemented research innovations that will have a lasting impact on the field, including collaboration

plans involving dispersed research institutions, standardization of sample processing protocols across multiple research sites, as well as patient recruitment strategies enhancing participation of underrepresented populations.

With support from ORWH and other NIH components, NIAMS provides a robust information dissemination and outreach program to distribute research-based information to patients, health care providers, and other members of the public. For example, NIAMS oversees the NIH Osteoporosis and Related Bone Diseases National Resource Center (ORBD~NRC), which is co-funded by the NIA, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, ORWH, and HHS Office on Women's Health.

NIAMS also disseminates results from funded studies by providing lay-friendly summaries on the Institute's website and contributing to NIH-supported information resources (e.g., the consumer-oriented *News in Health, NIH Research Matters, MedlinePlus Magazine*). Notable examples from fiscal years 2017 and 2018 included features on RA and on total knee replacement surgery. Additionally, NIAMS staff contributed background to or were quoted in many print and online articles in the mainstream and trade press about diseases within the Institute's mission.

II. Accomplishments and Activities

Fibromyalgia

Fibromyalgia syndrome is a common and chronic disorder characterized by widespread pain, diffuse tenderness, and a number of other symptoms. Scientists estimate that fibromyalgia affects 5 million Americans age 18 or older. For unknown reasons, between 80 and 90 percent of those diagnosed with fibromyalgia are women. Most people are diagnosed during middle age, although the symptoms often present earlier in life.

Pilot Data from Fibromyalgia Integrative Training Program for Teens (FIT Teens) Show Promise for Reducing Pain.

Juvenile-onset fibromyalgia (JFM) is a chronic, debilitating, painful condition that persists into adulthood for many patients. Cognitive-behavioral therapy (CBT) benefits adolescents with JFM. Moderate-to-vigorous physical activity is another crucial component of JFM pain management, yet JFM patients often have difficulty initiating and maintaining any level of regular physical activity. To address this gap, researchers have developed an intervention—the Fibromyalgia Integrative Training program for Teens (FIT Teens)—which supplements established CBT techniques with neuromuscular training exercises derived from evidence-based pediatric injury prevention research. Pilot studies of this training program demonstrated that this intervention is safe, produces excellent patient engagement, and has no adverse effects. Recent data, which remain to be confirmed in a larger study (ClinicalTrials.gov Identifier: NCT03268421), suggest that FIT Teens offers stronger treatment benefits than CBT alone, especially with respect to pain reduction. (Kashikar-Zuck et al., 2018)

Osteoarthritis (OA)

Osteoarthritis is the most common form of arthritis. Nearly 27 million Americans, age 25 and older, have OA. Before age 45, more men than women have OA; after age 45, it is more common in women. Although OA can develop without any obvious trauma to a joint, people who have torn their anterior cruciate ligament (ACL) are at high risk of developing knee OA. The ACL is a flexible, stretchable tissue that tunnels through the knee, connecting the femur, or thigh bone, with the tibia, or shin bone. According to the American Academy of Orthopaedic Surgeons, female athletes who participate in jumping and

pivoting sports, such as basketball and soccer, are between 2 and 10 times more likely to injure the ACL than male athletes who participate in the same sports. These types of injuries also increase the likelihood that a person will develop knee OA within one or two decades after the injury. Total joint replacement is the only treatment for end-stage OA. Data from the National Hospital Discharge Survey and the Healthcare Cost and Utilization Project State Inpatient Databases revealed that 7 million Americans, 4.4 million of whom were women, were living with a hip or knee replacement in 2010.

Intra-articular Steroid Injections may be Detrimental for Knee Health.

Intra-articular steroid injections are a standard treatment for OA pain, but their sustained clinical benefit is controversial. To address the long-term effects of this treatment, NIH-funded investigators examined 140 symptomatic knee OA patients (54% of whom were women) who received intra-articular injections of the steroid triamcinolone or saline once every 12 weeks for 2 years. While their findings neither prove nor negate the effectiveness of steroid injections for short-term relief of pain, the investigators found no long-term effect on knee pain. In fact, the group that received the steroid showed signs of more extensive cartilage loss than the control group, suggesting that long-term use may result in adverse effects on preservation of knee cartilage. (McAlindon et al., 2017)

Men and Women Tear their ACLs the Same Way in Non-contact Injury.

While women are more likely than men to tear an ACL, new research shows that the cause of this injury is no different between the sexes. This counters a common explanation for the higher incidence of the injury in women: that they are more susceptible to ACL tears because their knees move differently. Using a novel image processing program, investigators created three-dimensional models of injured knees from males and females based on magnetic resonance scans that showed the locations of femoral and tibial bone bruises. This enabled the researchers to determine and compare knee positions by aligning the bone bruises as the point of impact at the time of an ACL rupture. Their results showed no differences in the position of injury between males and females, indicating a similar mechanism of action in both sexes. (Owusu-Akyaw et al., 2018)

Altered Knee Joint Mechanics after ACL Reconstruction May Contribute to Early OA.

New research provides insight into the role abnormal joint mechanics play in the development of arthritis following an ACL tear and ultimately could provide a framework for the design of strategies to prevent post-traumatic OA. Compared with patients who had ACL reconstruction but did not develop OA within five years, patients who had radiographic knee OA five years after ACL reconstruction were more likely to have walked with a reduced range of motion six months after surgery. Altered movement patterns are common months after ACL reconstruction and likely contribute to articular cartilage breakdown and may need to be corrected to allow the repaired knee to safely withstand the demands of sports, leisure, and occupational activities. Given that healthy movement patterns can be restored through rehabilitation, the study results also highlight the potential that post-traumatic OA could be prevented after ACL injury. (Wellsandt et al., 2017)

Foundation for the National Institutes of Health (FNIH)

Biomarkers Consortium Launches Project Seeking Regulatory Qualification of Biomarkers for Measuring Knee OA.

In August 2018, the FNIH Biomarkers Consortium launched a project to seek regulatory qualification of new biological markers (biomarkers) that

predict joint damage from OA in the knee. The PROGRESS OA: Clinical Evaluation and Qualification of Osteoarthritis Biomarkers project, managed by the FNIH, will submit a comprehensive report, including imaging (i.e., MRI) and biochemical (i.e., urine, serum) biomarkers, for review by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). The acceptance of these biomarkers for use in drug development will pave the way for improved clinical trials and treatments for knee OA. The project team includes the NIAMS, leading academic experts in the field of OA, industry partners, and the Arthritis Foundation. https://fnih.org/news/announcements/measuring-knee-osteoarthritis?bblinkid=107211083&bbemailid=9023186&bbejrid=695387184

Osteoporosis and Bone Biology

Osteoporosis, or porous bone, is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures of the hip, spine, and wrist. In the United States, more than 53 million people either already have osteoporosis, or are at high risk of developing the condition due to low bone mass. Osteoporosis can occur in both men and women and at any age, but it is most common in older women. Hip fracture is the most devastating consequence of osteoporosis; it leads to short- and long-term functional impairment, loss of ability to live independently, and even death. According to the Healthcare Cost and Utilization Project, there were more than 300,000 hospital admissions for hip fractures among people aged 65 and older in 2012; three-quarters of these fractures occurred in women (Agency for Healthcare Research and Quality, 2012). Because the incidence of hip fracture increases with age, it is expected to become an even larger public health problem as the U.S. population ages.

Bone health depends on the balance between two tightly coupled, opposing processes that constitute the bones' constant remodeling activities: bone resorption, in which bone cells called osteoclasts remove old damaged bone, and bone formation, in which bone cells called osteoblasts lay down new bone. Basic NIH-funded research into the mechanisms underlying bone formation and removal—and how drugs influence these processes—could lead to new treatments for people who are at risk of osteoporotic fractures.

Hip Fracture Risk is Not Linked to Circulating Markers of Bone Turnover.

As mentioned above, hip fractures lead to significant health consequences, with most requiring hospitalization and surgery and leading to increased morbidity and mortality. Although circulating bone turnover markers CTX and PINP are associated with fracture risk and are recommended by current guidelines as reference markers for clinical studies, a recent study using data from the Women's Health Initiative shows that they may have little use in predicting hip fracture risk. Although identifying people at higher risk of hip fracture using non-invasive methods is important to help decrease the associated health and economic burdens, understanding which approaches are not informative also is essential. (Crandall et al., 2018)

Weight Loss Due to Bariatric Surgery Results in Bone Loss and Changes in Bone Marrow Fat.

Investigators studied thirty obese women with an average age of 48.2 years to address whether changes in glucose metabolism and fat depots following bariatric surgery affect bone. The researchers examined changes in bone marrow fat, which is a dynamic and unique fat depot thought to regulate the formation and maintenance of bone and fat throughout the body. Data from diabetic and non-diabetic women suggest that glucose metabolism and weight loss may influence marrow fat, which in turn seems to influence bone mineral density. Ultimately, understanding the role of marrow fat in bone metabolism could facilitate developing strategies

that target the skeletal complications of bariatric surgery, diabetic bone fragility, and the prevention and treatment of osteoporosis in general. (Kim et al., 2017)

The Transcription Factor Cbfβ Has a Role in Bone and Fat Cell Regulation.

At the cellular level, osteoporosis is associated with decreases in bone formed by osteoblasts (bone-forming cells) and increases in bone marrow fat formed by adipocytes (fat cells). While this switch in activity by osteoblasts and adipocytes is a much studied area in the bone field, it is not completely understood. Researchers found the transcription factor core-binding factor subunit beta (Cbfβ) acts to both increase bone formation and decrease fat development, potentially providing a new therapeutic target for osteoporosis. (Wu et al., 2017b)

Mechanistic Studies of Parathyroid Hormone Signaling Reveal New Targets for Osteoporosis Therapies.

An international team of researchers studying proteins that are regulated by parathyroid hormone identified the enzyme SIK2 and its down-stream signaling molecules as potential drug targets for strategies to boost bone mass. Follow-up studies showed that small molecule inhibitors of SIK2 hold promise as new drug candidates. The compounds mimic the bone building properties of teriparatide—an osteoporosis drug derived from parathyroid hormone that stimulates bone formation. In addition, one of the compounds reduced the number of bone-destroying osteoclast cells—a welcome, albeit unexpected effect for enhancing bone formation that may overcome teriparatide's limitations and allow for longer-term use. (Wein et al., 2016)

NIAMS and the National Institute on Aging Support Healthy People 2020 Osteoporosis Objectives.

NIAMS supports efforts with the HHS Office of Disease Prevention and Health Promotion and the Centers for Disease Control and Prevention for the completion of the Healthy People 2020 initiative and preparations for the implementation of Healthy People 2030. In FY 2017 and 2018, NIAMS continued as scientific leads in the Arthritis, Osteoporosis and Chronic Back Condition topic area and supported data collection to address the osteoporosis objectives "to reduce the proportion of adults with osteoporosis" and "to reduce hip fractures among older adults- aged 65 and older." These data will also establish a baseline for the future Healthy People 2030 data collection.

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) affects an estimated 1.5 million Americans. It is a debilitating autoimmune disease, characterized by chronic joint inflammation in which the body's natural defense system attacks its own tissues. RA occurs in all races and ethnic groups. Although the disease often begins in middle age and occurs with increased frequency in older people, children and young adults also develop it. Like many autoimmune diseases, RA occurs much more frequently in women than in men. About two to three times as many women as men have the disease.

Metabolic Interference Corrects Dysfunctional Immune Cells in RA.

Dysregulation of a type of white blood cell called a T cell plays a pivotal role in the development of autoimmunity in RA. Recent work has connected dysfunction of RA T cells with abnormalities in their energy supply and metabolism. For example, RA T cells have impaired glycolysis (breakdown of glucose), which leads to their hyperproliferation and secretion of proinflammatory mediators. To better understand how T cell dysfunction contributes to RA, NIAMS-supported researchers used a variety of pharmacologic and genetic techniques to manipulate T cell metabolism and function. The study showed that a small molecule targeting a protein involved in T cell energy metabolism could be used to reverse

metabolic abnormalities in RA T cells. The results suggest that this protein is a potential target for intervention to correct abnormal immune responses early in the development of RA. Further studies are needed to test whether metabolism-based treatment can be applied as a preventive therapeutic intervention. (Shen et al, 2017)

Specific Subsets of Tissue Cells in RA Joints Correlate with Disease Activity.

In RA, cells called fibroblast-like synoviocytes secrete pro-inflammatory factors, invade and degrade cartilage, and mediate the progressive destruction of the joints. Using cutting-edge technologies to analyze cell surface markers and gene expression, researchers discovered that fibroblast-like synoviocytes can be divided into subsets with distinct molecular functions and biological roles. Moreover, one subset was expanded in active RA and associated with increased immune cells and greater disease activity. Although further studies are needed to understand precisely how changes in fibroblast-like synoviocyte subsets are involved in a variety of clinical aspects in RA, the knowledge provided by this and future studies could be used to develop precise therapies for RA. (Mizoguchi et al., 2018)

Study Using Cells from RA Joints Identified Unexpected Association with Another Disease.

Building on findings that fibroblast-like synoviocytes collected from RA patients exhibit a distinct pattern of epigenetic alterations compared with the same type of cells from patients with OA, researchers used four cutting-edge technologies—ATAC-seq, ChIP-seq, RNA-seq, and whole genome bisulfate sequencing—to create a high resolution map of the RA cells' epigenetic landscape. The investigators used a new algorithm to integrate these diverse datasets to uncover RA-specific pathways and transcription factors. Unexpectedly, they discovered that a signaling pathway associated with Huntington's disease, a fatal genetic brain disease, ranked top among RA pathways, above the many pathways already known to be relevant to RA. The researchers went on to show that a protein involved in Huntington's disease is present in RA fibroblast-like synoviocytes and plays a role in these cells' invasion into cartilage. This startling overlap with Huntington's disease suggests the possibility of new therapeutic targets and drugs for both conditions. Of note, women who have Huntington's disease have a slightly more severe phenotype and a faster rate of progression, especially in the motor and functional domains, than men. (Ai et al., 2018)

Researchers Characterize Molecule that Contributes to Inflammation and Bone Erosion in RA.

Building on work showing that a protein called FLIP is necessary for differentiation and survival of inflammatory macrophages (cells that promote inflammation and lead to bone and cartilage destruction in RA), investigators determined that FLIP may also impact inflammation and bone erosions in RA through other mechanisms. A new mouse model that produces lower than normal levels of FLIP unexpectedly experienced joint swelling sooner than controls during the early phase of RA, but had lower peak disease scores and significantly less severe disease during the late phase of RA. Consistent with the reduced bone erosion during late-phase RA in FLIP-low mice, the number of bone-destroying osteoclasts present in the joints was markedly reduced, a finding that suggests FLIP may have a role in osteoclast formation or survival. Although the FLIP-low mice had a significantly lower number of anti-inflammatory tissue-resistant macrophages in the joints prior to the induction of arthritis, their macrophage numbers were elevated in the late phase of arthritis. Taken together, these findings provide insights into a potential target that could be exploited for development of new therapeutics for RA. (Huang et al., 2017)

Scleroderma/Systemic Sclerosis (SSc)

Scleroderma is a rare, severe, and heterogeneous autoimmune disease that involves progressive hardening of the skin and internal organs due to fibrosis. Systemic sclerosis (SSc) is one form of scleroderma and involves many parts of the body, such as skin, internal organs, and blood vessels. Women are approximately four times more likely than men to develop systemic SSc.

Dimethyl Fumarate has an Anti-Fibrotic Effect on Skin Fibrosis in Scleroderma.

The drug dimethyl fumarate, or DMF, is FDA-approved for multiple sclerosis and is approved for psoriasis by the European Commission. Because of DMF's effectiveness against these diseases and others where chronic inflammation is a key characteristic, researchers investigated whether it can modulate the skin fibrosis that is associated with scleroderma. They isolated skin fibroblasts from either healthy donors or scleroderma patients, treated the cells to induce expression of profibrotic genes, and found that follow-up treatment with DMF efficiently blocked fibrosis. Gene expression studies identified a set of pro-fibrotic genes that were suppressed by DMF. This and other findings from the same study support the potential use of DMF as a therapeutic treatment for scleroderma-associated fibrosis. (Toyama et al., 2018)

Scleroderma Patients with Fibrosing Myopathy have Increased Mortality Rates.

NIAMS intramural researchers have conducted the first study analyzing the clinical features of scleroderma patients with muscle weakness and fibrosing myopathy. Fibrosing myopathy scleroderma patients had more severe muscle weakness and higher mortality rates than scleroderma patients with inflammatory myopathy. Scleroderma patients with fibrosing myopathy reported muscle weakness, but did not express high levels of the muscle disease marker CK, which is commonly used by clinicians to define muscle disease severity. This study indicates that muscle biopsies may be necessary to identify the cause of muscle weakness and determine the appropriate therapeutic intervention in scleroderma patients. (Paik et al., 2017)

A Blood Biomarker (CCL2) Predicts Rapidly Progressing Lung Disease in SSc Patients.

Interstitial lung disease—the leading cause of death for patients who have SSc—has an unpredictable trajectory, especially for people who are in the early stages of SSc. To determine whether any changes in a patient's blood could predict the development of this complication, a group of researchers examined samples and data collected through two studies of scleroderma patients—the Genetics versus Environment in Scleroderma Outcome Study (GENISOS) and the Canadian Scleroderma Research Group (CSRG). Analysis of both groups independently revealed an association between higher blood levels of the chemokine C-C motif ligand 2, also known as CCL2, and faster declines in lung function, suggesting that CCL2 can be used to identify patients who are at highest risk of rapidly progressing interstitial lung disease. The findings also support earlier work that indicates CCL2 could be a potential target for SSc therapies. (Wu et al., 2017a)

Systemic Lupus Erythematosus (SLE; Lupus)

Lupus is a chronic autoimmune disease that, for unknown reasons, causes the immune system to mistakenly attack the body's own healthy cells and tissues. An estimated 90 percent of people diagnosed with lupus are women. Lupus is more prevalent in African Americans, Hispanics, and Asians. African American women are three times more likely to develop lupus than Caucasian women. African Americans and Hispanics/Latinas tend to develop lupus at a younger age and have more symptoms at diagnosis (including kidney problems).

JAK Inhibitor Tofacitinib has Therapeutic Potential for Lupus Treatment.

NIAMS intramural scientists along with colleagues from the NHLBI and the NIH Office of the Director investigated how the drug tofacitinib, a JAK inhibitor, affects lupus progression in a mouse model. In mice that received tofacitinib prior to lupus onset, signs of the disease were prevented. Administration of tofacitinib after disease onset and symptom development resulted in a reversal of symptoms. The results demonstrate that tofacitinib is both a preventative and therapeutic strategy for control of lupus in a mouse model. Future studies will examine if tofacitinib has the same effects, particularly on controlling lupus-induced blood vessel dysfunction, in patients. (Furumoto et al., 2017)

Immune Activation Products Predict Pregnancy Complications in Women with Lupus.

For years, patients with lupus and/or antiphospholipid (aPL) antibodies were advised not to get pregnant because of the high potential risk to the mothers and their babies. However, little was known about the risk factors that contribute to adverse pregnancy outcomes (APOs). New data from the long-standing PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study showed that 20 percent of patients with lupus and/or aPL experienced APOs. Compared with women without APOs, these women had elevated blood levels of two molecules known as complement activation products as early as 12 to 15 weeks of pregnancy, and levels remained high through 31 weeks. APO risk factors such as complement activation products could be used to stratify patients into low- and high-risk groups for future clinical trials that test interventions to prevent APOs. These findings may also enable physicians to better counsel and manage high-risk patients at an early stage, significantly impacting prenatal care. (Kim et al., 2018)

Studies of Mice and People Provide New Insight into Role of Estrogen in Lupus Kidney Disease.

Despite therapeutic advances, kidney disease still has a significant impact on prognosis and quality of life for patients with SLE. Researchers used a mouse model of lupus nephritis to demonstrate that estrogen signals through estrogen receptor alpha on immune cells and renal cells, causing a shift in metabolic pathways that leads to progression of severe kidney damage. Parallel observations with SLE patients show that these results may be translated to human disease and shed light on the influence of hormonal factors in lupus disease progression. While further studies are warranted, the insights from these findings could lead to approaches for treating or preventing lupus nephritis. (Corradetti et al., 2018)

Researchers Look for Predictors of Kidney Inflammation and Scarring in Lupus.

Renal injury is the most important predictor of mortality in patients with SLE, and a growing body of evidence indicates damage to the connective tissue between kidney structures (the tubulointerstitial component) is a better predictor of kidney failure than glomerular (i.e., the part of the kidney responsible for filtration) parameters. Investigators studied a comprehensive array of clinical and serologic factors in 203 people who had signs of lupus nephritis and found none that were associated with tubulointerstitial inflammation and scarring. However, use of hydroxychloroquine, a drug commonly used to treat SLE, was associated with a statistically significant reduction in the risk of kidney inflammation. Findings from this retrospective study highlight the need to identify alternative biomarkers for early identification of individuals at risk for serious kidney problems. Additionally, it suggests that continued use of hydroxychloroquine may protect against serious kidney damage even if a person with SLE already has lupus nephritis. (Jimenez et al., 2018)

Low Density Granulocytes Contribute to Cardiovascular Disease Risk in Lupus Patients.

A recent study from the NIAMS Intramural Research Program (IRP) Systemic Autoimmunity Branch compared 64 lupus patients with mild disease to healthy controls and found that lupus patients had increased inflammation, stiffness, and dysfunction of their blood vessels. Increased total coronary plaque burden was also observed in these patients. Importantly, noncalcified plaque burden, which confers enhanced cardiovascular disease risk, contributed greatly to their total plaque burden. Building on earlier work from the lab, the investigators looked at low density granulocytes, a subset of neutrophils that are abundant in the blood of lupus patients and were able to link these cells to vascular damage and cardiovascular risk in lupus patients. (Carlucci et al., 2018)

Juvenile Idiopathic Arthritis (JIA)

Children can develop almost all types of arthritis that affect adults, but the most common type is juvenile idiopathic arthritis (JIA). JIA is currently the most widely accepted term to describe various types of chronic arthritis in children. In general, symptoms include joint pain, swelling, tenderness, warmth, and stiffness that last for more than six continuous weeks. JIA is more common in girls than boys. Systemic juvenile idiopathic arthritis (sJIA) is a severe form of childhood arthritis that is marked by inflammatory episodes with recurrent fever, together with chronic arthritis, a characteristic skin rash, and enlargement of the lymph nodes, liver and spleen.

Genetic Analysis of Risk Factors Supports Reclassification of sJIA.

Researchers from the Translational Genetic and Genomics Unit in the NIAMS IRP used single nucleotide polymorphism (SNP) data from a study population of 770 sJIA patients and nearly 7,000 healthy individuals to identify genetic regions associated with sJIA risk. The genetic region that corresponded to the highest risk was in the major histocompatibility complex, a gene previously shown to be a major sJIA risk factor. In addition, 24 new regions associated with sJIA risk were identified. Importantly, the sJIA regions identified in this study did not overlap with regions associated with other forms of JIA. The data support the idea that sJIA is genetically distinct from other forms of JIA and should be reclassified as an autoinflammatory disease. (Ombrello et al., 2016)

Researchers Identify Therapeutic Biomarker in sJIA.

An international team of researchers led by the Translational Genetics and Genomics Unit of the NIAMS IRP identified a SNP region affecting a gene called IL1RN that is associated with sJIA risk. When they studied this region further, they discovered that SNPs associated with high expression of IL1RN, or its gene product IL1RA, correlated to protection against sJIA, while SNPs associated with low IL1RN or IL1RA expression correlated to increased disease risk. IL1RN expression also correlated with the patient's likelihood to respond to anakinra, a synthetic form of IL1RA used to treat sJIA. Non-response to anakinra was observed in patients carrying SNPs linked to high IL1RN expression. This study demonstrates that IL1RN is truly involved in sJIA susceptibility and highlights IL1RN as a potential biomarker to help clinicians determine sJIA treatment strategy. (Arthur et al., 2018)

NIH Strategic Plan for Women's Health Research

While all of the accomplishments and activities described in this document relate to the goals and objectives outlined in the NIH Strategic Plan for Women's Health Research, the following efforts are particularly noteworthy. Two relate to including sex parameters in the design of experiments using animal models (part of Goal 1), and one is an example of a NIAMS-led strategic alliance and partnership to maximize the domestic and global impact of women's health research (Goal 4).

Sex Affects Response to Therapy in the Skin Disease Pachyonychia Congenita.

Researchers exploring potential treatments for the painful palmar-plantar keratoderma (PPK) that is associated with skin disorders such as pachyonychia congenita discovered that their mouse model of PPK exhibits sexual dimorphism. To ameliorate PPK, male mice can be treated by sulforaphane, yet females need a dual drug treatment, such as sulforaphane+diarylpropionitrile (a drug that opposes estrogen-receptor beta), to effectively treat the condition. Therefore, these results are exceedingly important for designing PPK clinical trials. (Kerns et al., 2018)

Experiment into How Muscle Mass can be Altered by Manipulating Gene Splicing Reveals Sex Differences.

When splicing factors Rbfox1 and Rbfox2 were deleted in an adult mouse, muscle mass was lost due to a reduction in muscle fiber size, strength was decreased, and overall energy expenditure was increased. There were notable differences between male and female animals, however. 80 percent of males died within 3 weeks of Rbfox1 and Rbfox2 removal, but none of the male controls or females died during this time period. Affected males were less active, their blood glucose levels were lower, and they were hypersensitive to insulin relative to the male controls and female mice. (Singh et al, 2018)

NIAMS and the National Institute on Aging Lead a Pathways to Prevention Effort on Appropriate Use of Pharmacologic Therapies for Osteoporotic Fracture Prevention.

Despite short-term efficacy of osteoporosis therapies, data on their long-term use are limited. The Pathways to Prevention effort on Appropriate Use of Pharmacologic Therapies for Osteoporotic Fracture Prevention will clarify major questions related to the safe long-term use of osteoporosis drugs. A dozen NIH Institutes, Centers, and Offices (including ORWH) and other Federal entities are participating in this effort. As part of the workshop process, a panel of scientists who are unaffiliated with the osteoporosis field are issuing an expert panel report that will be published in a leading medical journal. It will lay the foundation for activities within and outside of the NIH and other federal agencies to develop research strategies and partnerships that can be pursued in FY 2020 and beyond.

III. Information Dissemination

Publications and Health Information Resources

Disseminating information about research progress continues to be an essential component of the NIAMS mission. ORWH has a long history of supporting the NIAMS-led NIH Osteoporosis and Related Bone Diseases ~ National Resource Center (ORBD~NRC), which provides health professionals, patients, and the public with information on osteoporosis, a disease that disproportionately affects women. The ORBD~NRC develops and distributes health information resources that are specific to women and bone health.

Social Media

NIAMS Hosted Scleroderma Twitter Chat. On June 29, 2017, partnering with the National Heart, Lung, and Blood Institute, the Scleroderma Foundation, and the Scleroderma Research Foundation, NIAMS hosted a Twitter chat on scleroderma. NIAMS intramural researchers and grantees were on hand to provide input on questions posted during the chat. The chat reached nearly 150,000 Twitter users with 2.6 million impressions.

NIAMS Participated in #LupusChat. On May 20, 2018, NIAMS participated in #LupusChat, a weekly Twitter chat hosted by the Lupus Online Community. During this chat, NIAMS presented

information about lupus clinical trials and how people can learn about and participate in them. NIAMS intramural researchers were on hand to answer questions that participants posted. The chat reached over 4 million impressions with 1,098 tweets.

NIAMS Hosted Osteoporosis Twitter Chat. In partnership with the National Osteoporosis Foundation, the American Society for Bone and Mineral Research, and the National Bone Health Alliance, NIAMS hosted a Twitter chat about osteoporosis on May 31, 2018. The chat focused on the causes, impact, and treatments of osteoporosis as well as current research, advances in understanding the disease, and strategies to reduce bone loss and live an active life. Over 195,000 Twitter accounts were reached with a total of nearly 2 million impressions.

IV. Funding Initiatives, Workshops, and Conferences

NIAMS Funding Opportunity Announcements

Rheumatic Diseases Research Resource-based Centers (P30): In FY 2017, NIAMS issued a funding opportunity announcement (RFA-AR-18-004) to invite applications for the NIAMS Resource-based Centers Program (P30) for rheumatic disease research areas within its mission. The awarded Resource-based Centers listed below will provide critical research infrastructure, shared facilities, services, and resources to groups of investigators conducting research on rheumatic diseases, many of which disproportionately affect women.

- Resource-based Center for the Study of the Joint Microenvironment in Rheumatology (Nunzio Bottini, University of California San Diego, Grant P30 AR073761)
- Oklahoma Rheumatic Disease Research Corse Center (Judith A. James, Oklahoma Medical Research Foundation, Grant P30 AR073750)
- Washington University Rheumatic Diseases Resource-based Center (Christine T. Pham and Deborah J. Lenschow, Washington University, Grant P30 AR073752)

Centers of Research Translation (P50): In FY 2017, NIAMS issued grants for its Centers of Research Translation (CORT) (P50) program under funding opportunity announcement (RFA-AR-17-001). Research topics could cover any area in the NIAMS mission. Two selected for funding (listed below) are related to diseases that disproportionately affect women.

- Translational Center of Molecular Profiling in Preclinical and Established Lupus (COMPEL) (Jill P. Buyon, New York University School of Medicine, Grant P50 AR070591)
- Translational Studies for Identifying and Targeting Novel Pathways in Systemic Sclerosis (Robert A. Lafyatis, University of Pittsburgh, Grant P50 AR060780)

Research Innovations for Scientific Knowledge (RISK): These NIAMS initiatives (RFA-AR-17-008 and RFA-AR-17-009) encourage applicants to pursue unusual observations, test imaginative hypotheses, investigate creative concepts, and build ground-breaking paradigms, all of which deviate significantly from the current prevailing theories or practice. The following awards directly relate to diseases or conditions that disproportionately affect women.

- Empirical Validation of a Novel HLA-Disease Association Theory in Skin and Rheumatic Diseases (Joseph Holoshitz, University of Michigan at Ann Arbor, Grant R61 AR073014)

- Deep Learning for Characterizing Knee Joint Degeneration Predicting Progression of Osteoarthritis and Total Knee Replacement (Sharmila Majumdar and Valentina Pedoia, University of California, San Francisco, Grant R61 AR073552)
- The Nervous Joint: New Concepts in the Development of Osteoarthritis (Anne-Marie Malfait and Richard J. Miller, Rush University Medical Center, Grant R61 AR073576)
- Polycystins/TAZ as a Novel Therapeutic Target to Treat Osteoporosis (L Darryl Quarles, University of Tennessee Health Science Center, Grant R61 AR073518)
- In vivo Discovery of the Osteocyte Protein Secretome: Identification of Novel Factors and Functions (Alexander G Robling, Indiana University-Purdue University at Indianapolis, Grant R61 AR073551)
- Mesenchymal Stem Cells Derived from Human Gingiva (GMSC) Inhibit Bone Erosion in Autoimmune Arthritis (Song Guo Zheng, Pennsylvania State University Hershey Medical Center, Grant R61 AR073049)

Participation in ORWH Funding Opportunity Announcements

NIAMS participated in funding opportunity announcements for the ORWH-led administrative supplements for Research on Sex/Gender Influences (PA-17-078 and PA-18-658) and for Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations (PA-17-101 and PA-18-676) and for the Specialized Centers of Research Excellence (SCORE) on Sex Differences (RFA-OD-18-004).

V. Health Disparities

Accomplishments and Activities

Osteoporosis and Low Bone Mass Are Common in Older Puerto Ricans.

Increasingly, data suggest that osteoporosis risk, fracture rates, and the cost of treatment are increasing in the Hispanic population. These studies have focused mainly on Mexican Americans despite evidence that Hispanic subgroups have different rates of bone loss. Now, data from the Boston Puerto Rican Osteoporosis Study suggests that Puerto Rican and non-Hispanic white women have similar rates of osteoporosis, and that the middle-aged Puerto Rican men in this study are more likely to have osteoporosis than older Puerto Rican men. This finding is important because understanding osteoporosis and low bone mass in different populations will allow for better screening, diagnosis, and treatment that can lead to decreased overall costs and improved quality of life for those at risk or with disease. (Noel et al., 2018)

Publications and Health Information Resources

In October of 2017, NIAMS launched a redesigned website that included improvements to the Community Outreach Initiative, a NIAMS effort to provide health information to diverse populations and specific audiences. It provides curated NIAMS and ORBD~NRC resources, such as a page dedicated to health information for women.

Many of the NIAMS web pages are available in both English and Spanish. In addition to Spanish resources, the NIAMS has a collection of health information available in Chinese (Mandarin), Korean and Vietnamese. Many of the multilingual topics focus on diseases or conditions that disproportionately affect women. Publications that were updated in FY 2017-2018 include:

- Living With Arthritis: Health Information Basics for You and Your Family (English, Spanish, Chinese)
- Joint Replacement Surgery: Health Information Basics for You and Your Family (English, Spanish)

NIAMS Videos

In FY 2018, NIAMS added a new video, "Delia's Story," to its series of videos featuring patients who participated in studies at the NIH Clinical Center. This was the first NIAMS video recorded in Spanish with English subtitles. It featured a Hispanic woman, Delia, describing her experience with the NIAMS Community Health Clinic after being diagnosed with RA. Videos are available through the Institute's Community Outreach Initiative website and the NIAMS YouTube channel.

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National Institute of Biomedical Imaging and Bioengineering

I. Executive Summary

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) (1) fosters, conducts, supports, and administers research and research training programs in biomedical imaging and bioengineering by means of grants, contracts, and cooperative agreements; (2) provides coordination, integration, and review of progress and planning of biomedical imaging and bioengineering research; (3) formulates research goals and long-range plans with the guidance of the National Advisory Council for Biomedical Imaging and Bioengineering; and (4) sponsors scientific meetings and symposia, collaborates with industry and academia, and fosters international cooperation regarding biomedical imaging and bioengineering.

NIBIB supports a research portfolio that pursues cutting-edge technology development in the area of women's health research. During FY 2017 and FY 2018, NIBIB funded grants focused on technologies aimed at improving healthcare for women included projects ranging from advanced imaging methodologies to tissue engineering activities designed specifically for women's diseases, such as breast cancer, to diseases with profound consequences for women, such as sexually transmitted diseases.

II. Accomplishments and Activities

Breast Cancer

Photon Tunneling: Shedding New Light on Biomedicine (DP1 EB016986): This grant developed a new photoacoustic imaging system that does not use x-rays, thus avoiding the use of ionizing radiation, shows early promise for sensitivity in radiographically dense breasts, and imposes less or no pain by only slightly compressing the breast against the chest wall. The entire breast can be scanned rapidly within a single breath hold (~15 seconds), and a 3D image can be acquired with negligible breathing-induced motion artifacts. In this pilot study, the new photoacoustic imaging system successfully identified tumors in a wide range of breast sizes, without resorting to ionizing radiation or contrast agents, and posed no health risks. NIBIB is helping to provide a promising tool for future clinical use including not only screening, but also diagnostic studies to determine extent of disease, assisting in surgical treatment planning, and assessing responses to chemotherapy. (Lin, et al., 2018).

Super Resolution Ultrasound for Detecting Microcalcifications (R21 EB024133): The presence of microcalcifications is indicative of malignancy in breast tissue. Improving the sensitivity of imaging techniques to detect microcalcifications would improve early detection and diagnosis of breast cancer. This project team developed a novel nonlinear beamforming technology for ultrasonic arrays that provides super resolution of ultrasonic images (up to 25 times improvement in resolution). They hypothesize that this imaging technique will perform well for the specific imaging task of detection of microcalcifications in tissues. This grant is to develop and validate this new imaging technique and examine its role in detecting microcalcifications in breast cancer.

Sensitivity Enhanced MR Imaging of Receptor Binding in Breast Cancer (R21 EB025295): Recent discoveries have identified that the cell

surface lactate receptor HCA1 is associated with tumorigenesis and metastasis and thus is a potential imaging and therapeutic target for breast cancer. This project develops a novel MRI-based tool for detecting the binding of lactate to HCA1 receptors in breast cancer that may significantly enhance sensitivity compared with currently available techniques. Importantly, this method can be implemented on standard MRI systems and thus be rapidly translated to the clinic. Although at its early stage, the research has the potential to open doors for early diagnosis and monitoring of targeted therapies for breast-cancer patients.

Visual Search In 3D Medical Imaging Modalities (R01 EB026427): Digital breast tomosynthesis is a new 3D imaging technology intended to make cancers more visible to the radiologist. However, there is insufficient understanding of the potential impact of these new 3D imaging technologies on diagnostic accuracy, and no knowledge of what eye movement strategies should be used by radiologists to minimize errors when searching through these volumes, while keeping manageable reading times. The project aims to develop a computational model for assessing the adequacy and efficiency of the 3D visual search of radiologists and then evaluating if the search strategy is well matched to the radiologist's detection capabilities. Together, these advances can potentially help reduce errors in breast cancer detection.

A High Resolution and High Detective Quantum Efficiency (DQE) Detector Optimized for Mammography Could Increase Sensitivity and Reduce Radiation Dose (R44 EB021125): This project is building a prototype new-generation mammography imaging camera to create images of breast tumors that reveal small structures not seen in current conventional mammography scans. This new and novel application of x-ray imaging for the breast (called x-ray interferometry) has the potential to improve diagnostic scans revealing macrocalcifications and tumor branches while achieving shorter exposure, lower radiation dose, and improved image quality. This technology holds the promise of greatly improved early detection of breast cancers.

Multi-Contrast X-ray Breast Imaging Could Improve the Sensitivity and Reduce Radiation Dose (R01 EB020521): This research project is developing a multi-contrast x-ray digital mammography and digital breast tomosynthesis imaging system that enables the detection of cancer masses and microcalcifications using a new and novel x-ray imaging mechanisms (phase contrast and dark field methods), while avoiding potential increases in imaging radiation dose. This new imaging system will enable the isolation of cancer masses and microcalcifications from the surrounding glandular and adipose tissues in different contrast mechanisms for radiologically dense breasts. This has the potential to further improve the sensitivity and specificity of mammography and digital breast tomosynthesis for screening and diagnostic applications. (Ji, et al., 2017; Ji, et al., 2018).

High Sensitivity, X-ray Detector Technology Based on Polycrystalline Mercuric Iodide for Volumetric Breast Imaging (R01 EB022028): This research focuses on developing an active matrix, flat-panel imager with high enough sensitivity to allow multiple 2D breast images to be acquired to create a 3D image of the breast. The resulting 3D image overcomes the complication of tissue overlap, which obscures cancer detectability in conventional 2D mammography. The characteristics of a Polycrystalline Mercuric Iodide flat-panel detector holds the promise of obtaining many 2D images with acceptably low radiation dose, permitting diagnostic 3D images with improved image quality for visualization of micro-calcifications associated with breast cancers. The successful completion of the specific aims of this project would result in the availability of a new x-ray imaging technology with sensitivities of 3 to 10 times higher than that

of the detectors presently used in digital breast tomography.

Novel Peptide Platform for Targeted PET Imaging and Radiotherapy of Breast Cancer. (F32 EB025050): Triple-negative breast cancer (TNBC), a subtype with particularly poor prognosis in part due to the lack of effective targeted therapies, is diagnosed in 10-20% of patients with breast cancer in the USA. This project has developed a novel peptide, called pH(low) insertion peptide (pHLIP®), which targets the acidic extracellular environment of cancer cells, and has high potential for use in oncologic clinical applications, particularly for TNBC. This research project is optimizing pHLIP®-based technologies for dual use: as a general diagnostic/imaging tool and as a targeted therapy agent for TNBC. (Carter, et al. 2018; Jannetti, et al., 2018; Krebs, et al., 2018).

New Fluorescent Agent for Intraoperative Image-Guided Breast Cancer Surgery (R01 EB023924): This project focuses on development of non-toxic imaging agent targeted to breast cancer cells to improve the accuracy of intraoperative identification of breast tumor margins, thus increasing the precision of breast cancer resection. The agent is based on indocyanin green, a fluorescent agent that could be used as intra-operative tumor marker, in conjunction with accurate tumor-targeting carrier. The focus of this grant is investigating if tumor-targeting carrier peptide p28, which preferentially enters and is longer retained in breast cancer cells, conjugated to indocyanin green, can clearly distinguish breast cancer from surrounding normal tissue during surgery.

Biomaterial-Based Breast Cancer Vaccine (R01EB015498): Cancer cells are generally ignored by the immune system because they tend to more closely resemble normal cells rather than pathogens, such as bacterial cells or viruses. The goal of cancer vaccines is to provoke the immune system to recognize cancer cells as foreign and attack them. This application proposes a new approach to cancer vaccines, in which biomaterials are introduced into the body in a minimally invasive manner (via injection) are used to program, in situ, host dendritic cells to generate a potent cytotoxic T lymphocyte response to kill the cancer cells. (Koshy et al., 2018; Cheung et al., 2018).

Ovarian Cancer

Protein/Polymer Implants to Eliminate Ovarian Cancer Cells and Prevent Recurrence by Slow-Release of Immunotherapies (R21 EB024874): Ovarian cancer is the leading cause of death among gynecologic diseases, with over 100,000 deaths per year worldwide, and prognosis is poor, because patients often present with disseminated disease. The researchers in this project are formulating a polymer implant to slowly release a plant-based virus that has been shown to be effective against ovarian cancer and induces immune memory to fight off recurrence of the cancer. The clinical utility of such a device would be immense by allowing initial surgical removal of visible tumors followed by placement of the implant in the intraperitoneal cavity, which will release the vaccine over the course of weeks-to-months to eliminate remaining cancerous cells and prevent recurrence.

Rare Earth Nanoprobes for Optical Imaging and Disease Tracking (R01 EB018378): This project is developing a library of new nanosized imaging agents that can identify and track microlesions in multiple organs, which is particularly important for early detection of small cancer metastasis and may enable earlier clinical intervention in the future. These agents are based on rare earth metals encased in protein albumin and are emitting short wave infrared light which can be imaged deeper in the tissue then other optical fluorescent agents. A combination of such nanoprobes appears to be more robust in identification of early bone, adrenal gland and liver metastases in mouse model of breast cancer

than conventional CT and MRI methods. This initial work will be accomplished in an ovarian cancer model.

Reproductive Health and Pregnancy

Microfluidic encapsulation of ovarian follicles for biomimetic 3D culture and cryopreservation (R01 EB023632): Isolation and cryopreservation of ovarian follicles for in vitro culture in order to obtain healthy fertilizable oocytes is considered a promising strategy for restoring and preserving female fertility. This project aims to develop a microfluidic device for selective extraction of follicle-laden microcapsules and to assess the use of the biomimetic ovary microtissue system for follicle development and ovulation and follicle cryopreservation. This study bears important research and clinical implications with respect to follicle biology, drug screening, and fertility restoration. (He, 2017a; He, 2017b; He and Toth, 2017; Liu, et al., 2018; Zhao, et al., 2017).

3D-Printed Integrated Microfluidic Devices for Preterm Birth Biomarker Analysis (R01 EB027096): Preterm birth is the most common complication of pregnancy and responsible for most neonatal deaths and newborn illnesses. This project aims to develop and evaluate 3D-printing methods to manufacture inexpensive, miniature devices that will determine risk for a preterm birth using a finger-prick blood sample from a pregnant woman, several weeks before contractions might occur. With this information, treatment can be initiated if needed, and the number of preterm births and their associated complications would be reduced significantly.

Point-Of-Care Device to Identify Patients at Risk for Preeclampsia (R44 EB024288): According to the World Health Organization preeclampsia is one of the leading causes of maternal morbidity and mortality worldwide. Affinergy is developing a point-of-care device that will capture, isolate, and allow rapid biomarker quantification leading to the unambiguous diagnosis of preeclampsia. This SBIR project is poised to improve the quality of podocyte capture and lead to significant cost savings by minimizing time and equipment cost.

Low-Cost Handheld Medical Device for Neuroaxial Anesthesia Guidance in the Obese (R44 EB015232): Epidural and spinal anesthesia is often performed by utilizing manual palpation of spinal bone landmarks to guide a needle. However, in overweight individuals spinal bone landmarks may not be detectable by palpation. X-ray fluoroscopy can be performed to guide needle placement, but it lacks portability, has a higher cost, and exposes patients to ionizing radiation. Additionally, imaging methods using ionizing radiation may not be used for epidural placement during pregnancy. As a result of this award to a small business, the company developed a handheld ultrasound device that utilizes a bone visualization algorithm and automatic detection of spinal bone landmarks to identify the needle injection site for epidural or spinal anesthesia. Potentially this device may be used for challenging obstetric epidural or spinal anesthesia administrations. The company has received FDA 510(k) clearance for this handheld ultrasound device. (Tiouririne, et al., 2017).

Advanced MRI for the Assessment of Early Brain Development (R01 EB018988): MRI imaging of infants and young children has always been challenging because of uncontrolled motion. The overall objective of this research is to dramatically improve technology and knowledge for in-vivo analysis of normal and abnormal white matter structure and neural connectivity before and early after birth when the brain undergoes its most rapid formative growth. Investigators aim to develop innovative, computationally driven methods to mitigate the limitations of current imaging technology to achieve motion-robust MRI of moving subjects. The developed methods and resources would open new avenues of research and clinical care in neurodevelopmental

disorders. (Gholipour, et al., 2017; Jia, et al., 2017; Marami, et al., 2017; Tourbier, et al., 2017).

Advanced Fetal Imaging (R01 EB017337): The fetal period is a time of unparalleled brain growth and development and is arguably the most important time for defining future cognitive potential. Therefore, when fetal brain development is impaired, abnormalities emerge in utero and contribute to lifelong cognitive impairment that cannot be corrected even with optimal postnatal care. This has led to an overwhelming public health need for methods that detect early in utero anatomical and physiological abnormalities to better counsel parents and to better guide development and optimization of fetal interventions (surgical or medical) to prevent or mitigate such long-term consequences. Although there has been ongoing optimism that fetal MRI could fulfill this role, it is still severely limited by the unique anatomy of the gravid abdomen, the small size of the fetus and, most importantly, fetal motion. As a result, fetal brain MRI lags far behind postnatal brain imaging. This project is focused on advancing fetal MRI using an integrated approach that addresses the entire imaging acquisition process. (Bilgic, et al., 2017; Im, et al., 2017; Zhao, et al., 2018).

Sexually Transmitted Diseases

Center for Point-of-Care Technologies Research for Sexually Transmitted Diseases (U54 EB07958): This center develops Point-of Care tests to rapidly and accurately diagnose sexually transmitted diseases, with the goal of improving the sexual health of individuals and prevent the spread of these infectious diseases in both the U.S. and in resource poor settings through the world. This center has addressed the diagnosis of several sexually transmitted diseases, including chlamydia, which is far more prevalent in women than in men, and trichomonas, a sexually transmitted parasitic vaginal infection. This center conducted needs and health impact assessments, and collaborates with experimental and computational scientists, clinicians, and patients to develop sexually transmitted disease diagnosing Point-of Care technologies for use in emergency departments, clinics, and at home. (Chen, et al. 2018; Gaydos, et al., 2017; Melendez, et al., 2018; Paterson, et al., 2017; Pittman, et al., 2018; Widdice, et al., 2018).

Sex and Gender Influences

Sensor Arrays Based on Molecularly Imprinted Polymers for Diagnosis of Sjögren's Syndrome (R01 EB022025): Sjögren's syndrome, which occurs predominantly in women, is an autoimmune disease initially affecting the mucous membranes and moisture-secreting glands of your eyes and mouth are usually affected first—resulting in decreased tears and saliva. Diagnosing Sjögren's syndrome in the early stages of the disease can help mitigate damage from systemic manifestations that occur later in the disease. This project aims to develop a low-cost sensor for detecting molecular evidence of Sjogren's without the need for invasive testing. This will be achieved using molecularly imprinted polymers (which serve as synthetic receptors) that detect multiple biomarkers and so provide a more robust diagnostic tool. (Culver, et al., 2017).

Computational (Virtual) Model to Optimize Surgical Treatment

Virtual Pelvic Surgery Simulator for the Prevention of Surgical Errors (R21 EB025272): In the more than 200 million surgeries performed annually worldwide, preventable complications occur. The overall goal of this project is to create a system to identify, model, and prevent surgical errors. This project will analyze a complex, high-risk step of the Midurethral Sling procedure, a common surgery to treat incontinence in older women. The researchers will quantitatively model the surgical procedure during the high-risk step in which the surgeon must guide a sharp, pointed steel trocar past vital structures, including the bladder, bowel, and major blood vessels. The researchers will develop a 3D pelvic simulator

and software to provide feedback to the surgeon during the simulation, ultimately providing a systematic way of identifying and modeling surgical errors that can be applied to high-risk steps in other surgeries and leading to effective error prevention and increased patient safety.

III. NIH Strategic Plan for Women's Health Research

A long running project, a point-of-care center on sexually transmitted diseases, aligns with Goal 1 of the ORWH Strategic Plan: "Increase Sex Differences Research in Basic Science Studies, objective 1.6, Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases including HIV/AIDS, urinary tract and sexually transmitted infections." Most NIBIB-funded projects in women's health align strongly with Goal 2 of the ORWH Strategic Plan: "Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs." Many other projects funded by NIBIB align with Objective 2.7: "Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls." Example projects aligning with this objective are the numerous projects on improve breast imaging for breast cancer diagnosis and treatment, and a biomaterial-based breast cancer vaccine.

IV. Inclusion

The NIBIB Inclusion Policy Officer works closely with Program Directors and Investigators to ensure compliance with inclusion policies and to promote opportunities related to women's health research. NIBIB staff work with grantees to assure compliance with the policies on sex as a biological variable and on how developing technologies may be applied to support women's health.

V. NIBIB Science, Technology, Engineering, and Mathematics (STEM) Training Efforts

NIBIB is committed to increasing the participation and success undergraduates in STEM. In 2018 NIBIB funded its first cohort of programs under the Enhancing Science, Technology, EnginEering, and Math Educational Diversity (ESTEEMED) initiative. This initiative relies on first-hand research experiences and mentoring activities to retain underrepresented undergraduate freshmen and sophomores STEM fields and ultimately prepare them to pursue a Ph.D. or M.D./Ph.D. degree and a biomedical research career in academia or industry.

As part of its STEM training efforts, NIBIB continues to hold an undergraduate prize competition for biomedical design projects. This annual competition, Design by Biomedical Undergraduate Teams (DEBUT) Challenge, receives numerous entries from across the country. The 2018 Third-Place winner was device named Neuraline, from Georgia Institute of Technology. Neuraline was developed to facilitate the placement of epidural anesthesia during labor and delivery. The current method of epidural insertion requires the technician to feel a loss of resistance in order to identify the epidural space in the spine. However, the loss of resistance can be highly variable depending on the individual patient and skill of the technician. One in eight attempts at this procedure results in complications ranging from post-dural puncture headaches to cardiac arrest, and even death. Neuraline is designed to provide an objective measure of bioimpedance—the resistance that different tissues have to electricity—that will alert the technician to the needle's location and when it has reached the correct epidural space. The project has the potential to impact women's health

by increasing the accuracy of epidural placements and enabling lesser skilled clinical staff to deliver epidurals in lower-resource settings.

NIBIB supports training programs at undergraduate, doctoral, postdoctoral and early faculty stages and strives to maintain gender balance in its training grants. All institutional programs are required to indicate the sex/gender of the supported trainees and asked to justify any imbalances and describe plans for overcoming them.

NIBIB supports the Bioengineering Experience for Science Teachers (BEST) program at University of Illinois at Chicago. High school science teachers participate in research in the laboratories of Bioengineering faculty over the summer. The majority of high school teachers participating in this program are women. Female science teachers who can engage their students in STEM topics are especially important as role models inspiring female students to go into STEM fields. Concurrently, College of Education faculty provide guidance to the science teachers in translating their research experiences into classroom material. This summer-research experience enhances the skills of science teachers and enables them to more effectively understand and communicate current trends in bioengineering research to their students and enhance overall science literacy. Moreover, by sharing the developed curricula on the internet, the BEST program extends its impact not only to participating science teachers and their students, but to those around the country and even the world.

VI. Funding Initiatives and Workshops

NOT-AG-18-008 & NOT-AG-18-039: Alzheimer's Disease and its Related Dementias (AD/ADRD)-Focused Administrative Supplements for NIH Grants That Are Not Focused on Alzheimer's Disease

Nearly two-thirds of Alzheimer's patients are women. This initiative allows current NIH awardees to apply for administrative supplements to expand existing awards that are not currently focused on Alzheimer's disease (AD) and its related dementias (ADRD) to allow them to develop a focus on AD/ADRD. Topics include new and improved imaging modalities and possible connections to existing conditions such as links to cardiovascular or other diseases, on common pathways of degeneration, on sex and gender influences in incidence, or on previously unidentified risk factors.

RFA-HL-19-016: Technologies for Healthy Independent Living for Heart, Lung, Blood and Sleep Disorders (R43 - Clinical Trial Not Allowed)

This initiative supports applications for the design and development of technologies to monitor health or deliver care in a real-time, accessible, effective, and minimally obtrusive way for older adults with a chronic heart, lung, blood, or sleep (HLBS) condition. These technologies may be novel sensor or monitoring systems, home-use point-of-care devices, home or mobile therapy or rehabilitation tools, or information systems and should have the goal of fostering healthy and independent living for aging adults with HLBS conditions. These technologies could yield more accurate and earlier detection of changes that may interfere with healthy and independent living for older adults. Approximately twice as many older women as older men live alone.

RFA-NS-18-007 & RFA-NS-19-011: NIH Blueprint Diversity Specialized Predoctoral to Postdoctoral Advancement in Neuroscience (D-SPAN) Award (F99/K00 Independent Clinical Trial Not Allowed)

The purpose of this initiative is to enhance the pool of well-trained diverse neuroscientists who will pursue academic/research careers. The D-SPAN will support mentored research training for late-stage graduate students from

backgrounds that are nationally underrepresented in neuroscience research and who have demonstrated interest and potential in pursuing careers as independent researchers. Both graduate students and postdoctorates report decreased interest in faculty careers over time, with women and underrepresented minorities (URM) reporting a comparatively greater decrease than men and well-represented trainees. This two-phase award will facilitate completion of the doctoral dissertation and transition of talented graduate students to strong neuroscience research postdoctoral positions and will provide career development opportunities relevant to their long-term career goal of becoming independent neuroscience researchers.

PA-18-592: Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (Admin Supp - Clinical Trial Not Allowed)

NIBIB participates in this program for administrative supplements to research grants to support individuals with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances. This program will provide administrative supplements to existing NIH research grants for the purpose of supporting full-time or part-time research by these individuals to update their existing research skills and knowledge.

PA-17-085: Rapid Assessment of Zika Virus (ZIKV) Complications (R21)

A possible association between ZIKV infection in pregnant women and severe microcephaly in their babies has been very concerning and prompted the World Health Organization to declare this potential association a public health emergency. Additionally, the virus detected in the blood has fueled growing concerns about the risk of transmission from transfusions, particularly for pregnant women. The purpose of this announcement is to provide support for research on ZIKV and its complications.

International Workshop on Breast Imaging (R13 EB026317): The International Workshop on Breast Imaging is the premiere international event for leading breast imaging research and is designed as a platform to present the latest technological developments and clinical experiences of novel breast imaging technologies, including but not limited to digital mammography, tomosynthesis, CT, MR, ultrasound, optical and molecular imaging. The workshops are designed to help advance the fields of breast cancer and medical imaging through the sharing of scientific discoveries, best clinical practices, and industrial innovations.

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Eunice Kennedy Shriver National Institute of Child Health and Human Development

I. Executive Summary

The mission of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is to ensure that every child is born healthy and wanted; that women suffer no harmful effects from the reproductive processes, that all children can achieve their full potential for healthy and productive lives, free from disease or disability; and to ensure the health, productivity, independence and wellbeing of all people through optimal rehabilitation. The NICHD supports essential research that plays a unique role in women's health, aiming to overcome or mitigate many of the complex health challenges that women may encounter in their lifetime. The Institute is home to much of the Nation's leading scientific research related to women's overall health, gynecological health, pregnancy, and childbirth, as well as studies of sex/gender influences on diseases and conditions related to pediatric and adolescent health, and medical rehabilitation.

Major Institute research areas include contraception, preconception care, pregnancy and lactation, maternal health, gynecological conditions (including vulvodynia, pelvic floor disorders, impaired fertility, uterine fibroids, and endometriosis); HIV and its associated co-infections as they affect women, and other critical aspects of women's health. NICHD incorporates analysis of sex/gender influences on health throughout its extensive portfolio, including such areas as pediatrics, medical rehabilitation, population health, and sex and gender minority (SGM) health. A strong Institute priority is training the next generation of researchers in women's health, with a special emphasis on career-building for women scientists. The Institute also maintains multiple, diverse outreach and dissemination activities. NICHD research in women's health and sex/gender influences on health and disease extend across the Institute. Key extramural branches include:

- The Gynecologic Health and Disease Branch (GHDB) supports basic, translational and clinical research and research training, emphasizing studies of the menstrual cycle, uterine fibroids, endometriosis, polycystic ovary syndrome, and pelvic floor disorders, as well as research on the mechanisms that underlie chronic pelvic pain, vulvodynia, and dysmenorrhea.
- The Contraceptive Research Branch (CRB) supports research in contraceptive development for both men and women, including new contraceptive methods, mechanisms of action and effects of contraceptive and reproductive hormones, drugs, and devices, and optimal formulations and dosages of contraceptive agents.
- The Fertility and Infertility Branch (FIB) supports scientific research to enhance understanding of strategies for the diagnosis, management, and prevention of conditions that compromise fertility, with the ultimate goal of promoting a better quality of life for all individuals.

- The Maternal and Pediatric Infectious Disease Branch (MPIDB)supports domestic and international research related to HIV infection and associated co-infections (such as tuberculosis, malaria, and hepatitis), as well as non-infectious complications of HIV in pregnant and non-pregnant women and children. MPID also studies congenital infections including Zika virus and cytomegalovirus.
- The Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB) supports research to improve the safety and efficacy of pharmaceuticals for children and pregnant women.
- The Pregnancy and Perinatology Branch (PPB) supports research to improve the health of women before, during, and after pregnancy, reduce the number of preterm births and other birth complications, and ensure the long-term health of mothers and their children.

Intramural divisions at NICHD also support women's health research. Within the Institute's Division of Intramural Research a major program in perinatal research and obstetrics focuses on pregnancy and pregnancy complications, including the long-term effects of preeclampsia on maternal health. The Division of Intramural Population Health Research designs and conducts innovative etiologic and interventional research, spanning preconception through adulthood, focusing on successful reproduction, the health and wellbeing of pregnant women and their infants, and related areas across the lifespan.

II. Accomplishments and Activities

Women's Health *(See also relevant items in Funding Initiatives and Workshops and Conferences)*

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). Mandated by the 21st Century Cures Act (P.L. 114-255), the NICHD-led Task Force reported its findings to the Secretary, HHS and Congress in September 2018. Task Force findings detailed the state of the science and widespread research gaps on the safety, efficacy, and dosing of drugs, vitamins, and herbal supplements commonly used in clinical management of pregnancy-related conditions and non-pregnancy related disorders (such as autoimmune diseases, infections, and cancer) in large majorities of pregnant and lactating women. Among Task Force recommendations was research on therapies appropriate for the unique patient characteristics of pregnant and lactating women. Task Force activities were responsive to Objective 2.7, "Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls," as well as Strategic Plan Objective 3.3, "Encourage research on safe and effective interventions for conditions affecting pregnant women."

The Human Placenta Project (HPP). The HPP is leveraging recent advances in scientific technology and techniques to discern, non-invasively and in real time at every stage of pregnancy, the origins and processes of healthy and atypical placental development and function. Once thought to be primarily a passive means of transport of oxygen and nutrients between the fetus and pregnant woman, the placenta is now understood to be involved in, and perhaps facilitate the direct maternal-fetal interaction and exchange of cells. Historically, most knowledge about the placenta has come from examining it after delivery. Real-time assessments during pregnancy are critical to understanding and addressing the causes of pregnancy complications and adverse outcomes. The HPP is responsive to Strategic Plan Objective 2.5, "Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and

treatment of diseases and conditions in women and girls."

PregSource™. This innovative NICHD project, launched in FY 2017, uses crowdsourcing methodology to collect a wide range of data from pregnant women, with a goal of understanding healthy pregnancies so as to better understand what can go awry in a pregnancy and why. The project leverages social media to create a national registry, which allows researchers with appropriate confidentiality and consent compliance to hear directly from women about their experiences during pregnancy, including preterm and term births. Participants can track their pregnancy data over time, print reports to share with their clinicians, and compare their data to that of other women in the initiative's data base. In addition, the project provides participants with links to trusted, evidence-based information from partner organizations about healthy pregnancy and pregnancy-related complications. The project's methodology and unique new data resources are responsive to Strategic Plan Objective 2.3, "Develop the information systems needed for collecting, sharing, and comparing clinical data for diseases and conditions of women and girls," and Objective 3.4, "Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.

Women's Health Scientific Accomplishments

FDA Approved a New Contraceptive Ring. Women in low-resource settings may face multiple barriers in obtaining effective contraceptive methods whose use is wholly within their control. However, research supported through the NICHD Contraceptive Clinical Trials Network led to the 2018 FDA approval of a vaginal contraceptive ring that a woman can insert and remove by herself, and that offers reliable protection against unintended pregnancy for a year. This contraceptive ring dispenses a hormone combination and does not require refrigeration, an important feature in low-resource settings. (Stifani 2018, Press release, CCTN contracts)

LARC Affects Post Abortion Contraceptive Use. Long-acting reversible contraceptive methods (LARC) have been shown to be highly effective in lowering the probability of repeated abortion, as well as to have high satisfaction, but high up-front LARC costs may keep women who wish LARC from using it. A prospective study of more than 500 women who had undergone abortions and who were enrolled in a specialized funding program for low-income, uninsured county residents compared them with two groups of women ineligible for the program: those who were also low0income and uninsured, but not county residents, and high-income or insured women. Women in all the groups preferred LARD to other contraceptive methods, but those in the special program were more likely to use and continue with LRC methods, while ineligible low-income women were more likely to use less effective contraceptives and more likely to have unintended pregnancies. (Goyal V 2017)

Compound Shows Promise as Potential New Treatment for Endometriosis. Up to 10% of reproductive-age women in the U.S. experience endometriosis, a chronic condition in which endometrial tissue that normally lines the uterus grows outside the uterus, causing many women to experience severe pelvic pain, infertility, and increased risk of cancers. Existing treatment options for endometriosis, including anti-inflammatory medication, hormonal treatment or surgery, all have drawbacks. Researchers recently found that bufalin, a naturally-occurring compound used in certain Chinese traditional medicines, disrupted SRC (a key protein in endometriosis) and reduced the proliferation of connective-tissue cells in endometrial lesions in experimental mice. In laboratory experiments, the scientists also showed that the compound suppressed the growth of certain human endometrial cells that had been isolated from

patients with endometriosis. The findings indicated that compounds that, like bufalin, inhibit SRC function may be a new class of drugs to treat endometriosis. (Cho YJ 2018)

Iodine Deficiency May Reduce Pregnancy Chances. Researchers analyzed data from 501 U.S. couples planning pregnancy, and found that women who had moderate-to-severe iodine deficiency had a 46% lower chance of becoming pregnant during each menstrual cycle, compared with women who had sufficient iodine concentrations in urine samples provided to the researchers. Women in the mildly-deficient range had a smaller, statistically insignificant increase in the time it took to conceive. (Mills JL 2018)

Diets Low in Sodium and Magnesium Linked to Problems with Ovulation. Anovulation, the failure of a woman's ovaries to release an egg during the menstrual cycle, can occur sporadically or over a long period of time and may thus contribute to abnormal cycle lengths and infertility. In a large study of women's reproductive health, researchers obtained data on diets and lifestyles and also collected blood samples at different phases of participants' menstrual cycle. Findings included increased risk of sporadic anovulation in women whose sodium intake fell below recommended daily levels. A similar risk of anovulation was found in women with below recommended daily levels of magnesium intake, but not with eight other nutrients that were also measured. (Kim K 2018)

Effects of Age on Treating Refractory Urgency Urinary Incontinence in Women. A comparison of two treatments for urinary urge incontinence in women showed that these treatments, assessed in separate clinical trials, both produced improvements, with reduced incidence of the urgent loss of bladder control that characterize the disorder, improved quality of life, and similar rates of adverse event associated with other treatments. The women receiving the two treatments of interest had refractory urinary incontinence that had not responded to other behavioral or pharmacological interventions. One of the two treatments was use of botulinum toxin to paralyze certain muscles; the other, neuromodulation, used a device to stimulate nerves leading from the bladder to the brain. Younger women, under age 65, experienced greater improvement than older women, but both groups experienced improvement that they had not experienced with other treatments. (Komesu YM 2018)

Identifying Causes of Maternal Deaths in Low- and Middle-Income Countries. In resource-limited countries, where maternal mortality (deaths associated with pregnancy) remain high, systems for identifying and classifying causes of these deaths require procedures such as autopsies that are typically not available. The recent test of a new classification system that relies exclusively on data that are readily available in limited resource countries suggests that it could be helpful in developing strategies to prevent maternal mortality. The test, in India, Pakistan, Guatemala, Democratic Republic of Congo, Kenya, and Zambia, found wide variation in maternal mortality ratios in these populations, but the three most common causes of maternal death were consistent across study sites. These were obstetric hemorrhage (39% of deaths), pregnancy-related infection (24%), and preeclampsia/eclampsia (18%). The researchers' algorithm-assigned causes of death closely matched health care providers' assignments of cause of death for hemorrhage and preeclampsia, although not for pregnancy-related infection. They also found that for major causes of maternal mortality, a substantial proportion of women had not received standard of care treatment, which suggested important opportunities for lowering maternal mortality rates. (Pasha O 2017)

Perinatal Suicidal Ideation among Women Living with HIV in South Africa. Pregnant women living with HIV in resource-limited countries are at high risk of suicidal ideation. To identify risk factors for such ideation

during pregnancy and in the postpartum period, researchers analyzed data from a large longitudinal study of mother-to-child HIV transmission in rural South Africa. They found that suicidal ideation was most likely to occur and last longer among women experiencing physical intimate partner violence. Younger age and reporting HIV status to a partner was associated with lessened suicidal ideation, despite the stigma of positive HIV status. The findings indicated that perinatal care may provide opportunities to identify and treat suicidal ideation, as well as depression. (Rodriguez VJ 2018)

Individualized Oxycodone Prescribing after Cesarean Birth. After cesarean delivery, the most common major surgical procedure in the U.S., individual patients do not use ten to 15 opioid tablets prescribed for post-operative pain. Total non-use annually is 13 to 20 million tablets, which could be diverted to non-medical uses. Clinicians typically prescribe a uniform quantity of opioids, however, regardless of likely individual patient need. Recent research compared post-hospitalization use of opioids in two groups of cesarean delivery patients: half of whom received a prescription based on their individual in-hospital use of opioids before discharge (12 to 16 tablets of 5 mg oxycodone), and half who received the standard prescribed amount of 30 tablets of 5 mg oxycodone. There was no difference in the percentage of women in each group who used no prescribed opioids, nor those who used all prescribed tablets. However, women receiving the individualized prescription used only half the number of tablets as the women using the standard prescription, and patient reports of post-discharge pain did not differ significantly between the two groups of patients. (Osmundson SS 2018)

Rare Disease Suggests Potential Targets for Developing Future Osteoporosis Treatments. There are only limited treatment options for osteoporosis, the progressive bone loss that disproportionately occurs in women. Recently, research with genetically engineered mouse models of a rare genetic disorder, Timothy syndrome (TS), suggested a possible target for developing new therapies for progressive bone loss. TS is caused by a mutation that renders the Cay calcium channel to close, resulting in increased flow of calcium into cells. Although the irregular heart rhythms of Timothy syndrome are explained by this excessive influx of calcium, its contribution to bone abnormalities also seen in the syndrome has not been studied. In investigating the calcium channel activity, the researchers found indications that the calcium influx regulated bone development, and could be used as a therapeutic to treat bone loss. Testing this idea in a mouse model for osteoporosis, in which estrogen deficiency causes bone loss in female mise — similar to that in post-menopausal women — the researchers discovered that when the TS calcium channel mutation was expressed in these female mice, the resulting increased calcium channel activity prevented bone loss that may have resulted from estrogen deficiency. This approach could be further explored to see if it could be harnessed to develop a new therapeutic strategy for osteoporosis. (Cao C 2017)

No Difference between Two Common Surgeries to Treat Vaginal Prolapse. Vaginal prolapse, a type of pelvic floor disorder, occurs when pelvic organs bulge into or extend beyond the entrance to the vagina, causing discomfort and compromise bladder or bowel emptying for some patients. A recent comparison of two surgeries commonly done to correct vaginal prolapse has found that five years after the surgeries, there were no significant differences in success rates. Most women having either of the surgeries — uterosacral ligament suspension or sacrospinous ligament fixation, reported improvements in their symptoms. While there were slight differences in rates of surgical failure, the differences were neither statistically nor clinically significant. (Jelovsek JE 2018)

More Frequent Doses of Buprenorphine May Be Needed During Pregnancy. For a

medication to treat a pregnant woman's opioid dependence safely and effectively, doses recommended for non-pregnant patients may not be sufficient, because the unique metabolism of pregnant women may cause the drug to "clear" too quickly for effective exposure. Researchers recently determined that pregnant treated with buprenorphine for opioid dependence need more frequent daily doses of the medicine than the currently-recommended dosing for non-pregnant patients. Their analysis of data from three different studies indicated that the standard dosing regimen for non-pregnant patients fails to produce a high enough blood concentration of the drug in pregnant patients to prevent opioid withdrawal symptoms for them. (Caritis SN 2017)

Antidepressants in Pregnancy Not Associated with Intellectual Disability in Offspring. Data in Swedish national registers on parents of almost 180,000 children, over a period of eight years, showed no relationship between maternal antidepressant use during pregnancy and intellectual disability in children. Some animal studies had raised the possibility that prenatal exposure to selective serotonin reuptake inhibitors (SSRI), commonly prescribed for depression or anxiety, could cause offspring to have problems with intellectual function and everyday social and life skills. The researchers focused on children of women who had been diagnosed with depression or anxiety, some of whom had taken antidepressants while others had not. After ruling out such "confounding" factors as parental age, education, or other psychiatric conditions, the researcher found no relationship between maternal antidepressant use and children's intellectual status. (Victorin A. 2017)

ADHD Medication Associated with Small Risk of Preeclampsia and Preterm Birth. Although ADHD medication is commonly used, there have been only limited data on the effects of ADHD medication on the placenta, which controls blood flow to the fetus in pregnancy and may be involved in pregnancy complications in some women. Researcher assessed possible ADHD effects in pregnant women and their infants enrolled in Medicaid from 2000 to 2010, using medical records to compare outcomes in about 5,300 women who had been exposed to ADHD medications in early and/or late pregnancy with outcomes in over 1.4 million unexposed women. Specific outcomes of interest were preeclampsia (high blood pressure and possible kidney involvement), placental abruption (separation of the placenta before delivery), small-for-gestational-age newborns, and preterm delivery (birth occurring before 37 weeks of gestation). Maternal use of the ADHD medications was associated with a small increased risk of preeclampsia and preterm birth, but the absolute risk was small. The researchers commented that their findings indicated that women with significant ADHD should not be counseled to suspend their treatment during pregnancy. (Cohen JM 2017)

Gut Microbiome Associated with Polycystic Ovary Syndrome (PCOS). Polycystic ovarian syndrome (PCOS), which affects 5% to 15% of women worldwide, is typically characterized by elevated patient levels of androgens (male hormones), irregular menstrual periods, and/or fluid-filled sacs (cysts) on one or both ovaries. Along with infertility, women with PCOS are at higher risk for miscarriage and other pregnancy complications, as well as obesity, type 2 diabetes, and cardiovascular disease. Research has suggested that women with PCOS have fewer varieties of the tiny microorganisms, known collectively as the "microbiome," in their gut, compared with other women. To explore this possibility, researchers investigated whether androgen levels and other PCOS symptoms were related to changes in their gut microbes, by comparing samples from women with PCOS, women with ovarian cysts, but not other PCOS symptoms, and women without the conditions. Women with PCOS had the least diverse gut microbiomes, while women with ovarian cysts had greater microbiome diversity – though less than women who had no signs of the condition.

Testosterone levels and overall androgen levels also correlated with microbial diversity – the higher a woman's levels of these hormones, the less diverse her gut microbiome. (Torres PJ 2018)

Women with Lupus Are More Likely to Develop Early-Onset Preeclampsia during Pregnancy. Preeclampsia is known to be a significantly elevated risk for pregnant women with systemic lupus erythematosus (SLE), an autoimmune disease in which the body's own immune system attacks a patient's tissue. Preeclampsia before 34 weeks of pregnancy is associated with even higher risk of such problems as detachment of the placenta from the uterine wall and stroke. It has not been known whether early onset of preeclampsia — as well as preeclampsia later in a pregnancy — is a significantly higher risk for women with SLE. A recent study that compared more than 700 pregnant Swedish women with SLE with more than 10,000 pregnant women without SLE found that early-onset preeclampsia was significantly more likely to occur in women with SLE, indicating that these women should be closely monitored for possible preeclampsia throughout pregnancy. (Simard J 2017)

Aspirin May Help Increase Pregnancy Chances in Women with High Inflammation. A daily low dose of aspirin may help a subgroup of women with a history of pregnancy loss to conceive, and carry a pregnancy to term, according to analysis of data from a clinical trial of aspirin to prevent pregnancy loss. Analysis found that women who benefitted from the aspirin treatment had high levels of C-reactive protein (CRP), a molecule in the blood that signals the presence of systemic inflammation, which aspirin is thought to counteract. For this analysis, the researchers assessed three groups of women separately — those with low, medium or high CRP. Among women with the low and medium CRP blood levels, there was no difference in birth rates between those receiving aspirin and those receiving the placebo. For those in the high CRP group, those taking the placebo had the lowest rate of live birth (44%) while those taking the daily aspirin had a live-birth rate of 59% — a 35% increase. (Lindsey A 2017)

Growth and Regression of Uterine Fibroids. Decades of research on the common non-cancerous uterine tumors known as fibroids have implicated the reproductive hormones estrogen and progestin as contributors to fibroid growth, and collagen fiber abnormalities as fibroid growth promoters. Limitations in cell culture studies prompted researchers to assess the effects of stopping estrogen and progestin in experimental mice that had been grafted with human fibroid cells. The researchers found that the grafted fibroid cells rapidly lost 60% of their volume. Contrary to current theories, however, the shrinkage did not result from cell death but shrinkage of cells and further, collagen fibers were initially well-aligned in the fibroids. The fiber disruption found in human fibroids occurred only when fibroids in animals treated with the hormones had grown to more than 20 times the volume of fibroids in untreated mice — so the fiber disruption was a result, not a cause, of tumor growth. (Serna VA 2018)

Sex/Gender Influences on Health and Disease. (See also relevant items in Funding Initiatives and Workshops and Conferences)

Research Activities and Scientific Accomplishments

NICHD research in this area is responsive to multiple Strategic Plan Objectives, including 1.1, "Encourage genetic and epigenetic studies to identify sex differences in gene expression" and 1.2, "Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems. A subset of NICHD activities in this area addresses the health of sexual and gender minorities (SGM), with focuses on biological, clinical, behavioral and psychological processes

that affect the health of lesbian, bisexual, and transgender women as well as other sexual and gender minority populations. Such research and related activities are responsive in part to Strategic Plan Objective 1.8, "Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral functioning to health and well-being." With regard to the population of individuals with disorders/differences of sex development (DSD), also known as intersex, NICHD activities respond in part to Strategic Plan Objective 1.7, "Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues and organs…" In focusing on atypical developmental processes of DSD from the earliest sex determination and differentiation to the phenotypic level, this research may also inform understanding of typical developmental processes underlying sex and gender influences on human health and disease. See also relevant examples in Funding Initiatives and Conferences and Workshops below.

Sex Differences in Sensitivity to Aripiprazole from Adolescence to Adulthood. Many studies on the efficacy of antipsychotic drugs, whose use in males and females has increased in recent years, have yielded data on males only and data on effects of these drugs on children at different stages of development have also been lacking. In behavioral tests with male and female experimental rates, researchers showed that repeated treatment of adolescent rats with the antipsychotic aripiprazole (brand name Abilify) increased the rats' sensitivity to the medication, lasting into adulthood, and that female rats were more sensitive to both short- and long-term effects than male rats. The researchers found similar sensitivity differentials in animals previously exposed to aripiprazole and subsequently dosed with two other antipsychotic drugs. (Freeman E 2017)

Evidence for the Roles of *FMR1* Gray Zone Alleles as a Risk Factor for Parkinsonism in Females. Idiopathic Parkinson's disease (iPD) is the most common form of the degenerative neurological disorder; "idiopathic" means its cause or causes are unknown. Accumulating findings that "gray zone alleles" (GZ alleles) of the fragile X intellectual and developmental disability 1 gene (*FMR1*) were significantly overrepresented in male iPD patients recently prompted a genetic search for GZ alleles in 601 adult female patients with iPD-associated movement disorders. Alleles are "intermediate" forms of a specific gene, meaning that they are not normal but also not fully mutated. The researchers found overrepresentation of the GZ alleles in the female patients at rates comparable to what had been reported for affected males. The finding consolidated evidence of a role for these alleles in the risk for the spectrum of disorders associated with Parkinson's and raised the possibility of standard testing for GZ alleles in iPD patients and, possibly, targeted treatment. (Loesch DZ 2018)

Differences in Major Depression among Adolescent Girls and Boys. Analysis of data from a nationally-representative survey of more than 100,000 American youth ages 12-17 found higher rates of depression in these young people, with more than one in five girls reporting experience with depression, compared with one in eight boys. At age 12, girls were more likely than boys to report depression and the difference widened over the course of adolescence. For girls, persistent depression was more strongly associated with poor functioning in school and the community, while for boys effects of persistent and more recent depression were similar. (Breslau J 2017)

Mental Health of Transgender and Gender Nonconforming Youth. Transgender and gender nonconforming individuals (TGNC) individuals, identified at birth as female or male but not identifying as that gender later can experience stress related to their experience gender identity difference and their minority

group status. Health plan medical records of TGNC children and adolescents have enabled researchers to better understand the magnitude of mental health problems experienced by male-to-female and female-to-male young people. Depressive disorders were found in 49 percent of transfeminine and 62 percent of transmasculine adolescents, significantly higher than in non-TGNC young people, and both self-inflicted injury and suicidal thoughts are significantly higher in the TGNC participants. (Becerra-Culqui TA 2018).

Cross-Sex Hormones and Acute Cardiovascular Events in Transgender Persons. Cross-sex hormone therapies can support a transgender individual's gender identity as a trans woman (male-to-female) or a trans man (female to male), although such therapies raise concerns about risks of acute cardiovascular events, including blood clots, ischemic stroke, and heart attacks. Analyses of electronic health records at three large health plans found that, compared with non-trans enrollees, trans women enrollees had elevated rates of blood clots and, to a lesser extent, ischemic stroke. These rates of risk were comparable to those in non-trans men and indicated that increased vigilance of effects of cross-sex hormone therapy among trans women may be warranted. (Getahun D 2018)

III. Inclusion

Highlights of data from the NICHD's *2016-2018 Triennial Advisory Council Report Certifying Compliance with the NIH Policy on Inclusion Guidelines* (included as an Appendix to this Biennial Report) indicate that at 2016 baseline, aggregate enrollment data for all NICHD projects (extramural and intramural) indicated that a majority of enrolled participants (67.6%) were female and only 1.7% were not identified by sex/gender. In 2017-2018, females remained the majority 62.4% and 60.2% respectively) of enrolled participants. There was a substantially higher percentage of females in intramural projects in all three years (88.4%, 90.4%, and 89.9% respectively). In response to the new 21st Century Cures Act requirements related to inclusion in Clinical Research, the NIH and NICHD updated policies, effective December 13, 2017, on the Inclusion of Women and Minorities as Subjects in Clinical Research. The updated policies require that both NIH-defined Phase III clinical trials and applicable clinical trials results/ gender and/or race/ethnicity to ClinicalTrials.gov. The new policies apply to competing grant awards on or after the effective date as well as to contract solicitations and intramural studies initiated after that date.

STEM Efforts

Among NICHD efforts are assessments of women's participation of women in programs providing training, mentorship and career development in research disciplines central to the Institute mission, and partial support of important scientific research conferences that typically address young investigator professional development specifically. Following are women's participation rates in the three major programs that focus specifically on women's health research.

Reproductive Scientist Development Program. During FY 2017-2018, 72% of K12 scholars participating in this program for any amount of time were women. The program's goal is ongoing development of a cadre of reproductive physician-scientists, based in academic departments who can employ cutting-edge cell and molecular technologies to address important problems in the field of Obstetrics and Gynecology. The mentored research experiences this program offers seek to assist junior faculty in their transition to productive, independent physician-scientists who are highly competitive for research funding. The program accepts approximately four scholars each year for a five- to six-year training period.

Women's Reproductive Health Research (WRHR) Career Development Program. During FY 2017-2018, 80% of K12 scholars participating in this

program for any amount of time were women. NICHD and ORWH support this national program of mentored institutional career development programs for junior faculty who have recently completed postgraduate training in obstetrics and gynecology, and are committed to independent research careers in women's reproductive health. The supervised research training assists junior faculty in their transition into productive physician-scientists.

Building Interdisciplinary Careers in Women's Health (BIRCWH) Program. During FY 2017-2018, 83% of K12 scholars participating in this program for any amount of time were women. NICHD participates in the ORWH-led program with nearly a dozen other NIH ICs. BIRCWH research centers provide "bridging support" to physician-scientists as they move between completion of clinical or post-doctoral training and independent research careers. BIRCWH research subjects span the spectrum of women's health topics and the program is open to all types of clinicians and non-clinicians.

IV. Funding Initiatives, Workshops, and Conferences

Funding Initiatives

The Role of Stem/Progenitor Cells in the Pathogenesis and Treatment of Gynecologic Disorders. The purpose of this FOA was to encourage research into the role of pluripotent progenitor/stem cells in the pathogenesis and treatment of selected gynecologic disorders, specifically uterine fibroids, endometriosis, adenomyosis, endometrial polyps, and pelvic organ prolapse. RFA-HD-19-013; published December 2017

Discovery of Molecular Targets for Pregnancy-Related/Induced Diseases and Development of Therapeutics to Prevent/Treat These Diseases. The purpose of this FOA was to advance research on molecular targets for pregnancy associated/induced disorders, to lead to the development of new safer and more effective medications for use in pregnancy. PAR-18-511

Translational Research in Pediatric and Obstetric Pharmacology and Therapeutics. The purpose of these FOAs was to encourage translational and clinical research as well as clinical trials that will advance knowledge about the underlying mechanisms of drug action, response, and safety in children at various developmental stages, and in women during pregnancy and lactation. The goal was to improve the safety and effectiveness of current drugs for pediatric or obstetric patients and to enhance the development of new drugs or a safer usage of the existing drugs for tailored therapies to meet the unique clinical needs of these populations. PAR-17-188; PAR-18-214

Drug Repurposing for Conditions Affecting Neonates and Pregnant Women. The purpose of this FOA was to repurpose already FDA-approved drugs for new neonatal and obstetric indications, with a goal of facilitating the safe and effective treatment of these populations by overcoming the difficulties associated with the traditional development of drugs appropriate for them. PAR-18-506

Safety and Outcome Measures of Pain Medications Used for Children and Pregnant Women. The purpose of these FOAs was to promote preclinical, translational, clinical and epidemiological research in pain medications use in children or in pregnant women and to develop effective instruments or approaches to assess and evaluate maternal and child outcomes of pain medication treatment. PA-18-038; PA-18-043; PA-18-044

Safe and Effective Devices for Use in Neonatal, Perinatal and Pediatric Care Settings. The purpose of this FOA was to foster collaboration between clinical and bioengineering

research communities to develop and test safe, accurate, and effective devices for neonatal, perinatal, and pediatric clinical settings. RFA-HD-19-001; published March 2018

Opioid Use Disorder in Pregnancy. The purpose of this NICHD FOA, cosponsored by NIDA, is to spur research on treatment of pregnant women with opioid use disorder and pharmacokinetic and pharmacodynamic studies of medications for such treatment. The FOA reflected outcomes of a 2016 scientific workshop on how best to recognize, treat, and manage this disorder in pregnant women, which were reported in a 2017 publication. RFA-HD-18-036 (Reddy UM 2017)

Advancing the Science of Multipurpose Technology for the Prevention of HIV and Unintended Pregnancy. The purpose of these FOAs was to advance the development of new and innovative multipurpose prevention technologies (MPTs), through the development of new combinations of agents and delivery systems, to prevent HIV infection and unintended pregnancy among adolescent girls and young women. RFA-HD-18-101; RFA-HD-18-102

Women's HIV/AIDS Cohort Study. The purpose of this FOA was to stimulate research on clinical course of HIV infection and treatment in a large cohort of HIV-positive young women of reproductive age, including a focus on the effects of HIV and antiretroviral treatment during pregnancies and post-partum periods. RFA-HD-18-018

Non-Invasive Diagnostics to Improve Gynecologic Health. The purpose of this FOA was to encourage small businesses, scientists, and clinicians to collaborate in developing, advancing, and validating new devices and methods for non-invasive diagnosis of endometriosis, adenomyosis, and/or uterine fibroids, so as to shorten time to diagnosis, decrease invasiveness of current techniques, and/or improve accessibility, safety, convenience, and costs of diagnosis. RFA-HD-19-006; published December 2017

Point of Care Technologies for the Evaluation and Management of Obstetrics, Neonatal, and Pediatric Critical Care Patients, and for Patients with Disorders of Reproductive Tract and Infertility. The purpose of this FOA was to advance research using advanced technologies (e.g., bio-chips, microfluidics, and mobile technologies) for novel point-of-care devices and implement existing technologies in clinical settings, with a goal of guiding diagnostic and therapeutic efforts for obstetric, neonatal, pediatric critical care and reproductive disorders. RFA-18-028

Pregnancy in Women with Disabilities. The goal of these FOAs was to encourage studies of the incidence, course, and outcomes of pregnancy among women with intellectual and developmental and/or sensory disabilities and their families. Areas of interest included studies to inform periconceptional and antenatal counseling and strategies for addressing barriers to prenatal care, and management of pregnancy, the puerperium, and the transition to parenthood in order to optimize outcomes. PA-17-451; PA-17-452

Multidisciplinary Research in Vulvodynia. The purpose of these FOAs was to encourage research in the etiology, prevention, diagnosis, and therapeutics in the field of vulvodynia; there was particular interest in multidisciplinary approaches and interdisciplinary investigative teams. PA-18-089; PA-18-096

Zika Virus (ZIKV) Complications. The purpose of this FOA was to advance research on complications of infection with the Zika virus (ZIKV), focusing on both infection in pregnant women and congenital anomalies of their infants, as well as potential severe risk of ZIKV transfusion-transmission. PA-18-048

Identification of Reproductive-Tract Specific Proteins/Transcripts for the Development

of Male and Female Non-Hormonal Contraceptives. The purpose of this FOA was to encourage the use of bioinformatics combined with analytics to identify reproductive-tract specific transcripts and proteins for potential development as non-steroidal female and male contraceptives. RFH-HD-18-002

Re-competition of Global Network Program. The purpose of this FOA was to support U.S.-based Research Units, partnered with research centers in low-income countries, as part of the Global Network for Women's and Children's Health Research, a project that addresses the major causes of maternal, neonatal, infant, and early childhood morbidity and mortality through the conduct of clinical research in resource-poor settings. RFA-HD-18-009

Contraceptive Research Centers Program. The purpose of this FOA is to advance development of new and/or improved contraceptive methods for women and men; the centers also provide for development of early stage investigators in contraceptive research. RFA-HD-18-035

Male and Female Contraceptive Development Program. The purpose of this FOA was to support and facilitate research on new contraceptives for women and men. RFA-HD-19-004; published February 2018

National Centers for Translational Research in Reproduction and Infertility (NCTRI). The purpose of this FOA was to continue centers for interdisciplinary research on gynecological disorders and infertility and provide for training and career development of junior scientists in these areas of research. RFA-HD-19-017

Oocyte Mitochondrial Function in Relation to Fertility, Aging, and Mitochondrial Diseases. The purpose of this FOA was to stimulate research to gain fundamental insight into the role of mitochondria and long-term consequences of their dysfunction in the oocyte, and to develop therapeutic or alternative approaches to treat mitochondrial dysfunction for improving oocyte quality and competency, with a goal of providing women with infertility or subfertility or other illnesses of mitochondrial dysfunction with practical approaches to these problems. PA-18-093

Reproductive Scientist Development Program. The purpose of this FOA was to recompete this program's national network of mentors and scholars who provide career development and support for obstetricians and gynecologists, with the overall goal of encouraging the application of contemporary science advances to clinical practice and facilitating the transition to independence of physician-scientists in areas related to obstetrics and gynecology and its subspecialties. RFA-18-103

The Health of Sexual and Gender Minority Populations. With multiple co-sponsors, NICHD published these FOAs, calling for basic, social, behavioral, clinical, and services research, to increase scientific understanding of the health status sexual and gender minority populations, including lesbian, gay, bisexual, transgender, and intersex populations and thereby improve the effectiveness of health interventions and services for these understudied populations. PA-18-037; PA-18-210; PA-18-040; PA-18-054; PA-18-210

Research on the Health of Transgender and Gender Nonconforming Populations. With multiple co-sponsors, the NICHD published these FY 2017 FOAs, calling for research addressing the medical, sociological, psychological and structural causes and consequences of transgender and gender nonconforming identities. PA-17-477; PA-17-478

Workshops and Conferences

Perinatal Research Society Annual Meetings, 2017, 2018. These 2017 and 2018 meetings brought together leaders and young investigators in all aspects of perinatal research for presentations and discussions of common research interests, together with

intensive mentoring and teaching for young investigators and informal opportunities to further their professional development. Supported in part by NICHD grants. R13HD036244-19; R13HD036244-20

Society for Reproductive Medicine Annual Meetings 2018. A NICHD grans supported travel costs for ten trainees and new investigators, as well as a senior U.S.-based investigator presenting an invited distinguished lecture, for the annual Society meeting to bring researchers and clinicians in all clinical fields of obstetrics and gynecology, reproductive sciences and women's health issues. R01HD095655-01

8th International Symposium on the Biology of Vertebrate Sex Determination. This 2018 meeting brought together researchers who investigate diverse vertebrate systems, including amphibians, fish, birds, and mammals, including domesticated animals and humans, used a comparative process to advance understanding of the process of sex determination and sex differentiation and DSD. Supported in part by an NICHD grant. R13HD094496-01

AUA Basic Sciences Symposium: Understanding Infertility and Disorders and Differences in Sexual Development. This 2018 symposium at the annual meeting of the American Urology Association brought together physicians, physician-scientists, researchers and other experts to prevent on a range of topics, including genetics of sex determination, gene-environment interaction in cryptorchidism and other topics. Supported in part by an NICHD grant for travel awards for trainees and early career investigators. R13HD095658-01

V. Health Disparities

Scientific Accomplishments

Genome-Wide DNA Methylation Associations with Spontaneous Preterm Birth in U.S. Blacks: Findings in Maternal and Cord Blood Samples. The highest proportion of preterm births in the U.S., 17%, occurs in Black women. Epigenetics, the study of biological mechanisms that control "on" and "off" switches in genes and thus affect cell function, is thought to offer possible clues to this disproportionate rate of preterm births but until recently, epigenetic studies in this area have been limited in number and largely enrolled only white women. Recent research on the epigenetic mechanism, DNA methylation (DNAm) in a large cohort of Black women found multiple DNAm loci (locations) in the blood of those women who had experienced spontaneous preterm birth. Further analysis confirmed the association, implicating specific regions of two genes. The reported associations could not be explained maternal cell composition or other factors and the associations were not found in cord blood of the preterm newborns. The findings highlight possible biomarkers of preterm birth risk, that could alert clinicians to the need for preventive measures. (Hong X 2018)

Maternal Outcomes by Race in Women Age 40 and Older. An analysis of U.S. hospital inpatient records on 1,724,694 deliveries in women who 40 to 54 years old found that rates of severe maternal disorders increased for all women from 1998-2000 to 2013-2015 but disproportionately so for Black women. Severe disorders included stroke, heart failure, and transfusion (indicating significant blood loss), as well as common pregnancy complications, including preeclampsia, gestational diabetes, and cesarean delivery. Black women also had the largest increase in risk for acute renal failure and disseminated intravascular coagulation. Compared with white women, Black women also had substantially higher risk of death than white women, while Hispanic women had more than twice the risk as white women of pregnancy-associated death. (Booker W.A. 2018)

Racial and Ethnic Differences in Metabolic Factors among Women with PCOS. Diabetes and the metabolic syndrome (MS: a cluster of chemical and biological factors associated with

diabetes and cardiovascular disease (CVD) risk) are among the complications of PCOS. The metabolic profile of PCOS, can offer clues about CVD risk, a later-life risk for women with PCOS, and disparities in outcomes for different races of women with PCOS. A study of the metabolic profiles of 702 non-Hispanic white, non-Hispanic Black, and Hispanic women has found that Hispanic women with PCOS had the most severe phenotype — that is, the expression of the disease, both in terms of metabolic criteria and hyperandrogenism (excessive male sex hormones). Non-Hispanic women had an overall milder PCOS syndrome than Hispanics and, in some respects, than non-Hispanic white women. The researchers suggested that providers may need different thresholds to assess risks of PCOS complications in women of different races and ethnicities. (Engmann L 2017)

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National Institute on Deafness and Other Communication Disorders

I. Executive Summary

In October 1988, Congress established the National Institute on Deafness and Other Communication Disorders (NIDCD). The NIDCD mission is to conduct and support biomedical research, behavioral research, and research training in the normal and disordered processes of hearing, balance, taste, smell, voice, speech, and language. The Institute conducts and supports research and research training related to disease prevention and health promotion; addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders; supports research evaluating approaches to the identification and treatment of communication disorders and patient outcomes; and supports efforts to create devices that substitute for lost and impaired sensory and communication function. To accomplish these goals, the NIDCD manages a broad portfolio of both basic and clinical research. Through research and education, the NIDCD strives to reduce both the direct and indirect economic burden of communication disorders on individuals, families, and society, thereby improving the quality of life for people living with a communication disorder.

For 30 years, NIDCD research support has led to tremendous strides in uncovering knowledge in communication sciences. The NIDCD's focus is to bring national attention to disorders of human communication and to contribute to advances in biomedical and behavioral research that will improve the lives of the millions of people who have communication disorders. This report highlights the activities and accomplishments of NIDCD's funded research and programs to better understanding of diseases, disorders, and conditions that affect women, promote a better understanding of sex differences and/or foster the advancement of women in research for FY2017 & FY2018.

II. Hearing and Balance Research

Loss of hearing or balance negatively impacts quality of life and imposes a significant social and economic burden upon individuals, their families, and the communities in which they live. Millions of Americans experience a hearing or balance disorder at some point in their life, especially as young children or older adults. Common examples include middle-ear infections (otitis media), noise-induced hearing loss, tinnitus, age-related hearing loss, dizziness, and vertigo. Hearing and balance disorders cross all ethnic and socioeconomic lines, some have a greater impact on women.

Women & Sex/Gender Differences in Hearing Health

Several NIDCD studies provide important insight with regards to the differences, effect and potential disparities related to hearing health for women.

- Utilizing ongoing large prospective studies involving more than 150,000 women (Nurses' Health Studies I and II), NIDCD investigators examine whether common pain relievers, vitamins, alcohol, menopausal status and postmenopausal hormone use are associated with the risk of developing hearing loss. By performing hearing tests in women to examine whether these factors influence

change in hearing sensitivity, the aim of this research is to identify factors that can be modified at an early stage to conserve hearing [U01-DC010811].

- Patients with hearing loss who self-identify as lesbian, gay, bisexual, transgender, queer, or questioning (LGBTQ) might or might not feel comfortable disclosing their sexual orientation or gender identity to a health care provider based on social stigma concerns and previous negative experiences with health care providers. After controlling for sociodemographic and patient-related variables, a recent NIDCD study showed cisgender women were significantly less likely to disclose their LGBTQ identities to health care providers compared with cisgender men. Being accepted as LGBTQ by loved ones and high perceived patient-centered communication increased the likelihood of coming out to providers. The presence of an ASL interpreter did not prevent or promote the patients' decision to share health information with their health care provider (Miller, Biskupiak, Kushalnagar, 2018).

- Prior reports indicated low breast cancer screening adherence in a local Southern California sample of women with hearing loss. A current NIDCD study is assessing whether disparities for breast and cervical cancer screening adherence persists for women with hearing loss compared to the general population and whether racial and ethnic disparity for adherence exists within this cohort [R01-DC014463].

- Ongoing research by NIDCD intramural scientist are being conducted to better understand hearing loss caused by the anti-cancer drug cisplatin, which results in permanent hearing loss for hundreds of thousands of cancer survivors each year. Research in mice has shown that the cholesterol-lowering drugs known as statins may have potential to reduce cisplatin-induced hearing loss. Analysis of the data for sex as a biological variable has found that male and female mice get similar hearing loss when treated with cisplatin, but their responses to the statins are different. While statins are protective in both male and female mice, the female mice responded to a lower dose of statins than did the males. A prospective study in humans with head and neck cancer is currently underway to determine if those individuals taking statins experience reduced cisplatin-induced hearing loss compared to those who are not taking statins. Both the animal studies and the human study are ongoing and not yet completed. Both will be analyzed for sex as a biological variable. The long-term goal of this project is to develop a clinical therapy that will protect the hearing of cancer patients undergoing cisplatin chemotherapy [ZIA-DC000060].

- NIDCD is also funding a study looking at the effectiveness of epigallocatechin gallate (EGCG), a major component of green tea, to protect against cisplatin-induced hearing loss with the hope of determining potential antitumor interference by EGCG on cisplatin antitumor efficacy against ovarian, breast, and colon tumor cells in xenograft mouse models as this would have clinical implications [R01-DC016835].

- Research conducted by NIDCD intramural scientist aims to better understand the genetic and molecular mechanisms underlying the development of hearing loss associated with enlargement of the vestibular aqueduct. Sub-analysis of sex as a biological variable will be conducted [ZIA-DC000060].

- NIDCD intramural scientists are working in collaboration on a study conducted by NHGRI to better understand why differences in the sex chromosomes cause various diseases and what clinical findings may

be caused with different sex chromosome variants. This study is seeking to learn more about the genetic and clinical characteristics of disorders related to the X and Y chromosomes. The NIDCD Audiology Unit is contributing to this project by phenotyping auditory function in study participants [12-HG-0181].

Otosclerosis

Otosclerosis affects more than three million Americans with white, middle-aged women most at risk. This condition is caused by abnormal bone remodeling in the middle ear. Bone remodeling is a lifelong process in which bone tissue renews itself by replacing old tissue with new. In otosclerosis, abnormal remodeling disrupts the ability of sound to travel from the middle ear to the inner ear. Otosclerosis is most often caused when one of the bones in the middle ear, the stapes, becomes stuck in place. When this bone is unable to vibrate, sound is unable to travel through the ear effectively and hearing becomes impaired. Currently, there is no effective drug treatment for otosclerosis, although there is hope that continued bone-remodeling research could identify potential new therapies. Mild otosclerosis can be treated with a hearing aid which amplifies sound, but surgery (with its limitations and risks) is often required.

- The complicated architecture of the ear makes it difficult to study. Because researchers can't remove and analyze a sample of the inner ear from a living person who has otosclerosis (or other hearing disorders), they must study ear bone samples from cadavers donated for research. These samples, called temporal bones, are in short supply. To encourage more research on otosclerosis, the NIDCD supports the National Temporal Bone, Hearing and Balance Pathology Registry at the Massachusetts Eye and Ear Infirmary (U24 DC013983). This Registry is an information center that coordinates and archives data about recruited temporal bone donors and location of specimens nationwide and maintains a network of contacts for timely procurement of tissue.
- The National Human Ear Tissue Laboratory Resource helps the auditory and vestibular research communities by improving the quantity, quality and availability of human specimens, by developing and sharing advances in methods for human ear tissue processing, by developing technologies for non-invasive imaging, and by providing technical instruction, all to enhance opportunities for needed research on human ear tissues [U24 DC015910].
- In 2018 the NIDCD also funded 8 one-year administrative supplements to facilitate researchers with an active NIDCD-funded R01 or R21 award to incorporate studies using human temporal bone specimens into their research program with the goal to help translate existing studies into the human inner ear.
- NIDCD scientists are utilizing lumped element models and computational statistics to simulate and classify clinical wideband acoustic immittance (WAI) data from patients with otosclerosis, ossicular discontinuity and superior canal dehiscence (SCD), and explore the use of finite element modeling techniques to study the mechanisms of how specific pathologies contribute to changes in WAI. The results of this research may help identify solutions to common conductive pathologies through improvements in diagnosis prior to surgery and monitoring of mechanical changes postoperatively using non-invasive diagnostic methods [F31-DC016761].

Maternal Transmission

Maternal transmission of Cytomegalovirus (CMV) is well recognized as a common cause of sensorineural hearing loss (SNHL) in infants.

CMV is the leading cause of nonhereditary deafness and is also recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. It is estimated that the sequelae of congenital CMV infection may account for as many as 40,000 new cases of SNHL per year. Infants born with CMV infection are at higher risk for progressive or late-onset permanent hearing loss. Hearing loss during childhood interferes with language acquisition, social development, and achievement of developmental communication milestones including speech, language, and literacy.

- NIDCD funded scientists developed a mouse model in which infected mice develop hearing loss with characteristics similar to humans. Findings from this model have suggested that virus-induced inflammation and not direct damage to the inner ear by the virus infection is responsible for hearing loss. New insights into mechanisms of disease provided by this model could point to new therapeutic approaches to limit hearing loss in infants following CMV infection [R01-DC015980].
- Antiviral therapy administered early in life has been shown to help prevent progressive hearing loss in infants born with symptoms and other clinical signs of CMV infection. However, in most cases, infants who are born infected with CMV show no symptoms of the virus and yet approximately 6%–23% may still have hearing loss or will develop hearing loss. An NIDCD-supported clinical trial aims to identify and treat infants born with CMV infection and hearing loss, who are asymptomatic. These asymptomatic infants are at the great risk of developing progressive hearing loss and the resulting communication difficulties. The researchers propose a targeted approach to identify those CMV-infected infants who have failed their hearing screening. The study will determine if antiviral valganciclovir therapy prevents further hearing loss in this high-risk group. The results will provide a better understanding of whether the therapeutic benefits of antiviral treatment outweigh the risks for infants with asymptomatic CMV [U01-014706].
- Zika infection during pregnancy can result in serious birth defects to the infant including mild to moderate hearing loss.
- To better understand the etiology of the hearing loss associated with Zika infection, chicken and mouse models are being utilized to determine whether and when different cell types in the embryonic inner ear can be infected. These studies may offer insight into whether Zika exposure during the first 14 weeks of pregnancy in humans leads to pathologies in key sensory cells and tissues of the inner ear (R21-DC016732).

HIV

- NIDCD research is underway to evaluate the hearing abilities of children living in Cape Town, South Africa who are either perinatally human immunodeficiency virus infected (PHIV+), perinatally HIV-exposed, uninfected (PHEU), or HIV-unexposed (HU). These hearing data will be analyzed along with magnetic resonance imaging (MRI)/functional MRI (FMRI) scans of auditory cortical structures. This research will provide a more thorough understanding of how HIV infection or exposure affects various components of the auditory system [R01-DC015984].
- NIDCD funded scientists are measuring speech reception thresholds under several noise conditions, gap detection thresholds, and auditory brainstem response latencies in a prospective study of HIV+ and HIV- women participating in the DC or Washington Metropolitan Women's Interagency HIV Study (WIHS) longitudinal cohort. Scientist will also measure speech audiometry and communication deficits under quiet and noisy conditions in the WIHS. This project

consists of studies designed to estimate the incidence of conditions and diagnoses potentially related to HIV infection. Hearing loss is a recognized consequence of HIV infection in adults and this research will provide a better understanding of the impact HIV infection itself, treatment of HIV, infectious complications resulting from HIV, or associated conditions on hearing loss [U01-AI034994].

Balance

Balance disorders affect a large proportion of the population, particularly the elderly. Normal balance is maintained by integrating inputs from the vestibular, visual, proprioceptive (position sensation), and musculoskeletal systems. All of these systems can deteriorate with trauma, disease, and/or age, and the number of aging Americans over 65 is rising rapidly. Vestibular dysfunction and disorders can lead to dizziness, vertigo, migraines, blurred vision, nausea, and various forms of balance disturbances including postural instability. More than 4 in 10 Americans, especially the elderly, will experience an episode of dizziness sometime during their lives that is significant enough to send them to a doctor. Some of these disorders are more common in women.

- Balance disorders are associated, with falling, which is the leading cause of injury deaths among older adults. Collecting the incident of falls and measuring vestibular function, posture and gait in a cohort of participants over 2 years, investigators will evaluate the magnitude of change in specific vestibular physiologic function and explore whether specific vestibular physiologic function influence subsequent fall risk [K23-DC01305].

Vestibular migraine (VM), a variant of migraine in which dizziness is a prominent feature, affects about 1% of the general population and 10% of patients seen in dizziness and headache clinics. Like conventional migraines, vestibular migraines are more prevalent in females. Little is known about the clinical course of this disorder or the functional impairment that it causes, and there is no proven therapy.

- NIDCD-supported investigators are conducting a phase II clinical trial to assess the efficacy of a drug, rizatriptan, in treating vestibular migraines. If successful, this study will provide the first data for an evidence-based treatment of vestibular migraines and insight into the mechanism of VM [U01-DC013256].
- NIDCD is also funding research to assess whether CGRP-sensitized mouse models that have been shown to mirror the photophobia of migraine can also mirror deficits observed in VM. Result will contribute towards establishing a mouse model for vestibular migraine which will facilitate the development and testing of new drug treatments [R01-DC017261].

Ménière's disease is another vestibular disorder that is more common in women. Ménière's disease is a disorder of the inner ear that causes severe dizziness (vertigo), ringing in the ears (tinnitus), hearing loss, and a feeling of fullness or congestion in the ear. Ménière's disease can develop at any age, but it is more likely to first occur in adults between 40 and 60 years of age NIDCD estimates that approximately 615,000 individuals in the United States are currently diagnosed with Ménière's disease and that 45,500 cases are newly diagnosed each year.

- NIDCD is funding research for the optimization of an implanted inner ear vestibular neurostimulator prosthesis that could potentially restore function to the vestibular system for treatment of Ménière's disease [R01-DC014002].

Benign Paroxysmal Positional Vertigo (BPPV) is balance disorder that results in sudden onset of dizziness, spinning, or vertigo when moving the

head. BPPV is also more common in women, resulting in a brief, intense episode of vertigo that is triggered by a specific change in the position of the head.

- NIDCD is supporting research evaluating a multi-faceted behavioral and educational strategy of guideline-supported evidence-based processes for the management of BPPV. Investigators are studying this strategy in real world care in the emergency department setting with the goal to simultaneously improve patient outcomes and healthcare efficiencies [R01-DC12760].

III. Voice, Speech, and Language Research

Communication allows us to participate in society and is a defining characteristic of what it is to be human. Other organisms clearly communicate; however, in no other species does it appear that communication—specifically the use of language in communication—is as highly developed as in humans, nor as central to an organism's function and identity. Communication impairments that involve voice, speech, or language often limit a person's ability to participate in society, whether the activity is educational, occupational, or social. In addition, because effective communication is needed to get aid in life-threatening situations, loss of communication can put people at risk for compromised physical safety and survival.

Sex Differences in Vocal Health

NIDCD supports research which will directly contribute to a better understanding of the impact of sex differences.

- To help develop strategies to reduce the increased incidence of women's vocal health problems, research is being conducted increase the understanding of the gender discrepancy in vocal health issues with the goal of identifying the compensatory adjustments women use in different communication environments and better knowledge of how these adjustments may contribute to their increased risk of voice issues [R01 -DC012315].

- NIDCD funded investigators studying novel and fundamental tissue engineering approaches to repair vocal folds are developing and utilizing female primary and immortalized vocal fold fibroblasts to investigate sex differences in the response to biomaterials that are engineered to alter macrophage phenotypes [R01-DC013508].

Voice

Approximately 7.5 million people in the United States have difficulty using their voices. Vocal fold tissue is a complex biological structure needed for normal voice production. Voice production and quality are important for daily function. Damage to voice may affect a person's ability to communicate resulting in a reduction of productivity and quality of life. The NIDCD supports basic, clinical, and translational research on laryngeal structures and functions with respect to normal and disordered voice, including new prevention and treatment strategies.

- NIDCD scientists conducted research which provided a better understanding of the prevalence of voice disorders in young adults. A cross-sectional analysis of data from the National Longitudinal Study of Adolescent to Adult Health of 14,794 young adults, aged 24 to 34 years, who reported their health conditions and behaviors found that females had 56% greater odds of voice disorders than males (Bainbridge, et al., 2017 doi: 10.1002/lary.26465).

Voice disorders are not trivial, although they are overwhelmingly under-recognized. Ongoing research funded by NIDCD will help to identify factors which result in a higher prevalence of voice disorders in women than men.

- NIDCD investigators hypothesize that ovarian hormonal fluctuations (menstrual cycle, pregnancy, and menopause) correspond to adverse changes in the female voice. Comparing Long-Evans rats (strain of rat has a high rate of spontaneous vocalizations) that have surgically-induced menopause to controls, investigators hope to better understand the impact of estrogen levels on laryngeal neuromuscular mechanisms and ultrasonic vocalizations. [F31-DC017053].

Spasmodic dysphonia (SD), also know as laryngeal dystonia, is a neurological voice disorder that predominantly affects women, with estimates as high as 80% of affected individuals being female. In SD, the muscles inside the vocal folds experience sudden involuntary movements—called spasms—which interfere with the ability of the folds to vibrate and produce voice. SD causes voice breaks and can give the voice a tight, strained quality. However, SD is usually more severe and spasms may occur on every other word, making a person's speech very difficult for others to understand. SD is a rare disorder, occurring in roughly one to six of every 100,000 people. The first signs of this disorder start to appear in individuals aged 30 to 50 years, then continues throughout a person's life.

- Work is ongoing to identify the neural markers and causative gene(s) of spasmodic dysphonia. This research will elucidate the mechanistic aspects of abnormal brain organization and underlying genetic factors related to SD to establish the enhanced and objective criteria for improved clinical management [R01-DC011805].

- NIDCD research is currently being conducted to determine the central mechanisms and functional markers that underlie the clinical response to a novel pharmacological agent, sodium oxybate (Xyrem®), in spasmodic dysphonia with and without voice tremor. Results will help to establish the central mechanisms of drug's action that are specifically linked to the disorder pathophysiology and translate this novel treatment into clinical practice[R01-DC012545].

- Assessment of techniques developed by NIDCD funded laboratories to directly test sensory mechanisms of voice control in healthy participants and in clinical participants with voice disorders associated with Adductor Spasmodic Dysphonia and Parkinson's Disease offer insight that may directly impact strategic approaches to voice treatment [R01-DC014519].

Speech and Language

The NIDCD supports research to understand these communication systems, their acquisition and development, and their use when spoken language systems are damaged by trauma or degenerative diseases, or when speech is difficult to acquire due to early hearing loss or injury to the nervous system.

- Research is currently being conducted to examine the role of estrogen on facilitating social interactions and enhancing auditory social cue learning and memory formation. By utilizing the ultrasonic vocalization (USV) system between mouse pups and adult female mice model, the goal of the studies are to elucidate the molecular signaling pathways for establishing and maintaining memories modulated by estrogen in the mammalian auditory cortex during experience-dependent, communication sound learning [F31-DC015395].

IV. Taste and Smell Research

The chemical senses—more commonly known as taste, smell, and chemesthesis (chemically provoked irritation)—enable us to use chemical

signals to communicate with the environment and each other. For people, memories of taste and smell experiences are vivid, long lasting and play an important role in our enjoyment of life. The chemical senses accomplish three major purposes:

- Nutrition: Seeking out safe and nourishing food.
- Protection: Helping us to avoid spoiled food and toxic chemicals.
- Communication: Conveying important information to others.

More than 200,000 people visit a doctor each year for problems with their ability to taste or smell. Scientists believe that up to 15 percent of adults might have a taste or smell problem, but many don't seek a doctor's help.

Phantom Odor

Phantom odor is an olfactory dysfunction in which individuals perceive an odor in the absence of an external stimulus.

- Using data from 7,417 participants over 40 years of age from the 2011-2014 National Health and Nutrition Examination Survey (NHANES), NIDCD scientists found that 1 in 15 Americans (or 6.5 percent) over the age of 40 experiences phantom odors. The study found that about twice as many women as men reported phantom odors, and that the female predominance was particularly striking for those under age 60. Women 60 years and older reported phantom odors less commonly (7.5% and 5.5% among women aged 60-69 years and 70 years and older, respectively) than younger women (9.6% and 10.1% among those aged 40-49 years and 50-59 years, respectively). The prevalence among men varied from 2.5% among men 70 years and older to 5.3% among men 60 to 69 years old. (Bainbridge, et al., 2018 doi: 10/1001/jamaoto.2018.1446)

V. Inclusion of Women in Research

In 2017 NIDCD (both Extramural and Intramural) had 52.2% females and 44.9% males enrolled in NIH-defined clinical research; in 2018 51.2% females and 47.7% males were in NIDCD NIH-defined clinical research.

NIDCD ensures inclusion of women in scientifically relevant research projects. Program Officers carefully review Inclusion data submitted by grantees and monitor progress of research projects. When needed, NIDCD Inclusion Officer will communicate with investigators, guide them through the policy and eRA systems, and resolve complicated issues. Inclusion data are analyzed qualitatively and quantitatively to proactively detect anomalies which will be explained or corrected. After all Inclusion issues are resolved, Grants Management will issue award notices. In particular, because of Inclusion Officer's direct involvement, minor errors are corrected in one day and all NIDCD data are reconciled by the end of each fiscal year. NIDCD's successful operation is based on teamwork and effective communication among Program Officers, Inclusion Officer, and Grants Management.

VI. Building a Well-Trained, Diverse, and Vigorous Health Research Workforce

The NIDCD recognizes the importance of research training and career development opportunities to prepare investigators focused on communication disorders. NIDCD's overall research-training goal is to increase the number, quality, and diversity of well-prepared and skilled investigators with knowledge and expertise in all areas supported by the Institute: hearing, balance, taste, smell, voice, speech, and language. Our training programs aim to foster the next

generation of productive, creative, innovative, and qualified scientists in basic, clinical and translational research. NIDCD supports fellowship, mentored-career development, and institutional research training programs at universities and institutions nationwide (extramural training), as well as at the NIDCD laboratories and clinics in Bethesda, Maryland (intramural training). It also supports training-related administrative supplement programs to enhance the diversity of the research workforce and the loan repayment program for individuals pursuing independent research careers. Lastly, NIDCD developed specific training opportunities to support audiologists interested in research careers, as well as for established investigators aiming to enhance their research skills to further their research programs in NIDCD research areas.

The NIDCD Early Career Research (ECR) Award (R21) is intended to support both basic and clinical research from scientists who are beginning to establish an independent research career. These investigators are no more than 7 years beyond the date that the first professional, advanced professional, or terminal academic degree was awarded, whichever is most recent. They may be an independent early stage investigator or a late-stage postdoctoral fellow still in his/her mentor's laboratory.

The NIDCD ECR Award R21 grant mechanism supports different types of projects including secondary analysis of existing data; small, self-contained research projects; development of research methodology; translational research; outcomes research; and development of new research technology. Irrespective of the type of project, the intent of the NIDCD ECR Award R21 help investigators advance in their careers obtaining sufficient preliminary data for a subsequent R01 application.

The NIDCD provides support for a number of scientific meetings that are directed toward research objectives within the field of communication sciences and disorders. Although they don't specifically target female scientists, a number of these meetings have been successful in serving as an important resource for women with biomedical careers in research.

- Lessons for Success aims to provide intensive training to a promising group of early career scientists in the areas of (a) grant preparation and funding opportunities, (b) development and management of a successful program of research, and (c) advancement of professional competencies. With participants completing assignments prior to and during the conference, this grant-writing "boot camp" provides invaluable advice and guidance from senior faculty with strong histories of research funding. In 2017 70% of participants and 76% Program Faculty/Presenters were female scientists. In 2018 86% of participants and 87% Program Faculty/Presenters were female scientists. [R13-DC007835].
- The Research Symposium bring together clinicians and researchers at ASHA's Convention to discuss current research that has important implications for the study of communication sciences and disorders (CSD). The Research Mentoring-Pair Travel Award (RMPTA) is given in conjunction with the Research Symposium. The award is designed to foster the professional development of students and early-career scientists who have expressed an interest in, or are pursuing, research careers in communication sciences and disorders. In 2017 95% of mentors and 96% proteges and in 2018 63% mentors and 76% proteges were female scientists [R13-DC003383].
- In 2018, the Association for Research in Otolaryngology (ARO) initiated the planning of their first Women's Roundtable Discussion to be held during the February 2019 at the annual Midwinter Research Meeting (MWM). The MWM is a unique meeting

where current basic and clinical research related to otolaryngology is presented. *The Women's Round table* will provide a forum for female student/postdoc/young scientist to discuss women-related issues, particularly in the scientific community, with more senior women scientists/clinicians [R13-DC013966].

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National Institute of Dental and Craniofacial Research

I. Executive Summary

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to promote the general health of the American people by improving dental, oral, and craniofacial health through research and research training. NIDCR funds clinical and basic research to understand, prevent, and treat oral diseases and craniofacial conditions, including those that disproportionately or solely affect women. Among these diseases are orofacial pain conditions, including temporomandibular joint disorders (TMD), osteoporosis of the craniofacial complex, and autoimmune salivary gland diseases. NIDCR also supports research on the oral health of pregnant women, mothers, and their children, and research on craniofacial and tooth development in unborn children. Recognizing the importance of gene-gene, gene-environment, and behavioral interactions, NIDCR has long emphasized basic, genetic, behavioral, social science, and epidemiological research. This report highlights accomplishments and initiatives in key areas related to women's health and research focused on advancing the understanding of sex as a biological variable and gender differences.

In Fiscal Years (FY) 2017 and 2018, NIDCR supported a variety of studies designed to identify risk factors and characterize diseases affecting women. This includes a robust orofacial pain research program, with studies on TMD and other pain conditions. NIDCR supports basic science studies examining growth and development of teeth, cartilage, and bone that provide the scientific foundation for understanding oral diseases. NIDCR-funded investigators use animal models and human cohorts to study osteoporosis, which disproportionately affects women. Researchers continue to study the pathophysiology of osteonecrosis of the jaw, a condition associated with several drugs used to treat osteoporosis. NIDCR supports studies on Sjögren's syndrome (SS), an autoimmune disease that affects women nine times more frequently than men and has dramatic oral health consequences. This includes support of the Sjögren's International Collaborative Clinical Alliance (SICCA) biorepository, which distributes clinical samples to investigators worldwide. NIDCR also supports research to define the best methods to eliminate disparities in oral health that impact women and their children. Researchers supported by NIDCR continue to identify genes associated with craniofacial anomalies, which could lead to improved prevention, diagnosis, and treatment of these abnormalities.

II. Accomplishments and Activities

Pain Research

NIDCR continues to build on previous NIDCR studies on orofacial pain that have demonstrated that men and women respond differently to painful stimuli, that distinct immune cells may mediate pain differently in men and women, and that women are more likely than men to develop certain chronic pain conditions.

Temporomandibular Joint Disorders

TMDs are a diverse group of orofacial conditions associated with persistent orofacial pain and jaw dysfunction. Approximately 5 to 10 percent of the U.S. population will seek care for TMD in

their lifetime. Although most cases resolve with minimal or no treatment, some individuals develop a chronic, painful disorder that is associated with significant jaw dysfunction and emotional and financial burden. Chronic TMD is more prevalent in females than males, and women report higher levels of pain than men. Gender differences are an important emphasis in several ongoing studies examining the anatomy and mechanics of the temporomandibular joint, risk factors for TMD, potential advances in diagnosis of TMD, and approaches to treatment.

Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) Study

Since 2004, NIDCR has supported the OPPERA study, designed to assess biological, psychological, and social factors that increase the risk of developing TMD and transitioning to chronic TMD. OPPERA confirmed the role of catechol-O-methyltransferase (COMT), an enzyme responsible for breaking down molecules that transmit pain signals, in TMD. OPPERA also found that multiple overlapping health conditions were predictors of initial TMD development. These results are being confirmed with data generated in the second phase of OPPERA, which follows individuals with first onset TMD, to explore genetic risk factors for TMD. Recently, OPPERA II researchers have identified three distinct genetic loci that are significantly associated with TMD in combined or sex-segregated analysis. One of these, a single nucleotide polymorphism on chromosome 3, was significantly associated with TMD in males only. Functional analysis in human dorsal root ganglia and blood indicate that this variant is associated with decreased expression of the nearby muscle RAS oncogene homolog (MRAS) gene. In a rodent experiment designed to test the functional consequence of the genetic variant, male but not female mice with a null mutation of MRAS displayed persistent mechanical allodynia in a model of inflammatory pain. Genetic and behavioral evidence support a novel mechanism by which genetically-determined MRAS expression moderates resiliency to pain. This effect is male-specific and may contribute to lower rates of painful TMD in men (Smith, 2018).

OPPERA researchers showed that epidermal growth factor receptor (EGFR) inhibitors—currently used as first-line treatment for non-small cell lung cancer—are analgesic against a variety of chronic pain modalities in mice and that the pain apparatus by which this occurs may be conserved across species. The investigators then assessed three cohorts of TMD patients. They found that genes for EGFR and its ligand, epiregulin (EREG), are associated with development of this chronic pain condition and suggested that higher levels of EREG may contribute to hyperalgesic states in these patients. The association of EGFR and EREG with chronic pain in a clinical cohort is an important translational complement to the mouse model data and supports the potential value of targeting EGFR for chronic pain management in humans (Martin, 2017).

Other Examples of NIDCR-Supported TMD Research

- Temporomandibular joint (TMJ) disc dysfunction occurs in approximately 30 percent of TMD patients, with the mean age of onset between 25 and 35 years. Articular tissue failure in synovial joints is thought to involve mechanical fatigue and, thus, be dependent on magnitudes and frequencies of applied mechanical stress. Investigators reported that during asymmetric jaw closing, contralateral TMJ energy densities were twofold and significantly larger in healthy females versus males, due to 1.5-fold and significantly smaller TMJ disc cartilage volumes under stress fields in females versus males. These results suggest that in healthy individuals, asymmetric jaw closure in females compared to males has higher TMJ mechanical fatigue liabilities (Gallo,

2018). Mechanical function differences and sex could be predictive determinants of TMJ integrity and of development of disc dysfunction.

- A recent cross-sectional analysis of females with TMJ osteoarthritis found several local and systemic biomarkers were significantly correlated with morphological flattening of the lateral pole of the condylar articular surface, suggesting this bone resorption profile could contribute to the initial diagnosis of TMJ osteoarthritis. NIDCR-funded researchers developed a Bone Texture Tool method as an open-source software package that is now widely available for use in classifying TMJ osteoarthritis (Paniagua, 2017). This tool is now part of a flexible web-based system for data storage, computation, and integration of high dimensional imaging, clinical, and biological data that uses an innovative neural network methodology to classify TMJ osteoarthritis (de Dumast, 2018).
- NIDCR supports research on tissue regeneration of the TMJ. Project types span from 3-dimensional printing of biological scaffolds to replace the TMJ disc, to regeneration of the TMJ by incorporating a host of matrix, signaling, and stem cell components to induce cartilage formation and improve maintenance of tissues in the jaw. The incorporation of cartilage cells into a scaffold-free tissue engineered implant has shown promise. These implants had mechanical properties akin to those of the native TMJ disc, and experiments in a minipig model indicated that animals with the implant had improved defect closure and reduced degenerative changes in the jaw joint compared to untreated controls (Vapniarsky, 2018).
- The National Dental Practice-Based Research Network (PBRN) conducts oral health research studies in dental practices on topics of importance to practitioners and their patients. A longitudinal prospective PBRN study is seeking to identify practitioner treatment decisions for patients with TMD pain and assess change in pain and function over time with different treatments. This study also is assessing the influence of practitioner and patient gender upon practitioner treatment decisions and patient response to treatment (U19 DE022516, Gilbert).
- An NIDCR-funded randomized controlled trial recruited 156 women diagnosed with TMD to test the effectiveness of interventions targeting sleep and pain catastrophizing. Analysis of baseline data demonstrated that, relative to white females, African American females exhibited higher levels of clinical pain, insomnia severity, and pain catastrophizing, yet there was no ethnic group difference in negative sleep-related cognitions. These findings identify pain catastrophizing as a potentially important link between ethnicity and clinical pain and may inform interventions that target insomnia and catastrophizing to assist in reducing TMD pain in women (Lerman, 2018).
- NIDCR recently funded a multisite study to test the effectiveness of a tailored online self-management training program in decreasing jaw pain and preventing chronic pain and addiction in patients with TMD. The intervention will be compared to traditional self-care and the study will also examine factors that may impact its effectiveness. This intervention is designed to empower, engage, and educate patients in a personalized program of exercise and behavioral changes supported by a telehealth coach (U01 DE027938, Fricton).
- NIDCR-supported researchers are using a state-of the-art technology called high-definition transcranial direct current stimulation to investigate the possibility of providing longer-lasting TMD pain relief. The researchers are testing the ability of

this stimulation method to turn on a receptor protein, called the μ-opioid receptor, that receives a signal from endorphins or opioids to relieve pain. Additional studies in this area could lead to new non-opioid pain management therapies to treat TMD and other pain conditions (U01 DE025633, DaSilva).

- Investigators are analyzing results of a randomized clinical trial that enrolled 200 chronic TMD patients to investigate whether a variation in the COMT gene alters a person's response to propranolol used as a pain reliever. This research will help determine whether doctors can tailor propranolol treatment to individuals with TMD based on genetic differences and determine if this non-opioid medication is effective in reducing TMD pain (U01 DE024169, Tchivileva).
- Botox (Botulinum Toxin A; BTA) is increasingly used to treat TMD, but efficacy and safety for this off-label use are largely untested. Injection of BTA into masticatory muscles, which act on a load-bearing joint, introduces potential for unknown adverse effects on bone resulting from diminished load. NIDCR is funding an observational cohort study to assess bone-related risks of BTA injection into the masticatory muscles. The study compares bone quality in a small number of women before and after masticatory BTA injections. It also compares the bone quality of TMD-affected women who have received BTA injections with menopausal status-matched TMD-affected women who have not received BTA. Condylar volume of each of these cohorts is compared to a reference group of historical controls. (R01 DE024522, Raphael).

Neuropathic Pain

Neuropathic pain is a complex, chronic pain that may occur when nerve fibers are damaged or become dysfunctional. Accumulating evidence points to an important role for glial cells, including astrocytes, the most abundant glial cell type in the central nervous system in neuropathic pain pathophysiology. Little is known about the role that sex/gender may play in neuropathic pain processes. An NIDCR study compared sex differences in spinal cord astrocyte signaling in neuropathic pain using biochemical, behavioral, and electrophysiological approaches. Researchers investigated the effects of several microglial and astroglial modulators on inflammatory and neuropathic pain following intrathecal injection in male and female mice. Findings confirmed male-dominant microglial signaling and revealed sex-independent astroglial signaling in both models (Chen, 2018).

Approximately one-third of patients who develop herpes zoster (HZ) or "shingles" experience a chronic pain condition termed post-herpetic neuralgia (PHN), which occurs after the herpetic lesions heal. Approximately 20% of HZ patients have orofacial involvement, with women reporting PHN 30% more often than men. NIDCR-funded researchers are studying a rat model of varicella zoster virus (VZV) infection, which recapitulates clinical features of PHN pain. Female rats given a lower dose of VZV have longer affective responses than male rats, and estrous cycle affects aversive pain responses (Stinson, 2017). Additional research is being conducted to determine whether estrogen attenuates VZV-induced orofacial pain by increasing expression of two neuron inhibitory genes within the thalamus. This research could provide insights into the mechanisms underlying this sex difference and explain why females suffer greater pain (R01 DE026749, Kramer).

Studies in several animal models have implicated complement proteins in both neuropathic and inflammatory pain, but their role in human pain mechanisms remains unknown. NIDCR is funding a study using human dental pulp to test the hypothesis that the neurotransmitter

serotonin elicits a greater release of complement peptides from the peripheral tissues of women compared to men, leading to a sexually dimorphic increase in capsaicin-sensitive receptor activity in trigeminal sensory neurons and a concomitant increase in orofacial pain. Findings from this study could provide mechanistic insights into sexually dimorphic pain conditions where serotonin has been implicated, such as trigeminal neuralgias, migraine, fibromyalgia, and vestibulodynia (R01 DE026139, Hargreaves).

While sex differences in oral cancer pain severity have been observed in animal models and humans, little is known about whether these differences are manifested in the molecular character of cancers or whether they could influence treatment outcomes. NIDCR investigators are studying sex differences in the genome of cancers arising in a mouse model of human oral squamous cell carcinoma and the impact of forced mu-opioid receptor gene expression on cancer gene expression. This project has the potential to generate genomic and transcriptomic data that could identify different levels of analgesia or analgesia mediated via different pathways in males and females (R01 DE025393, Schmidt).

Chronic Overlapping Pain Conditions (COPCs)

Women are at greater risk for most common forms of chronic pain and evidence suggests significant rates of overlap among a cluster of pain disorders predominantly affecting women. Approximately two-thirds of patients with COPCs carry variants in the COMT gene, which codes for decreased levels of COMT enzyme with corresponding increases of catecholamines (epinephrine and norepinephrine) that promote pain and inflammation. NIDCR-funded researchers assessed whether manual acupuncture would resolve persistent pain and neuroinflammation in rodents with sustained COMT inhibition, a model that captures genetic and phenotypic characteristics of patients with COPCs. Acupuncture alleviated mechanical pressure pain (a hallmark of COPCs), reduced neuroinflammation, and reduced activation of spinal astrocytes involved in the development/maintenance of persistent pain. Analgesic effects were similar among male and female mice. These findings suggest that acupuncture may alleviate pain and reduce neuroinflammation in part by restoring deficiencies in catecholamine metabolism (Kim, 2018).

Pain Management

Well-controlled experimental studies suggest that patient demographic characteristics play a causal role in providers' pain management decisions, but that providers are unaware of this influence. An NIDCR-funded study recruited both male and female physicians and dentists to assess the providers' views of gender differences in pain sensitivity, pain endurance, and willingness to report pain. Results indicated that both male and female healthcare providers believed that the typical male was less willing to report pain than the typical female. Overall, healthcare providers did not believe there was a significant difference in the pain endurance of men versus women, or that men and women were differentially sensitive to pain. However, compared to female physicians and men in both professions, female dentists rated men as having less pain endurance than women (Wesolowicz, 2018). Future studies could examine mechanisms of gender and provider differences in pain assessment and treatment.

Mineralized Tissue Studies in Health and Disease

The study of teeth, bone, and other mineralized tissues has been a mainstay of NIDCR research since the Institute's inception. Bone is an active and dynamic tissue that continuously remodels throughout life. In aging bone, an imbalance of resorption over formation induces loss of bone mass, and can lead to osteoporosis, a skeletal disease that affects bone architecture

and increases the risk of fracture. Osteoporosis disproportionately affects women. Other diseases that affect mineralized tissues of the craniofacial complex include dental caries (decay), periodontal (gum) disease, and drug-induced osteonecrosis.

Development and Maintenance of Mineralized Tissue

NIDCR-funded investigators are studying the basic biological processes involved in the development and maintenance of bone, cartilage, and teeth.

- Bone growth, development, and mineral balance are orchestrated by a complex repertoire of molecular switches. Problems with any of the components may lead to debilitating bone disorders and serious consequences, such as fragility fractures resulting from osteoporosis, aging, or diabetes. Transforming growth factor-beta (TGFB) signaling is one pathway regulating bone mass and quality. Using inhibitors and mice with intrinsic TGFB signaling defects in osteocytes, the mature cells of bone, NIDCR investigators found that TGFB controls bone quality through perilacunar/canalicular remodeling (PLR), a process seen in demanding metabolic situations such as lactation. In PLR, osteocytes engage osteoclasts and osteoblasts to resorb and deposit bone matrix. It is now clear that PLR is a mechanism that helps maintain homeostasis and the lacuno-canalicular network of bone (Dole, 2017).
- The extracellular collagen-degrading matrix metalloproteinase MMP-13, a target regulated by TGFB, is important for maintaining bone quality. Using an administrative supplement to compare sex differences, NIDCR researchers are studying molecular processes associated with bone quality in bone remodeling that occurs when there is great demand to release calcium stores from bone, such as during lactation. This work also has implications for understanding bone changes and fragility that accompany steroid-induced osteoporosis (R01 DE019284, Alliston).
- The Iowa Fluoride Study has followed a birth cohort from childhood through adolescence, collecting longitudinal data on bone growth, physical activity, fluoride exposure, diet, and oral health. The study has found only weak associations between fluoride intake and cortical bone mineral density, but some differences were observed between boys and girls, suggesting the need for further study of possible gender-specific effects of fluoride on bone measures (Levy, 2018). Another analysis examined the etiology of caries development in adolescents ages 9, 13, and 17 to identify behavioral mediators of the relationship between socioeconomic status (SES) and caries incidence and investigate the role of sex on caries-preventive behavior and caries. The analysis found that the relationship between SES and caries incidence in the permanent dentition is mediated by adolescent behaviors. Female participants had worse caries than male participants, despite lower self-reported percentages of sugar-sweetened beverage intake and more frequent brushing and dental attendance (Curtis, 2017). These differences could be related to multiple factors, suggesting the need for further investigation.
- Proteoglycans (PGs), a major structural component of mineralized tissues' extracellular matrix, bind and retain chemokines and cytokines, providing an accessible reservoir of growth factors. NIDCR researchers are using genetically altered animals to unravel the roles of PGs in molecular processes of normal skeletal development and maintenance and in bone pathologies and their repair. Mice deficient in small leucine rich PGs (SLRPs) exhibit low bone mass, impaired architectural structure

and ectopic bone formation. Though the phenotype is the result of osteoblast/osteoclast interaction in both sexes, some parameters display sexual dimorphism. The bone formation rate impairment is more pronounced in females than in males. Changes in females are seen at an older age only, while male mice show changes in their cortical compartment throughout their life. Given that low bone mass is evident at a young age, sex hormones are probably not a primary determinant of the phenotype; rather these sex-related differences may be due to SLRP's ability to alter the bioavailability of crucial growth factors (Kram, 2017).

Osteonecrosis of the Jaw (ONJ)

Bisphosphonate drugs (BPs) block bone resorption by inhibiting the activities and functions of osteoclasts and perturbing the differentiation of osteoblasts. Intravenous BPs are primarily used to treat pain associated with cancer metastasis to bone, Paget's disease, and multiple myeloma. Oral BPs are used to prevent bone loss in patients with osteoporosis or osteopenia, conditions which are more common in women than in men. Use of BPs has been linked to development of nonhealing, exposed necrotic bone in upper or lower jaws, a clinical condition called medication-related ONJ. Medication-related ONJ has also been reported in patients treated with the antiresorptive drug denosumab, which inhibits the osteoclastogenic factor RANKL.

Additional risk factors may play a role in ONJ, including inflammatory conditions such as periodontitis. NIDCR-supported investigators have developed and refined animal models that reflect these risk factors. The relationship of ONJ to dose and duration of antiresorptive drug treatment has been studied in the rice rat, an animal that develops food impaction-induced periodontitis (Messer, 2018). A mouse model with a ligature-induced inflammatory periodontal lesion has shown that localized periodontitis exacerbates ONJ induced by tooth extraction and that removal of the inflammatory stimulus ameliorates ONJ development in the presence of antiresorptive drugs (Kim, 2018).

Bisphosphonate molecules accumulate in the bone matrix, and researchers have hypothesized that this contributes to BP-related ONJ. NIDCR-supported investigators have tested how removing BP by chelation affects the healing of post-tooth extraction alveolar bone necrosis in rats, and results suggest that the use of topical chelating agents is a promising strategy for the prevention of ONJ following dental procedures in BP-treated patients (Elsayed, 2018).

Periodontal Health in Women

NIDCR funded the Osteoporosis and Periodontal Disease (OsteoPerio) study to examine periodontal disease status and progression over 15 years in postmenopausal women who participated in the Women's Health Initiative Observational Study (1342 initial participants, 1026 participants at 5 years, 518 participants at 15 years). Biospecimens collected at the three time points are currently being examined to determine the composition and diversity of the subgingival microbiome; determine the extent to which the oral microbiome composition changes over time; identify which oral microbiome compositions are associated with periodontal disease presence, severity, and progression over time; and determine the influence of key personal characteristics on the oral microbiome composition and its relationship to periodontal disease status and progression. Results to date have supported the link between bone mineral density and periodontal disease. Compared with women with normal systemic bone mineral density T-scores, women with osteoporosis are nearly twice as likely to have oral bone loss. The study has found a strong positive association between specific oral bacteria and severe oral bone loss. In pilot analyses on small groups of participants with and without periodontal disease,

noticeable differences have been found in the relative abundance of commensal and pathogenic periodontal bacteria (Banack, 2018).

Prevalence of severe periodontal disease is reported to be greater in people living with HIV. NIDCR-funded researchers will comprehensively study the severity of periodontal disease and response to treatment in aging women with HIV (pre- and post-menopause). An Office of Research on Women's Health (ORWH)-funded administrative supplement will allow the study to also enroll aging men with HIV. The prospective study will assess the relative impact of HIV-associated inflammation on the periodontium and will evaluate whether periodontal health is modulated by sex hormones in this population (R01 DE026924, Yin).

Oral Human Papillomavirus (HPV) Infection and HPV-positive oropharyngeal cancer (HPV-OPC)

The incidence of HPV-OPC has risen rapidly in recent decades among men in the United States. To assess the population-level effect of prophylactic HPV vaccination on the burden of oral HPV infection, investigators conducted a cross-sectional study of men and women 18 to 33 years of age enrolled in the 2011 to 2014 National Health and Nutrition Examination Survey (NHANES), a representative sample of the US population. Oral HPV infection was compared by HPV vaccination status. Between 2011 and 2014, 29.2% of women and 6.9% of men reported receipt of at least one dose of the HPV vaccine before the age of 26 years. The prevalence of oral HPV infection was significantly reduced in vaccinated versus unvaccinated individuals (0.11% v 1.61%, respectively). Accounting for vaccine uptake, the population-level effect of HPV vaccination on the burden of oral HPV infection was 17.0% overall, 25.0% in women, and 6.9% in men (Chaturvedi, 2017).

To understand the prevalence of oncogenic oral HPV infection and HPV-OPC in groups of people with different risk factor profiles, NIDCR-supported investigators combined and analyzed clinical data from 13,089 people ages 20–69 within NHANES 2009 to 2014, OPC case data from the Surveillance, Epidemiology, and End Results registry, and OPC mortality data from the National Center for Health Statistics. Oncogenic oral HPV DNA is detected in 3.5% of all adults aged 20–69 years; however, the lifetime risk of oropharyngeal cancer is low (37 per 10,000). Oncogenic oral HPV prevalence was twice as high in women with ≥2 versus 0–1 lifetime oral sexual partners (1.5% versus 0.7%). Oncogenic oral HPV prevalence was highest among men who currently smoked and had ≥5 lifetime oral sexual partners (14.9%). The combination of a low prevalence of oncogenic oral HPV in most groups and the low lifetime risk of developing OPC among those with oral infection suggest that screening based on oral HPV detection would be challenging (D'Souza, 2017).

Autoimmune Diseases and Sjögren's Syndrome (SS)

Autoimmune disorders cause destruction of the body's own tissues and disproportionately affect women. SS, an autoimmune disease characterized by reduced secretions from salivary and lacrimal glands, affects an estimated 1–4 million people, 90 percent of whom are women. Patients with SS have increased numbers of lymphocytes and other immune cells in their salivary and lacrimal glands and an increased risk for developing malignant lymphoma, which occurs an estimated 40 times more frequently in patients with SS.

In 2003, NIDCR, the National Eye Institute, and ORWH provided support for the Sjögren's International Collaborative Clinical Alliance (SICCA). The SICCA is an integrated research network and large international SS patient registry that spans seven countries (Argentina,

China, Denmark, India, Japan, the United Kingdom, and the United States). The SICCA registry, designed by an international expert panel of ophthalmologists, rheumatologists, and oral medicine/pathology specialists, used standardized tests to evaluate more than 1,900 enrolled participants. All had possible signs and/or symptoms of SS typical of patients seen in a clinical practice. This registry provides data and linked biospecimens to investigators to promote research on SS. In one NIDCR supported study, investigators examined the genetic etiology of SS across ancestry and disease subsets in Asian and European ethnic groups. Striking differences were observed between the European and Asian gene associations, with high heterogeneity especially in the major histocompatibility complex region. Also, new associations in Asian populations were identified that were previously not measurable in Europeans, due to low allele frequency (Taylor, 2017). Further, a separate study to explore natural history and predictors of progression to SS found that there was stability over a 2-3-year period of both individual phenotypic features and status of SS; hypergammaglobulinemia and hypocomplementemia at study entry were predictive of progression to SS (Shiboski, 2018).

With co-funding from ORWH, NIDCR-funded investigators are conducting preclinical research on mechanisms of sex differences of SS, specifically how extracellular nucleotides released from injured or diseased salivary gland tissue contribute to chronic inflammation. The study will determine if differences in expression levels of P2 purinergic receptors for extracellular ATP in male compared to female salivary glands contribute to the accelerated development of Sjögren's-like immune pathologies in female SS mouse models (R01 DE007389, Weisman). In another ORWH co-funded study, NIDCR researchers are studying sexual dimorphism in salivary gland tissue regeneration, analyzing the effect of inflammatory response on integration and vascularization of biomaterial scaffolds, and assessing correlations between the number of macrophages and formation of new vasculature in both male and female mice (R01 DE022971, Baker).

NIDCR intramural scientists are following a cohort of patients with SS and are collecting clinical data and biospecimens over time to better understand the natural history of the disease. Recent progress includes:

- Autoantibody detection is a key tool for the diagnosis of SS. A new streamlined immunoassay called LIPSTICKS, employing light-emitting proteins, was able to measure SS-associated autoantibodies in SS patients in less than one minute and was found effective for point-of care detection of autoimmunity (Burbelo, 2017).
- Using laser microdissection coupled with deep RNA transcript sequencing of salivary biopsies from subjects with and without SS, scientists identified marked alteration in gene expression in the ductal cells and inflammatory infiltrate compared to the acinar cells. The inflammatory infiltrate showed the most dramatic differences and contained up-regulated genes associated with dendritic cells, natural killer cells and T-cells. Two chemokines, CCL21 and CCR7, were validated as up-regulated proteins and may be involved in the recruitment of immune cells to the salivary gland, causing inflammation and loss of secretory function (Tandon, 2017).
- Ro52/TRIM21 is a major diagnostic autoantigen in SS and normally functions in antibody-dependent pathogen neutralization. Using deletion and point mutant analyses, NIDCR scientists explored the autoantigenicity of Ro52 and found previously hidden robust autoantibodies directed against its C-terminal immunoglobulin-binding domain. Another autoantibody, rheumatoid factor, strongly overlapped with Ro52 seropositivity. These convergent mechanistic findings support a model

whereby intracellular Ro52-bound antibody-coated pathogen complexes, released or misprocessed from infected cells, drive autoantigenicity against Ro52 (Burbelo, 2018).

- In a mouse model of SS, cystic fibrosis transmembrane regulator (CFTR) expression is markedly reduced. Treatment with a CFTR vector or a CFTR corrector restored salivation, rescued CFTR expression and localization, and nearly eliminated the inflammation and tissue damage caused by SS. Most notably, the markedly reduced acinar cell signaling and fluid secretion were restored by rescuing ductal CFTR. These findings reveal that correcting ductal function is sufficient to rescue acinar cell function and suggest that CFTR correctors are strong candidates for the treatment of SS (Zeng, 2017).

Oral Health Disparities Research

NIDCR's strategic plan includes as a goal the elimination of disparities in oral health. Vulnerable populations include women of racial and ethnic minority backgrounds, those with low income, and those with developmental or acquired disabilities. In addition, NIDCR supports research on the oral health of children, including the impact of primary caregivers, often mothers, on the oral health of their children.

A complex relationship exists between maternal behaviors, maternal oral health, and children's oral health. Behavior change strategies targeting mothers of newborns have shown promise in improving health outcomes in their children. A randomized controlled clinical trial by NIDCR-funded investigators with 579 mother-infant participants tested the effectiveness of motivational interviewing (MI) in helping American Indian mothers initiate positive oral health behavior changes to prevent early childhood caries (ECC) in their newborns. MI was shown to increase mothers' oral health knowledge, but it did not affect their oral health behaviors or the progression of their children's ECC. The findings suggest that social factors may be more important determinants of oral health than previously thought and that these should be considered when initiating behavior change strategies for mothers and caregivers (Batliner, 2018).

NIDCR-funded investigators employed the Extended Health Belief Model (EHBM), a conceptual model used in health promotion research, to conduct a cross-sectional study with 100 Latino mother-child participants to assess the relationship between mothers' health beliefs, self-efficacy, and cultural factors and children's oral health outcomes. Survey items assessed for the EHBM were found to be valid as measures of maternal factors influencing children's oral health outcomes in this Latino population. Maternal education was the strongest predictor of health beliefs (Wilson, 2017).

Many pregnant women do not receive dental care or education regarding optimal infant oral health. Since most women access prenatal care, it may be possible to use various prenatal care settings to deliver maternal oral hygiene instruction and infant oral health education. NIDCR is funding a clinical trial to test a CenteringPregnancy® Oral Health Promotion (CPOP) intervention. Two maternal and infant oral health educational and skills building modules will be integrated into the established CenteringPregnancy group prenatal curriculum to determine if the CPOP intervention is effective in improving maternal and infant oral health (U01 DE027340, Chung).

Poor oral health during pregnancy is a significant public health issue because of its prevalence, impact on women's oral health and their future children's oral health, and evidence suggesting links with adverse pregnancy and birth outcomes and other chronic health conditions across the life-course. Both medical and dental professional organizations have endorsed guidelines

promoting oral health education, assessment, and treatment efforts during pregnancy; however, barriers and facilitators to implementing these guidelines into practice remain unknown. An NIDCR-funded project is exploring multilevel system factors that influence guideline implementation among prenatal care and oral health care providers, with a goal of improving oral-systemic health among women and their offspring (R03 DE0244633, Vamos).

Craniofacial Anomalies

Craniofacial abnormalities may be the result of spontaneous or inherited genetic variants. The causes often are complex, involving environmental factors and gene-gene and gene-environment interactions.

Craniofrontalnasal syndrome (CFNS), typified by craniofacial, skeletal, and neurological anomalies, is an X-linked disorder resulting from inactivation of the *EFNB1* gene. While X-linked conditions typically have a more severe impact on males due to the presence of just a single copy of the X chromosome, CFNS primarily affects females. This unusual disease characteristic was hypothesized to be due to the biological consequences of random inactivation of the X chromosome, which would generate a mixed population of affected and unaffected cells in females with this condition. Using human induced pluripotent stem cells from CFNS patients, investigators demonstrated that affected cells containing mutated Ephrin B1 segregated from cells carrying a functional copy of the gene. This cell-level defect likely leads to the anomalies observed in CFNS patients, although the exact mechanism is still to be determined (Niethamer, 2017). Ongoing work will further investigate the role of the genes that code for the Eph/Ephrin family of signaling molecules in craniofacial morphogenesis (R01 DE023337, Bush).

Puerto Ricans, the second largest Hispanic group in the US, have a high birth prevalence of oral cleft lip/cleft palate, at 16 per 10,000. NIDCR-supported researchers are studying 250 case-parent Puerto Rican ancestry families and 250 controls to examine genetic variation, sub-clinical phenotypes, and maternal nutritional biomarkers related to oral cleft risk. This research has the potential to identify genetic and phenotypic variants of oral clefts in Puerto Ricans and maternal nutritional biomarkers such as those associated with folate and vitamin deficiencies during pregnancy (R00 DE024571, Buxo).

NIDCR-supported researchers have made progress toward defining the genetic pathways regulating palatogenesis. Both *Pax9* and the Wnt signaling pathway defects have been previously implicated in craniofacial development, but the relationship between them is poorly understood. Two research groups, using different technical approaches, were able to demonstrate that *Pax9* mutants overexpress a class of secreted Wnt inhibitors in the *dickkopf* family of genes *(Dkk)*. These results suggested that an overall reduction in the inhibition of Wnt signaling could rescue the cleft palate phenotype of *Pax9* mutants. Such a reduction can be accomplished genetically through deletion of genes encoding Wnt pathway inhibitors or by using chemical antagonists of those inhibitors. As predicted, genetic manipulation of this pathway in embryos rescued secondary palate fusion in more than half of the embryos. *In vivo* administration of two different inhibitors of DKK resulted in a similar rescue frequency of secondary palate closure. Small anterior clefts remained after drug treatment and none of the experimental approaches rescued all of the phenotypes associated with *Pax9* mutations (arrest of tooth development, parathyroid and thymus agenesis, etc.). These studies suggest that, in the future, appropriate combinations of these small molecules could possibly have clinical utility in the treatment of craniofacial dysmorphologies (Li, 2017; Jia, 2017).

III. NIDCR Activities that Support the Goals of the NIH Strategic Plan for Women's Health Research

The following examples support the objectives of **Goal 1: "Increase Sex Differences Research in Basic Science Studies."**

1.2: Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

The articular tissue integrity of synovial joints is likely to be dependent in part on energy density (ED), the amount of mechanical work per volume of cartilage imposed during function. NIDCR-funded investigators found that during asymmetric jaw closing, contralateral TMJ EDs were twofold and significantly larger in healthy females versus males, due to 1.5-fold and significantly smaller TMJ disc cartilage volumes under stress fields in females versus males. These results suggest that in healthy individuals, asymmetric jaw closure in females compared to males has higher TMJ mechanical fatigue liabilities (Gallo, 2018).

1.4: Include sex parameters in the design of experiments using animal models.

Women report post-herpetic neuralgia following herpes zoster (shingles) 30% more frequently than men. NIDCR-supported investigators studied both males and females in a rat model of varicella zoster virus (VZV) infection, finding that the female rats given a lower dose of VZV had longer affective responses than male rats, and that estrous cycle affected aversive pain responses (Stinson, 2017). The researchers are continuing investigations into the mechanisms underlying this sex difference.

The examples below support objectives of **Goal 3: "Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women."**

3.2: Study sex/gender differences in embryonic development, including epigenetic changes.

NIDCR-funded researchers are studying craniofrontalnasal syndrome (CFNS), an unusual X-linked disorder in that females are more severely affected than males, who have only one X chromosome. The disorder is caused by a mutation in EFNB1, the gene that encodes the signaling molecule Ephrin B1. Using human induced pluripotent stem cells from CFNS patients, investigators demonstrated that affected cells containing mutated Ephrin B1 segregated from cells carrying a functional copy of the gene, providing evidence that Eph/ephrin-mediated cell segregation is relevant to pathogenesis in human CFNS patients (Niethamer, 2017).

3.9: Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.

A randomized controlled trial in American Indian mother-child dyads tested the effectiveness of motivational interviewing as a maternal behavior change strategy for improving child oral health. While the MI intervention appeared to improve maternal oral health knowledge, it did not show an effect on oral health behaviors or on the progression of early childhood caries in the children. This suggests that social factors may be important oral health determinants that may interfere with the ability for caregivers to benefit from behavioral strategies to improve health (Batliner, 2018).

Initiatives: Funding Opportunity Announcements (FOAs)

Immune System Plasticity in the Pathogenesis and Treatment of Complex Dental, Oral, and Craniofacial Diseases (R01), PAR-15-192; and (R21), PAR-15-193: These FOAs encouraged research projects to elucidate the role of immune system plasticity in health and in the pathogenesis of dental, oral, and craniofacial (DOC) diseases. The goal was to advance knowledge of the immunological basis of DOC diseases, and to develop tools and technologies for precise modulation of the immune system to restore or maintain health.

Factors Underlying Differences in Female and Male Presentation for Dental, Oral, and Craniofacial Diseases and Conditions (R01), PA-16-295; and (R21), PA-16-296: These FOAs encourage research on mechanisms underlying the manifestations of sex-based differences in DOC diseases and conditions. They encourage studies aimed at understanding immune reactivity, genetic variation, environmental triggers, aging, and hormonal changes as they affect sex-based differences in DOC-related diseases and conditions.

Genetic Susceptibility & Variability of Human Structural Birth Defects (R01), PAR-17-236: This FOA supports innovative applications that will inform our understanding of structural birth defects through the use of animal models in conjunction with translational/clinical approaches. Applicants are encouraged to take advantage of advances in genetics, biochemistry, molecular, and developmental biology to identify specific genetic, epigenetic, environmental, or gene/environment interactions associated with the susceptibility to and variability of structural birth defects in human populations.

Research on Chronic Overlapping Pain Conditions (R01), PA-18-937; and (R21), PA-18-939: The purpose of these FOAs is to encourage epidemiological, clinical, and translational research that will increase our understanding of the natural history, prevalence, biological mechanisms, psychological variables, and clinical risk factors responsible for the presence of multiple chronic pain conditions in people with pain.

Neuroskeletal Biology of the Dental and Craniofacial Skeletal System (R01) RFA-DE-18-005, (R21) RFA-DE-18-006: These FOAs encouraged research on the role of the nervous system in metabolism, homeostasis, remodeling and/or regeneration of the postnatal dental and craniofacial skeletal system (DCS) in health and disease. Specific areas of research interest included investigations on molecular, genetic, cellular, and other factors that influence these interactions including sex-based differences. These FOAs also sought to develop new or optimize existing tools and technologies to characterize nervous system-DCS interactions.

Mechanisms, Models, Measurement, & Management in Pain Research, PA-18-141 (R01); PA-18-159 (R21): The purpose of these FOAs, issued by the National Institute of Nursing Research in conjunction with members of the NIH Pain Consortium, is to inform the scientific community of the pain research interests of the various NIH Institutes and Centers (ICs) and to stimulate and foster a wide range of basic, clinical, and translational studies on pain as they relate to the missions of these ICs.

Small Research Grants for Establishing Basic Science-Clinical Collaborations to Understand Structural Birth Defects (R03- Clinical Trial Not Allowed), PAR-18-734: The purpose of this FOA is to promote initial establishment of basic science-clinical

collaborations by providing small grants to teams of basic scientists, physician scientists, and/or clinicians to increase understanding of the developmental biology, genetics, and/or environmental basis of structural birth defects.

Workshops, Conferences, Symposia, and Consortia

Women's Oral Health Symposium

A symposium titled "Oral Health of Minority Women and Mothers" was held March 24, 2017 at the International Association for Dental Research meeting in San Francisco, CA. A panel of speakers from academia and the NIDCR addressed reproductive health and oral disease, maternal general and oral health and children's oral health, oral health behaviors, and the potential role of general and dental health networks.

12th and 13th Annual NIH Pain Consortium Symposia

The 12th annual NIH Pain Consortium Symposium was held at NIH May 31–June 1, 2017. The symposium titled "Multidisciplinary Strategies for the Management of Pain" brought together basic, translational, and clinical researchers to discuss pain management and opioids, models of integrated pain care, and multidisciplinary pain management. On May 31 and June 1, 2018, the NIH hosted the 13th Annual NIH Pain Consortium Symposium titled "From Science to Society: At the Intersection of Chronic Pain Management and the Opioid Crisis," which focused on chronic pain management and opioid addiction. Panelists addressed access to pain control during the opioid epidemic, factors affecting opioid response, the use of NIH BRAIN Initiative technologies in pain research, and disparities in pain management. Each symposium included poster presentations by young investigators.

MDEpinet TMJ Patient Roundtable

The MDEpinet TMJ Patient Roundtable, held on May 11, 2018, was organized by the TMJ Association and the Food and Drug Administration (FDA) to address TMJ implant performance, surgical outcomes, and adverse events, with an emphasis on patient input and patient-centered outcomes. It brought together TMD patients, patient advocates, clinicians, and representatives from industry, NIH, FDA, and the Agency for Healthcare Research and Quality.

National Academies Consensus Study on Temporomandibular Disorders (TMD)

NIDCR and the NIH Office of the Director are supporting a National Academy of Sciences consensus study on Temporomandibular Disorders (TMD): From Research Discoveries to Clinical Treatment. This activity will convene an expert committee to assess the current state of knowledge regarding TMD research, education and training, safety and efficacy of clinical treatments of TMD, and burden and costs associated with TMD. The committee's findings will inform development of policies related to evidence-based treatment and clinical management of TMD patients. http://nationalacademies.org/hmd/Activities/PublicHealth/TemporomandibularDisorders.aspx

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National Institute of Diabetes and Digestive and Kidney Diseases

I. Executive Summary and Overview

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports biomedical and behavioral research to address some of the most common, costly, and chronic diseases and conditions affecting the U.S. and global populations, including diabetes, obesity, endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematologic diseases. Many of the diseases and conditions within its research mission affect women solely, disproportionately, or in unique ways. For example, only women develop gestational diabetes mellitus (GDM); women lose their comparative cardiovascular disease risk protection when they develop chronic diabetes; African American women experience the highest rates of obesity; obesity increases risk for myriad health problems of special interest for women, including cardiovascular disease, gallbladder disease, and GDM; women are more prone to autoimmune disorders, including autoimmune thyroid and liver diseases; bowel and bladder control problems are much more prevalent in women; and women are most highly affected by chronic pain syndromes associated with the bladder (interstitial cystitis/bladder pain syndrome) and gut (irritable bowel syndrome). The NIDDK supports a diverse portfolio of research important to women's health, including studies of:

- Diabetes in women (including type 1, type 2, and gestational diabetes)
- Diabetes health complications, including urologic problems, sexual dysfunction, and depression
- Obesity prevention and treatment
- Thyroid and parathyroid conditions and diseases
- Endocrine regulation of bone metabolism and osteoporosis
- Irritable bowel syndrome (IBS)
- Interstitial cystitis/bladder pain syndrome (IC/BPS)
- Fecal and urinary incontinence
- Kidney diseases and kidney failure
- Liver and biliary diseases
- Urinary tract infections (UTIs)

Sex/gender differences research is also revealing new information about how susceptibility, onset, progression, or treatment efficacy for diseases and conditions within the NIDDK mission may differ between women and men. Similarly, microbiota and microbiome studies intersect with a number of these areas and are providing new insights.

The scope of NIDDK women's health research crosses the Institute's three extramural research divisions—the Division of Diabetes, Endocrinology, and Metabolic Diseases; the Division of Digestive Diseases and Nutrition; and the Division of Kidney, Urologic, and Hematologic Diseases—and the NIDDK's Division of Intramural Research. Their efforts are enhanced by activities of the NIDDK's Office of Obesity Research, Office of Minority Health Research Coordination, and Office of Nutrition Research. The NIDDK and NIH Office of Research on Women's Health (ORWH) also work together to

foster research in many of these areas. Some NIDDK-supported research, such as study of the relationship of obesity and diabetes to cardiovascular disease and study of diabetes during pregnancy, may also have an important impact on diseases and conditions that are primarily within the mission of other Institutes and Centers, and the Institute will often seek to synergize IC efforts. The NIDDK promotes public health education and awareness through the efforts of its Office of Communications and Public Liaison. Finally, the NIDDK conducts strategic planning efforts for research in major areas of its portfolio on a regular basis; many of these are germane to women's health and include input and/or partnership from the ORWH. Examples of women's health and sex differences research accomplishments and activities supported by the NIDDK in FYs 2017 and 2018 follow, categorized under diabetes; obesity; pregnancy; microbiota and microbiome studies; liver disease; chronic pain conditions; kidney disease; and urologic health.

II. Accomplishments and Activities

Diabetes

Identifying Factors That Could Influence Prevention of Type 2 Diabetes or Related Health Complications in Women

Information important to diabetes prevention in women continues to emerge from the Diabetes Prevention Program (DPP) and its long-term follow up, the DPP Outcomes Study (DPPOS). In 2002, the DPP clinical trial results showed that, in a racially, ethnically, and age-diverse cohort of obese and overweight adults with elevated blood glucose levels, an intensive lifestyle intervention (ILI, exercise and diet to induce moderate weight loss) reduced risk of developing type 2 diabetes by 58 percent. The diabetes drug metformin reduced diabetes risk by 31 percent (Knowler et al, 2002). Sixty-eight percent of the DPP study participants were women, of whom 16 percent had a history of GDM. With co-support from ORWH, investigators have been leveraging the DPP and DPPOS cohorts to conduct secondary analyses that could elucidate the impact of endogenous sex steroid hormones and reproductive functions on risk for health complications in this population. For example, an analysis focused on the DPP, weight loss, and changes in sex steroid profiles, researchers found that reductions in adiposity were significantly associated with sex hormone changes that differed by gender and fat depot; in women, reductions in visceral adipose tissue and subcutaneous adipose tissue were associated with increases in sex hormone binding globulin (SHBG). This analysis is suggestive that significant decreases in adipose tissue depots can affect sex hormone profile (Kim et al, 2017). Now in its third 5-year period and co-funded by ORWH, DPPOS is investigating whether starting metformin during prediabetes leads to lower rates of cardiovascular disease and cancer; the DPPOS cohort is 67 percent female and sex/gender differences in the rates of these outcomes will be examined. A study focused on diabetes prevention leveraged a long-term study of young black and white women ages 18 to 30 years without diabetes at baseline; the researchers found longitudinal biochemical evidence that maternal lactation duration is independently associated with lower future incidence of diabetes (controlling for factors such as GDM); additional research will be needed to understand the mechanism(s) that could account for this protective effect (Gunderson et al, 2018).

Interventions and Treatments for Type 2 Diabetes—New Targets, Elucidating New Benefits

Diet improvement can reduce complications of diabetes, but dietary patterns vary between women and men and other differences may exist

as well. Researchers surveyed a multi-ethnic cohort of nearly 800 women and men with type 2 diabetes about social aspects of diet based on 24-hour recalls; their analyses indicate that greater meal frequency at home was associated with significantly better scores on diet quality indices for men (but not women), while meal frequency outside the home was associated with poorer diet quality and energy intake for women (but not men) (Pachucki et al, 2018). This intriguing difference lends urgency to pursuing better measurement of social dimensions of eating to inform ways to improve nutrition, especially for persons with diabetes. At the same time, analysis of data from the Look AHEAD study, a trial that enrolled or obese older adults with type 2 diabetes and randomly assigned them to a 10-year intensive lifestyle intervention (ILI) or diabetes support and education (DSE), has shown that ILI increased disability-free years of life in women and participants without cardiovascular disease (CVD) but not in men or participants with CVD—a health benefit that could help in motivating women with type 2 diabetes who meet similar criteria to pursue weight loss strategies (Gregg et al, 2018; NCT00017953).

Women with Type 1 Diabetes—Urologic and Other Disease Complications

Diabetes affects nearly every organ and tissue in the body, with a spectrum of ensuing health complications. Insights into urologic complications in women with type 1 diabetes continue to emerge from the Diabetes Control and Complications Trial (DCCT) and its ongoing observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC). A recent study of the cumulative burden and overlap of urinary and sexual complications among women and men in this population found that, of sexually active women who completed a 2010/2011 survey, 35 percent reported no complications, 39 percent had one, 19 percent two, 5 percent three, and 2 percent four. Sexual dysfunction was most prevalent (42 percent of women and 45 percent of men) followed by urinary incontinence in women (31percent) and low sexual desire in men (40 percent). Similar data collected 7 years earlier enabled researchers to observe remission in a small subset of the study population, indicating a rationale for future studies that may mitigate the onset or impact of urological complications of diabetes (Wessells et al, 2018). Another study has attempted to fill a gap in knowledge regarding prevalence of systemic rheumatic diseases (SRDs), which predominantly affect women, in people with type 1 diabetes; the results indicate that there is an age-dependent enrichment of SRDs in women with type 1 diabetes, with 9.2 percent prevalence in women overall and 14 percent in women over age 50 in the study population, information that can now be utilized in clinical care of women with type 1 diabetes (Bao et al, 2018).

Obesity

Genetic, Epigenetic, and Other Molecular Factors

Obesity is a multifaceted metabolic problem involving such diverse factors as genetic variation, physiologic development and modification over time (including the impact of the intrauterine environment), signaling to and from the central nervous system, and the intersection of diverse environmental cues, stressors, and other elements, all contributing to the accumulation of excess fat. Sex/gender differences in the onset, development, and prevention or treatment of obesity are being recognized across the spectrum of obesity-related studies. For example, in the largest-scale human genetics study of its kind, with samples from a racially and ethnically diverse cohort, researchers have identified seven new gene regions associated with individual variability in the deposition of fat, including one that was associated with subcutaneous fat in women only and another that was associated with visceral fat and body mass index in women only (Chu et

al, 2017). A newly funded grant will investigate the role of epigenetics in driving individual variation in metabolism, including examining sex differences in epigenomic and phenotypic variability (1DP1DK119129-01). With the ORWH, the NIDDK is also newly supporting a Specialized Center of Research Excellence (SCORE) on Sex Differences focused on studying the role(s) of sex chromosomes, overall genetic variation, and the estrogen receptor in sex differences in risk factors and treatments for obesity, insulin resistance/diabetes, dyslipidemia, fatty liver, and similar metabolic dysfunctions (1U54DK120342-01).

Insights into Metabolic Pathways Influencing Fat Deposition and Cardiovascular Health

The liver is an important center for regulation of fat metabolism. Studies have shown that loss of hepatocyte estrogen receptor α (ER α) worsens fatty liver, dyslipidemia, and insulin resistance in high-fat diet fed female mice. A new study has found that ER α also plays a role in reverse cholesterol transport (the net movement of cholesterol from peripheral tissues to the liver)—in female mice fed a high-fat diet, deletion of hepatocyte ERα increased serum cholesterol levels and increased high density lipoprotein particle sizes, and also increased adiposity and worsened insulin resistance to a greater degree in female than male mice; all of the changes lead to a 5.6-fold increase in the size of early atherosclerotic lesions in the mutant female mice compared to controls, indicating that intact hepatocyte ER α is protective against lipid retention in the artery wall during early stages of atherosclerosis in female mice fed this type of diet, with potential implications for human disease (Zhu et al, 2018).

Obesity and the Brain

Clinical and basic studies are both leading to new insights into sex differences in how the brain influences obesity. For example, an imaging study of intrinsic brain activity and connectivity in women and men across a spectrum of body mass indices (BMIs) has revealed a stronger relationship between increased BMI and decreased connectivity of core reward network components with cortical and emotion regulation regions in women, which may in turn be related to the greater prevalence of emotional eating in women (Gupta et al, 2018). Complementing this, a study in rodents investigating brain pathways underlying food-seeking behaviors in the absence of hunger—of importance to humans in modern food cue rich environments—focused on the a brain region called the ventromedial prefrontal cortex (vmPFC) and found that experimentally silencing vmPFC neurons in males disrupted renewal of responding to a food cue, while stimulating vmPFC neurons in females induced this behavior (Anderson et al, 2018). While more research is needed, findings from both these studies further reinforce the importance of understanding and developing personalized treatments for obesity that consider the sex of the affected individual.

Potential Benefits of Weight-loss Surgery to Women

Weight-loss surgery remains an active area of investigation for treatment of extreme obesity because of its potential health benefits beyond weight loss (*e.g.*, reversal of type 2 diabetes) and its potential health complications, including death. Girls and women are the majority of participants in studies of weight-loss surgery, reflecting the real-world patient population. In a recent study, researchers investigated the relationship between three different types of weight-loss surgery and the incidence of macrovascular events (coronary artery disease and cerebrovascular diseases) through retrospective analysis and comparison with a matched cohort with type 2 diabetes that did not undergo surgery; 75 and 76 percent of participants, respectively, were women. They found that weight-loss surgery was associated with a lower composite incidence of macrovascular events at 5 years as well as a

lower incidence of coronary artery disease; the incidence of cerebrovascular disease was not significantly different between groups at 5 years (Fisher et al, 2018). These findings will require confirmation through randomized clinical trials. In another encouraging finding, the first U.S.-based, 12-year, observational study of bariatric surgery in adults indicates long-term durability of weight loss after the weight loss surgical procedure known as "Roux-en-Y" gastric bypass. Moreover, the weight loss was associated with improvement and prevention of type 2 diabetes and obesity-related cardiovascular conditions (Adams et al, 2017).

Pregnancy and the Health of Women and Their Offspring

Diabetes, Obesity, and Other Metabolic Factors

Numerous observational studies have linked pre-existing overweight/obesity and/or excessive gestational weight gain during pregnancy to short-term and long-term adverse health consequences in both mothers and offspring. However, additional research is needed to identify effective interventions that will improve weight, glucose levels, and other pregnancy-related outcomes in mothers and determine whether these interventions affect obesity and metabolic abnormalities in the offspring. An estimated 7 percent of women will develop GDM during pregnancy; about half of these women will develop type 2 diabetes 5 to 10 years post-partum (Kim et al, 2002), and offspring of GDM-affected pregnancies are at increased risk for obesity and diabetes. Moreover, racial disparities during pregnancy also exist—for example, pregnant African American women are more likely than White women to have complications such as GDM, preeclampsia, stillbirth, preterm birth, and weight retention after giving birth. Two key clinical efforts include:

- **HAPO Follow Up Study:** The NICHD-led Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study reported in 2008 a strong linear relationship between increasing maternal blood glucose concentrations—below those used in the United States to diagnose GDM—and adverse neonatal outcomes, although without any clear glucose level threshold; based on these results, many organizations adopted a new definition of GDM (*note, current U.S. criteria for GDM remain essentially the same as pre-HAPO*). The NIDDK-led HAPO Follow Up Study, co-supported by NICHD, has now reported a strong relationship between maternal glucose levels during pregnancy that would meet that new GDM definition and subsequent type 2 diabetes in women and obesity in children 10 to 14 years post-delivery; the study did not find a significant relationship between those maternal glucose levels and the combined outcome of overweight and obesity in children (Lowe et al, 2018). The results reinforce importance of trying to prevent GDM in high-risk women and of research that could potentially improve screening and mother/child outcomes, spurring multiple new efforts; *e.g.*, a newly funded grant proposes to leverage a large health care delivery system to help identify characteristics predictive of higher risk for low engagement in lifestyle programs for diabetes prevention among women with a recent history of GDM, with the goal of improving health in this high risk population of women (1R03DK113325-01).
- **LIFE-Moms Consortium:** LIFE-Moms has been testing lifestyle interventions in overweight and obese pregnant women that may reduce inappropriate gestational weight gain and/or improve metabolic status, with potential short- and long-term health benefits for mothers and offspring. The consortium has consisted of seven clinical studies in a broad range of populations, including minority and socio-economically disadvantaged groups, and a research

coordinating unit. Different intervention strategies have been tested—such as home visits by parent-educators, and individual or group lifestyle programs in clinical settings—and results have now been published from several of the individual trials (Phelan et al, 2018 (NCT01545934); Cahill et al, 2018 (NCT01768793); Redman et al, 2017 (NCT01610752); Gallagher et al, 2018 (NCT01616147)). A meta-analysis of the clinical trials conducted at the seven LIFE-Moms sites shows that the interventions overall resulted in a significantly lower proportion of women with excess gestational weight gain (Peaceman et al, 2018). Follow up continued through 1 year post-delivery for the women and 1 year of age for the offspring, and a manuscript describing the outcomes is in preparation. LIFE-Moms has been co-sponsored by the NIDDK (lead), NHLBI, NICHD, NCCIH, ORWH, ODP, and OBSSR.

Further, a recent study has shown that an Internet-based weight loss intervention produces greater weight loss in low-income women (majority Hispanic cohort) who have recently given birth than a standard care program alone (Phelan et al, 2017 (NCT01408147)). In related efforts, a number of new reports have provided insights into calorie consumption, physical activity, and sleep during pregnancy (Most et al, 2018a; Most et al, 2018b (NCT01954342); Hawkins et al, 2018). The reports suggest further research to develop interventions addressing these factors could help support healthier pregnancies, reduce racial and ethnic disparities, and improve health outcomes for mothers with obesity and their children. Finally, the Intervention Nurses Start Infants Growing on Healthy Trajectories (INSIGHT) randomized clinical trial, a home-based responsive parenting intervention for infant prevention of weight gain that is primarily focused on first time mothers, has been shown to improve child weight through age 3 (Paul et al, 2018; NCT01167270).

Preeclampsia

Pregnant women, especially those with preexisting high blood pressure or diabetes and those who develop GDM, are at risk for preeclampsia, a condition of dangerously high blood pressure and proteinuria that can occur during the second half of pregnancy. Variants in a gene called *APOL1* that are carried at higher frequency in persons of African ancestry confer higher risk of kidney disease in this population. In an intriguing finding, a collaborative team of NIDDK intramural and extramural researchers has discovered that a high risk *APOL1* genotype in the fetus (as ascertained post-delivery)—not in the mother—is associated with risk for the mother developing preeclampsia, possibly through affecting placental function (Reidy et al, 2018). Further research will be needed to assess whether *APOL1* genetic testing can predict preeclampsia and improve pregnancy outcomes.

Microbiota and Microbiome in Health and Disease

Gut Microbiome

Research to understand the trillions of microbes living in various body niches—*e.g.*, gut, urogenital tract—and their interaction with their hosts is providing new insight into health and disease states and is already showing potential for clinical therapies. Obesity, digestive diseases, and nutrition have been some of the immediate targets, but studies of the microbiota (microbes) and gastrointestinal (GI) tract microbiome (the collective microbial genetic material) are also providing insights into other conditions. While potentially life-saving, antibiotics can also adversely alter gut microbial communities. For women, this can be of particular importance during pregnancy, as gut microbes and the microbiome are passed down from mothers to their offspring at birth and play an essential role in the development of a healthy immune system. A new advance in a rodent model has

demonstrated that the alterations induced by antibiotic use can pass from pregnant mice to their offspring and increase the offspring's risk for intestinal inflammation similar to human inflammatory bowel disease (IBD). Findings such as this indicate that further research is needed to inform health care decisions weighing the benefits and risks of antibiotic use in women and their children (Schulfer et al, 2018). There is evidence in animal models that gut microbial complement influences social, emotional, and certain sensory responses or behaviors, little is known in humans. A study in women has found distinct and different relationships between certain gut bacterial groups and brain responses to emotionally-stimulating images, supporting the concept of brain-gut-microbiota interactions in healthy humans; further examination of the interaction between gut microbes, brain, and affect in humans is needed to inform preclinical reports that microbial modulation may affect mood and behavior (Tillisch et al, 2017). A grant newly funded by NIDDK will build on a previous report (Li et al, 2016) to study influence of the gut microbiome on normal bone and on osteoporosis (bone homeostasis in health and disease) by testing the impact of probiotics in a mouse model of sex steroid deficiency and investigating underlying mechanisms (1R01DK112946-01A1).

Female Urinary Microbiota

The relatively recent discovery of a "female urinary microbiota" (FUM) that exists in the bladder of many adult women has led to numerous questions, including its role in health and disease—for example, what is its essential composition, and whether and how does it affect urinary incontinence and urinary tract infection (Brubaker et al, 2017). In a key advance, researchers have developed a detailed characterization of bacteria present in the urinary tract of healthy women and comparison to vaginal and gut bacteria in the same group, resulting in the novel findings of similarities between vaginal and bladder microbiota with functional capacities that are distinct from those observed in gut microbiota; moreover, analyses of intra-individual bacterial complements in these two niches suggest the existence of an interlinked female urogenital microbiota that shares both pathogens and health-associated commensal organisms, with important implications for how to view bacteria present in the pelvic floor and for treatment of urinary tract diseases and conditions (Thomas-White, et al 2018).

Sex/Gender Influences in Liver Disease

Basic and clinical research studies are elucidating both sex differences and sex/gender-specific facets of liver disease. For example, primary sclerosing cholangitis (PSC), a potentially fatal liver disease in which the ducts that drain the bile from the liver are damaged, affects both women and men but is more common in men. However, in a certain genetically modified mouse model that spontaneously develops features of PSC, female mice develop more severe liver injury than do males. Researchers studying this model found that the female mice have dramatically higher levels in bile duct cells of a molecule, long noncoding RNA (lncRNA) H19, that regulates cell proliferation and differentiation into specific cell types; reducing the levels of lncRNA H19 reduced liver injury in the female mice. Samples from human males and females with PSC showed the same alterations in lncRNA H19 and other molecules as in the mouse model, highlighting potential sex-related differences in disease progression and a new target for the development of future therapies against diseases such as PSC (Li et al, 2017); a newly funded grant will build and expand upon these findings (1R01DK115377-01A1). Pituitary growth hormone (GH) governs and imparts important sex differences in liver physiology, metabolism, and disease; a study in mice has identified two microRNAs (miRNAs), miR-1948 and miR-802, as important factors in effecting GH-regulated male- and female-biased

patterns of liver gene expression, respectively (Hao et al, 2017). Nonalcoholic fatty liver disease (NAFLD) is a form of chronic liver disease that affects both women and men and is associated with obesity and other metabolic disorders; yet, a robust animal model for studying the disease has been sorely lacking, in particular because in the best mouse model females do not develop human-like disease under usual laboratory housing conditions. In an important advance, researchers found that increasing the temperature at which the mice are housed to align with mouse metabolism rather than human comfort leads to more pronounced NAFLD-like disease and related physiological changes, even in the female mice—a finding not only important for studying this disease but for general consideration of modifications that could affect sex differences in animal models of disease (Giles et al, 2017). Interestingly, whereas premenopausal women are at lower risk of NAFLD than men, a study has found that being a premenopausal woman or a female user of synthetic hormones (pre- or post-menopausal) is associated with increased histologic severity of hepatocyte injury and inflammation among persons with NAFLD at given levels of hepatic metabolic stress (Yang et al, 2017).

Chronic Pain Conditions

IBS

The functional GI disorder IBS causes pain and constipation or diarrhea and is more common in women than in men. While diet and stress contribute to this disorder, the underlying causes are unknown. Symptoms may be influenced by abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. A key goal for IBS research is to understand the respective roles and interplay of gut and brain pathways, and to build upon this knowledge to design effective treatments. For example, resilience, the ability to recover and adapt positively to stress, has not been well-studied in people with IBS; researchers have now reported from a study in 256 women and men that resilience is lower persons with IBS compared to healthy controls and further that decreased resilience is associated with worse symptoms and with an altered biological stress response (Park et al, 2018). The importance of mental/cognitive functions in IBS is further keenly illustrated by clinical trial results showing improvement of GI symptoms after cognitive behavior therapy for refractory IBS in adult women and men (Lackner et al, 2018 (NCT00738920)). At the same time, researchers are seeking out other fundamental drivers that could be contributing to IBS, such as genetic variants or the tissue-specific expression of certain genes. For example, an international research team leveraged a large, population-based cohort to perform a genome-wide association study to uncover IBS risk variants. The study yielded a female-specific association of self-reported IBS with variants on chromosome 9 in a locus previously linked also to age at menarche, and eight candidate risk genes were identified. The findings provide additional support for investigating the role of sex hormones and autonomic nervous system dysfunction in IBS (Bonfiglio et al, 2018). Many of these and other important advances in understanding and potential treatment for IBS were facilitated by ORWH co-support.

Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

The multi-center MAPP Research Network is conducting innovative, collaborative studies of two common pelvic pain conditions—interstitial cystitis/bladder pain syndrome (IC/BPS) (in women and men), and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (in men)—collectively referred to as urologic chronic pelvic pain syndrome (UCPPS). Since its inception in 2008 and renewal/expansion in 2014 with co-support from ORWH, the Network's unique approach to the study of UCPPS has entailed

searching “beyond the bladder/prostate” to find the causes of these conditions, including studying the possible relationships between these conditions and other chronic pain disorders, such as IBS, fibromyalgia, and chronic fatigue syndrome. The Network has now published critical insights about pain patterns and other symptoms in women and men with UCPPS and the detection of future pain trends. One report provides the results of capturing and analyzing pain location, severity, and associated health and quality-of-life factors in women and men with UCPPS enrolled in the Network study at baseline. Among its many intriguing findings, this study has revealed that the majority of participants had both pelvic and non-pelvic pain, but also that more women than men had widespread pain, women were more likely to report a greater burden of nonpelvic and nonurinary symptoms and conditions as their pain locations increased, and that there were gender-specific differences in these conditions (Lai et al, 2017). A second report studied the majority of this same cohort to examine baseline clinical and psychosocial characteristics that predict 12-month symptom change in UCPPS. While more than half of participants had stable symptoms during that time, the results show that significant numbers showed clear symptom worsening or improvement; for pain and urinary outcomes, the extent of widespread pain, amount of nonurological symptoms and poorer overall health were predictive of worsening outcomes, while the extent of pain catastrophizing and self-reported stress were associated with pain outcome. Notably, the prediction models did not differ between men and women (Naliboff et al, 2017). Complementing the latter findings, numerous Network studies have uncovered brain changes in people with UCPPS compared to people without these conditions; now, a Network research team study in a subset of participants has shown the predictive value of an imaging and analysis strategy focused on measuring the strength of functional interactions among different brain regions, finding that it correctly predicted pelvic pain symptom trends in 73 percent of participants for the 3-month period following the scan (Kutch et al, 2017). These studies are significant advances in understanding the biology of pain and differences in women and men with UCPPS, and potentially improving symptom management. Based upon these and many other important insights already gained, NIDDK intends to support a 3-year MAPP Research Network Extension Phase beginning in late FY 2019 that would enable further characterization of participants currently enrolled in Network studies for an additional 12 months, enriching the Network’s unique clinical dataset and biological sample archive and allowing for unprecedented assessment of disease progression over time. MAPP Research Network web site: http://www.mappnetwork.org/

Sex/Gender Differences in Kidney Health and Disease

Researchers continue to assess sex and gender differences in the healthy and diseased kidney, and a complex picture is emerging. For example, whereas the prevalence of chronic kidney disease (CKD) is slightly higher in women than in men, small studies with limited ethnic diversity have suggested that progression in males is worse prior to any renal replacement therapy (dialysis or kidney transplant), such that men have a higher incidence of kidney failure than women. New findings are expanding this picture not just in women but also in girls. For example, a study leveraging data from nearly 4,000 women and men enrolled in the Chronic Renal Insufficiency Cohort Study (CRIC), a long-term prospective study of CKD and cardiovascular disease (CVD) in a highly racially and ethnically diverse population, has found that over an average of 7 years, women had a lower risk of CKD progression and death compared to men (Ricardo et al, 2019). In 2018, the Chronic Kidney Disease in Children Prospective Cohort Study (CKiD), co-supported by NIDDK, NICHD, and NHLBI,

presented data at a national meeting indicating that among pre-pubertal and pubertal children with non-glomerular kidney disease, girls had slower progression of disease (NCT00327860; 2U24DK066116-16). By contrast, a retrospective study of children aged 2 to 19 years registered in the U.S. Renal Data System who started renal replacement therapy between 1995 and 2011 found that the mortality rate was substantially higher for girls than for boys; it also found that access to transplantation was lower for girls than for boys, but that this difference accounted for only a small proportion of the survival differences by sex (Ahearn et al, 2019). Collectively, findings such as these point to the need for greater study and delineation of underlying biological mechanisms and external factors that influence sex and gender differences in kidney disease overall and by type. Studies in animal models continue to provide critical insights. For example, a recent study in rodents found sex differences in the pattern of renal transporters affecting water and sodium reabsorption along the nephron, findings that provide not only baseline sexual dimorphic information concerning nephron organization in rats and mice, but also potentially provide insight into the human female cardiovascular advantage (Veiras et al, 2017). Another animal study has identified a putative epigenetic factor that could explain lower levels in women versus men of a molecule that promotes kidney injury (Bourgeois et al, 2017). A workshop on the role of sex and gender in kidney disease co-sponsored by NIDDK and ORWH in 2017 should help spur further studies in this area.

Urologic Health

Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium

Problems affecting the bladder and the urethra, including urinary incontinence (UI), urinary tract infections (UTIs), overactive bladder, and interstitial cystitis/bladder pain syndrome (IC/BPS), as well as many others, occur much more frequently in women than in men. The term lower urinary tract symptoms, or LUT symptoms, refers to symptoms associated with any type of lower urinary tract dysfunction or condition, as well as those with as-yet unidentified cause. LUT symptoms and their associated conditions not only have a direct negative impact on health, but also exacerbate or contribute to other chronic health problems in women, including obesity, diabetes, and depression. The PLUS Research Consortium, established in 2015 in collaboration with NIA, OBSSR, and ORWH, is a multi-center, transdisciplinary consortium undertaking qualitative and quantitative research studies necessary to establish the scientific basis for future prevention-intervention research targeting LUT symptoms and conditions in women and girls (Harlow et al, 2018; Brady et al, 2018). PLUS recently developed and published a novel, multi-faceted research definition of bladder health that can inform approaches for evaluation of bladder health promotion and prevention of LUT symptoms both in research and in public health initiatives (Lukacz et al, 2018). PLUS investigators also conducted a review and meta-analysis of published studies between 1990-2017 to try and shed light on suspected associations between occupation, industry, and work environment and the risk of LUT symptoms in women; they found that data in the available studies limited the ability to evaluate LUTS by occupation types, a profound gap indicating that future studies should characterize voiding frequency and toilet access in a consistent manner by occupation and explore its relation to LUTS development (Markland et al, 2018). PLUS website: https://plusconsortium.umn.edu/

Urinary Tract Infections

Women are especially prone to UTIs, primarily due to differences in female and male anatomy of the urinary tract, and many women suffer from recurrent infections. The leading cause of UTIs is exposure to uropathogenic *Escherichia*

coli (*E. coli*) bacteria, also referred to as UPEC. While UTIs are currently treatable with antibiotics, the emergence of antibiotic resistant microbes, combined with the personal and medical costs of care, makes finding better therapeutic strategies a priority. Researchers continue to gain insights into host and bacterial factors that contribute to UPEC UTIs, and those that could lead to a new treatment or a vaccine. For example, a key study focused on "pili"—protein fibers on the bacterial surface with "sticky" tips, or adhesins, that are part of how UPEC attach to and gain entry into bladder cells—revealed that UPEC deliver a "one-two" punch, using one pilus/adhesin to enable initial attachment and then deploying a second pilus/adhesin that adheres to inflamed bladder tissue, providing an advantage in establishing chronic infection in mice. Vaccination against the adhesin on the second pilus protected mice from infection progression, suggesting that this could be a viable therapeutic target (Conover et al, 2016). Microbes need metals such as iron and copper to survive, and during infection there is a tug of war between microbial acquisition of these metals and host defenses that limit their availability. Researchers have now found evidence suggesting that UPEC use a small iron scavenging molecule (siderophore) called Ybt more broadly to also modulate uptake of copper, increasing the importance of Ybt to UPEC (Koh et al, 2017). Encouragingly, a research team has shown that vaccinating mice with Ybt or another siderophore (Aer) reduces acute bacterial burden in the mouse bladder by 12- and 19-fold, respectively (Mike et al, 2016). On the flip side, another research team has isolated a set of novel molecules from non-E.coli bacteria, including a molecule called NicA, that show promise as inhibitors of UPEC growth under low iron conditions (Mike et al, 2017). Many of these advances were made possible in part with co-support from the ORWH. Whereas past studies of UTIs have focused almost exclusively on females, a grant newly funded by NIDDK will examine sex differences in UTI susceptibility and severity in an animal model (1R01DK111541-01A1). Beyond these basic and preclinical studies, a recent report highlights a successful effort, spearheaded by AHRQ, to prevent catheter-associated urinary tract infection (CAUTI) in people residing in nursing homes (Mody et al, 2017). This effort, to which the NIDDK contributed co-funding, subsequently led the NIDDK to hold an interagency meeting in 2018 on how to address CAUTI and spurred further planning efforts in this area on the part of the Institute.

III. Supporting Implementation of The NIH Strategic Plan for Women's Health Research

NIDDK Activities Mapped to Strategic Plan

1. **Sex/Gender Influences in Liver Disease**

Goal 1: Increase Sex Differences Research in Basic Science Studies

Top objective: 1.4: Include sex parameters in the design of experiments using animal models

Other objectives: 1.2: Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

2. **Pregnancy and the Health of Women and Their Offspring**

Goal 3: Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women

Top objective: 3.4: Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.

Other objectives: 3.3: Encourage research on safe and effective interventions for conditions affecting pregnant women.

Other NIDDK Activities Relevant to the Strategic Plan

As noted under "Accomplishments," the NIDDK has fostered both basic and clinical research resulting in advances in understanding of sex/gender differences in disease areas within its mission. In addition to continued sex/gender analysis in basic research and in or ancillary to large-scale clinical studies, other new efforts will promote analysis of sex/gender differences or sex/gender-specific effects. For example, the NIDDK made career development awards for research focused on how exercise training causes changes to adipose tissue metabolism in women and men with and without obesity, which may lead to the development of new therapies for obesity and type 2 diabetes (1K23DK114550-01A1), and on the role of sex hormones on NASH progression in women, which could elucidate a possible novel mechanism for intervention (1K23DK111944-01A1), and is newly supporting a research project in animal models focused on how observed sex/gender differences in visceral hypersensitivity (pain) develop (1R01DK111819-01A1), another that will study molecular factors in specific brain neurons that may be involved in mechanisms governing observed sex differences in how the body maintains energy balance (important to weight) (1R01DK117281-01), and a clinical study to investigate a biological factor that may explain why women with type 2 diabetes have more arterial stiffening—a risk factor for cardiovascular disease—than men with type 2 diabetes (1R21DK116081-01A1). The NIDDK also participated in ORWH-led effort to provide administrative supplements for research on sex/gender differences in FYs 2017 and 2018 and will continue to work with ORWH to identify new opportunities to promote sex/gender differences research.

NIDDK Positions Relevant to Women's Health

The NIDDK scientific staff includes a Program Director for Women's Urologic Health who, with input from ORWH, the HHS Office of Women's Health, and other ICs, is spearheading the prevention-focused research program to improve for women's urologic health described previously. The NIDDK's healthy pregnancy program involves the efforts of program directors from two extramural research Divisions plus the NIDDK Office of Obesity Research. The NIDDK CCRWH representative works closely with the NIDDK Director, facilitates efforts across the NIDDK, and works with the ORWH to foster partnerships in areas of joint interest.

IV. Inclusion Efforts

NIDDK activities that have expanded or lay the foundation to expand participation of girls and women in clinical research trials and studies include the PLUS Consortium, which is bringing girls and women into clinical research focused on prevention of urologic symptoms across the lifespan, as well as a planned GDM initiative that, if successful, will increase the number of pregnant women included in research. Studies powered to enable analysis of differences by sex include long-standing efforts such as CRIC and new studies such as the Vitamin D and Type 2 Diabetes (D2d) Study (NCT01942694; LeBlanc et al, 2018).

Information and Education Initiatives

The NIDDK continues to support a number of education and awareness campaigns important to women's health, including the *Sisters Together: Move More, Eat Better* program and specific outreach and promotion related to women's health, including the *National Kidney Month (NKM), Preventing Kidney Disease: Healthy Women, Healthy Families* awareness campaign and the *National Diabetes Month (NDM),*

Promoting Health After Diabetes awareness campaign that in 2018 focused on women with a history of GDM.

V. Career Development Efforts In STEM Fields

Ongoing research training initiatives developed by the NIDDK Office of Minority Health Research Coordination focus on developing and training new and young investigators. Specifically, efforts and programs focus on individuals who are underrepresented in biomedical research, including students with disabilities, those from disadvantaged backgrounds, and those from certain racial and ethnic minorities in the United States; while not focused solely on girls and women, these initiatives—Short Term Research Experience for Underrepresented Persons (STEP UP) (high school); STEP UP (undergraduate); and Diversity Summer Research Training Program (DSRTP)—encourage entry into NIDDK-relevant STEM areas by girls and women who might not otherwise have an opportunity to do so. In FYs 2017 and 2018, girls and women constituted the majority of participants in all three programs.

VI. FY 2017-2018 Funding Initiatives, Workshops, And Conferences

Requests for Applications (RFAs)

Limited Competition for the Continuation of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network Discovery Sites (U01 Clinical Trial Not Allowed) (RFA-DK-18-513), Limited Competition for the Continuation of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network Data Coordinating Core (DCC) (U24 Clinical Trial Not Allowed) (RFA-DK-18-514), and Limited Competition for the Continuation of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network Tissue and Technology Core (TATC) (U24 Clinical Trial Not Allowed) (RFA-DK-18-515): The purpose of these limited competition RFAs is to extend the MAPP Research Network for an additional 3 years to enable continued collection of longitudinal phenotypic data and biological samples from UCPPS participants currently enrolled in the Trans-MAPP Symptoms Patterns Study protocol and continue to conduct highly-collaborative, integrated data analyses for identification of new insights into UCPPS.

NIDDK Partnerships with Professional Societies to Enhance Scientific Workforce Diversity and Promote Scientific Leadership (R25) (RFA-DK-17-015): The over-arching goal of this NIDDK R25 program is to support educational activities that enhance the diversity of the biomedical, behavioral and clinical research workforce; women are one of the groups encouraged to apply as either program directors/principal investigators or as program faculty/mentors.

NIDDK also participated in Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54) (RFA-OD-18-004)

Program Announcements (PAs)

NIDDK participated in:

Research Supplements to Promote Diversity in Health-Related Research (Admin Supp - Clinical Trial Not Allowed) (PA-18-906, PA-18-586)

Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations (Admin Supp) (PA-18-713, PA-17-098)

Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH (FY18/FY17) Administrative Supplement (Admin Supp - Clinical Trial Optional (FY18)) (PA-18-676/ PA-17-101)

Administrative Supplements for Research on Sex/Gender Differences (Admin Supp - Clinical Trial Optional) (PA-18-658, PA-17-078)

Underactive Bladder and Detrusor Activity in Aging (R01 Clinical Trial Optional) (PA-18-570)

Conferences and Workshops

Individualizing Treatment for Urinary Incontinence - Evolving Research Questions into Research Plans: February 1-2, 2018. The purpose of this meeting was to facilitate development of fundable, interdisciplinary, investigator-initiated research proposals that may lead to better outcomes for currently available UI treatments by individualizing them to each patient, considering a broad spectrum of factors.

Sex and the Kidneys: Sex Differences in Renal Disease: July 13-14, 2017. The purpose of this workshop was to provide a forum for kidney researchers to revisit the role of sex in kidney disease risk and etiology, in light of advances in the understanding of sex steroid action in somatic tissues and the role of sex chromosome complement in disease pathophysiology.

Workshop on Best Practices for Studies of Diet and the Intestinal Microbiome: June 13-14, 2017. The purpose of this workshop was to improve rigor and reproducibility in microbiome research by identifying important dietary information that should be reported and parameters to consider in design of studies, particularly clinical studies on diet and the intestinal microbiome.

Individualizing Treatment—Broadening the Framework for Urinary Incontinence Research: March 30-31, 2017. The purpose of this meeting was to set the stage on the status of existing UI treatments and the factors that may predict treatment success.

GDM Treatment Workshop: Aug 2-3, 2017. The purpose of this workshop was to convene experts to address current gaps in research important to understanding GDM and improving management and treatement. Co-sponsor: ORWH

VII. Health Disparities in Women

Several of the diseases that disproportionately affect racial and ethnic minority populations in the United States are high priority research areas for the NIDDK. Some of these diseases, such as obesity and type 2 diabetes, also affect women and men differently within these disproportionately affected groups. The NIDDK Office of Minority Health Research Coordination (OMHRC) oversees Institute efforts to address these disparities. Several major NIDDK-supported research efforts pertain to health disparities in women—e.g., the DPP/DPPOS and TODAY/TODAY2 study cohorts, which have more females than males, are highly ethnically and racially diverse, reflecting the disproportionate burden of diabetes in racial and ethnic minority girls and women. LIFE-Moms emphasized participant recruitment from disproportionately affected minorities and low SES populations. The NIDDK intramural research program also supports projects highly relevant to health disparities in women, such as a new clinical trial recruiting overweight and obese Hispanic and African American women to determine the impact of consuming an artificial sweetener on medication metabolism (NCT03407079), and studies of obesity and GDM in Pima Indian women through participation in DPPOS, Look AHEAD, and LIFE-Moms, and through other efforts. In addition to support for pertinent “Information and Education Activities,” NIDDK communications activities important to health disparities in women include providing a variety of health information publications in Spanish, and some in multiple languages.

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National Institute on Drug Abuse

I. Executive Summary

As the foremost authority on drug use disorders, sponsoring the vast majority of the world's research on the subject, the National Institute on Drug Abuse (NIDA) supports science that addresses the most fundamental and essential questions about drug use disorders. The Institute does this by monitoring emerging trends, identifying and studying underlying biological and psychosocial factors and consequences, and determining how best to use this knowledge to develop, test, and implement prevention and treatment programs. Within NIDA's mission is a focus on studying issues specific to women and identifying and studying sex/gender differences in both clinical and preclinical research. Research over the past few decades has shown that there are male/female differences in the initiation and progression of drug use disorders; the risk and protective factors; and in the consequences of drug use disorder. Research has also revealed that intervention outcomes may be enhanced by sex/gender-specific considerations. In recognition of the important role of sex/gender differences in drug use disorders, NIDA continues its commitment to support research to identify sex/gender-specific aspects of drug use and addiction across the lifespan and to apply these findings to improve outcomes for both men and women.

This FY 2017–2018 biennial report highlights NIDA's research accomplishments on women and sex/gender differences and its many activities to promote research in this area. It also includes Science, Technology, Engineering, and Mathematics (STEM) efforts, which have been very successful in attracting women investigators to the field.

A striking feature of the research presented in this report is a translational emphasis. Preclinical studies, for example, that are revealing sex differences in basic mechanisms that underlie opioid analgesia could lead to sex-based pain treatments with low abuse liability. Other preclinical studies are holding promise for possible sex-based treatments for addictions and associated psychiatric comorbidities. In NIDA's nicotine and smoking research program, a study that used network meta-analyses to estimate sex differences in the comparative efficacy of transdermal nicotine, varenicline, and sustained release bupropion, yielded findings for sex-based smoking cessation clinical guidance. Potential new sex-based smoking targets for smoking cessation are being suggested by brain imaging studies. NIDA's research program on drugs and pregnancy spans from agonist therapies for opioid-dependent pregnant and nursing women to studies on cannabis, tobacco, and alcohol and their co-use in pregnancy, outcomes in children, and a promising intervention targeting pregnant women. Increasing cannabis use by pregnant women, especially young women, is a growing concern given reports of adverse outcomes in offspring with prenatal cannabis exposure. In NIDA's treatment research program, promising therapies for women are emerging, both pharmacologic and behavioral. In clinical trials for opioid use disorder, cannabis use disorder, and stimulant use disorder conducted by NIDA's Clinical Trials Network, differential characteristics of men and women at treatment entry and during treatment point to special treatment needs that could enhance short-term and long-term treatment outcomes in women.

Collectively, these and other research accomplishments described herein continue to provide evidence demonstrating the importance of conducting research specific to women, taking a sex/gender-based research approach, and analyzing data separately for males and

females. Ultimately, this approach will provide the information needed to tailor prevention and treatment interventions that will optimize outcomes for both men and women. This is at the heart of the Precision Medicine Initiative laid out in the *New England Journal of Medicine* perspective article by Dr. Francis Collins, Director of NIH, and Dr. Harold Varmus, then Director of the National Cancer Institute, in which they described precision medicine as "prevention and treatment strategies that take individual variability into account" (Collins and Varmus, 2015). Sex is the most basic, fundamental individual difference. Thus, NIDA is pleased to present examples of research that exemplify the Precision Medicine Initiative.

NIDA's scientific research accomplishments on women and sex/gender differences and efforts to promote this research as described in this report reflect the following goals of the NIH Strategic Plan for Women's Health Research:

Goal 1: Increase sex differences research in basic science studies.

Goal 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs.

Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women.

Goal 4: Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research.

II. The Women and Sex/Gender Differences Research Program at NIDA

NIDA's Women and Sex/Gender Differences Research program was established in 1995. It's Program Coordinator, along with NIDA's Women and Sex/Gender Research Group (WGRG), leads NIDA's efforts to promote research on women and sex/gender differences in drug use. The WGRG has membership representing research areas that span from molecular biology and genetics to risk and protective factors, prevention, consequences, and treatment and services, as well as members representing grant review, NIDA publications, and minority programs. From its inception, the overarching goals of NIDA's Women and Sex/Gender Differences Research Program have been to infuse the study of women and sex/gender differences research throughout all areas of drug use research, to disseminate resultant findings, and to target the next generation of drug use researchers. The program uses a variety of strategies, including funding opportunity announcements, travel awards, symposia, scientific presentations, and publications, as well as a landing page, Substance Use in Women, on NIDA's website specifically devoted to this research. The Program Coordinator represents NIDA on the Office of Research on Women's Health Coordinating Committee for Research on Women's Health (CCRWH), leads NIDA's efforts on ORWH ICO programs, and serves on the Trans-NIH Sex as a Biological Variable Working Group.

III. Research Accomplishments

Preclinical Research

Studies in NIDA's basic research program are revealing sex differences in brain mechanisms that underlie opioid analgesia and which could lead to sex-based pain treatments with low abuse liability. Other studies are uncovering sex differences in brain mechanisms underlying addiction and the role of stress and gonadal hormones. These studies are shedding light on differences in vulnerability to addiction in males and females. They also hold promise for possible sex-based treatments for addictions and associated psychiatric comorbidities.

- **Females show blunted intracellular, neural circuit, and behavioral responses to the G protein-mediated actions of KOR agonists.** Kappa opioid receptor (KOR) agonists have been tested in clinical trials for treating pain disorders based on their analgesic properties and low addictive potential. However, the molecular mechanisms underlying sex differences in KOR actions were previously unknown. A study has now identified an intracellular mechanism involving estradiol regulation of G protein-coupled receptor kinase 2 that is responsible for sexually dimorphic analgesic responses following opioid receptor activation. Understanding this mechanism will be critical for developing effective nonaddictive opioid analgesics for use in women and characterizing sexually dimorphic effects in other inhibitory G protein-coupled receptor signaling responses (PMID: 30076211).

- **Efficient opioids bypassing innate immune receptor activation contribute to a more potent analgesia effect in females.** Morphine's primary metabolites, morpine-3-glucuronide (M3G) and morphine-6-glucuronice (M6G), exert distinctive pharmacological properties to regulate pain. Concentrations of these metabolites as well as M3G:M6G ratio can determine the efficacy of morphine. Females have twice the amount of M3G concentrations in serum, which contributes to activation of innate immune receptors and attenuation of morphine analgesia to a greater degree in female animals. Remarkably, exogenous administration of M6G produces a near maximal analgesic effect in females via mu opioid receptor action, bypassing the opposing effects mediated by M3G induced pro-inflammatory responses. This finding suggests that M6G may be further developed as an improved treatment strategy for pain management in women (PMID: 29199028).

- **Molecular and functional sex differences of noradrenergic neurons in the mouse locus coeruleus.** In the brain the locus coeruleus is a small nucleus of neuromodulatory neurons whose projections release norepinephrine to brain regions involved in a broad range of functions including mood, anxiety, executive function, decision making, learning and memory. Researchers used translating ribosome affinity purification to identify 3000 transcripts from mouse LC neurons. Interestingly, they found 152 transcripts that were differentially expressed between males and females. To see if these gene expression differences were functionally important, the researchers chose the female-enriched prostaglandin E2 receptor EP3 for further study and showed that the EP3 agonist sulprostone could selectively reduce anxiety-like behavior in female but not male mice. Overall this work begins to reveal some of the molecular differences between male and female brains and may lay the foundation for future sex-specific treatments for certain neuropsychiatric diseases including addiction and its commonly occurring neuropsychiatric comorbidities. (PMID: 29791834).

- **Sex differences in morphine-induced trafficking of mu-opioid and corticotropin-releasing factor receptors in locus coeruleus neurons.** Stress is associated with non-medical opioid use, escalation to addiction, and promotion of relapse, thereby negatively influencing addiction recovery. The locus coeruleus (LC)-norepinephrine system is a key brain nucleus in which two opposing systems—the endogenous opioid system and stress systems—intersect to regulate the stress response. Delineating the neurobiological adaptations produced by chronic opioids will enhance our understanding of stress vulnerability in opioid-dependent individuals and may reveal how stress negatively

impacts addiction recovery. In the present study, the effect of chronic morphine on the subcellular distribution of mu-opioid receptors (MOR) and corticotropin releasing factor (CRF) receptors (CRFR) in the LC was investigated using immunoelectron microscopy. Results showed that placebo-treated females exhibited higher MOR and CRFR cytoplasmic distribution ratio when compared to placebo-treated males. Chronic morphine exposure recruited CRFR to the plasma membrane of LC neurons in both male and females. In contrast, chronic morphine exposure induced a shift in the distribution of MOR from the plasma membrane to the cytoplasm in males but not females. These findings provide a potential mechanism by which chronic opioid administration increases stress vulnerability in males and females via an increase in surface availability of CRFR in LC neurons. The results also support the notion that cellular adaptations to chronic opioids differ across the sexes as redistribution of MOR following morphine exposure was only observed in male LC neurons. It remains to be investigated how these outcomes may be related to the sex differences that have been observed in humans, including during initiation of opioid use, craving and relapse, as well as in stress-related risks for opioid use and relapse (PMID: 30391476).

- **Effects of ovarian hormones in dorsal striatum and nucleus accumbens.** In female rats, estradiol and progesterone rapidly induce changes in dopaminergic signaling within the dorsal striatum and nucleus accumbens–two major brain sites involved in drug addiction. In ovariectomized females, estradiol rapidly enhances dopamine release and modulates binding of dopamine receptors. Progesterone further potentiates the effect of estradiol on dopamine release. The effects of both estradiol and progesterone are time course dependent, with increases in dopamine release immediately after acute hormone administration followed by later inhibition of dopamine release. Importantly, these changes are also seen in naturally cycling females, indicating their importance for normal physiological states and relevant reproductive behaviors. A review article by researchers at the University of Michigan summarized the literature establishing the rapid effects of estradiol and progesterone on dopamine release and receptor expression in dorsal striatum and nucleus accumbens of both males and females. Integrating this literature with the larger body of work focusing on dopamine regulated behaviors, the authors offer hypotheses for adaptive reasons (i.e., ultimate causes) as to why changes in ovarian hormones modulate dopamine release. Finally, they describe the importance of these studies for understanding sex differences in vulnerability to drug addiction. Understanding how and why gonadal hormones influence drug taking has a large clinical relevance and holds the potential for targeted therapeutic treatment for substance use disorders (PMID: 29626485).

- **Sex differences in the in vivo neural response to cocaine.** Manganese enhanced magnetic resonance imaging (MEMRI) has been previously used to determine the effect of acute cocaine on calcium-dependent synaptic activity in male rats. However, there have been no MEMRI studies examining sex differences in the functional neural circuits affected by repeated cocaine. In the present study, MEMRI was used to investigate the effects of repeated cocaine on brain activation in female and male rats. In females, a single cocaine injection reduced MEMRI activity in hippocampal CA3, ventral tegmental area (VTA), and median Raphé, whereas repeated cocaine increased MEMRI activity in dentate gyrus and interpeduncular

nucleus. In males, repeated cocaine reduced MEMRI activity in VTA. The results provide evidence for sex differences in the in vivo neural response to cocaine, which involves primarily hippocampal, amygdala and midbrain areas (PMID: 28236167).

- **THC-induced sex differences in rat model.** Δ9-Tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, produces its characteristic "high" through activation of CB1 receptors in the brain. Animal model studies show that repeated exposure to THC produces a decrease in the number of the CB1 receptors and a decrease in the percentage of the receptors that are activated. The receptor number varies in various brain regions. A recent study focused on the possible effect of sex on receptor number, and activation/deactivation in four areas of the adult rat brain—cerebellum, hippocampus, prefrontal cortex, and striatum. With exception of enhanced receptor activation in the hippocampi of female rats compared to males, rats that were not exposed to THC exhibited minimal sex differences in CB1 receptor densities or G-protein coupling. Rats receiving repeated treatment with THC exhibited pronounced CB1 receptor desensitization and downregulation in both sexes in all four brain regions with a greater magnitude of change in females. This result is consistent with a finding that women tend to progress to tolerance and dependence quicker than men after initiation of cannabis use. (PMID: 30391834).
- **History of prenatal stress widens the higher compulsion to chronic cocaine in female rats compared to male rats.** In rats, prenatal stress facilitates the rewarding and neurochemical-stimulating effects of drugs, suggesting that prenatal stress (PS) may represent a risk factor for drug abuse in humans. Very little, however, is known about its effects in females, even though sex differences in drug susceptibility have been well documented in no PS (NPS) controls. Thus, researchers conducted a study to test for independent effects and interactions between maternal restraint stress during the last week of gestation and sex of the offspring exposed to an extended regimen of drug self-administration. Male and female rats were provided daily access to a large but controlled amount of cocaine for seven weeks. Drug pursuit during the final week was used to indicate susceptibility to developing an addiction-like phenotype, based on reports that drug use becomes increasingly compulsive-like after weeks of testing. Results indicated that females satisfied more addiction-like criteria than males, and the same was true for PS rats when compared to NPS controls. In addition, sex and PS interacted to disproportionately promote drug pursuit of females with a history of PS. These results indicate that sex differences in drug susceptibility persist with continued drug exposure, and that PS exacerbates this difference by more severely affecting females. In all, PS may be a risk factor for drug addiction in humans, and to a greater extent in women vs. men (PMID: 29055747).

Nicotine and Smoking Research

Differences in smoking between men and women are well documented, including the health consequences, reasons for smoking, quit success rates, barriers to cessation, and success with nicotine replacement treatments. Studies presented in this section highlight: (a) brain imaging studies exploring mechanisms that may contribute to these sex differences, (b) trends in waterpipe tobacco smoking studies among men versus women and among sexual minorities, and (c) sex (and other) differences in menthol smoking among individuals in substance use disorders treatment. These studies point to

possible avenues for prevention and treatment. Research on smoking in pregnancy and on smoking cessation treatment is described in other sections below.

- **Different brain mechanisms in male and female smokers.** Investigators examined brain fMRI measures in smokers and non-smokers, and males versus females, to identify differences in the strength of connectivity between brain regions. They found that, compared to nonsmokers, connector hubs in smokers emerged primarily in limbic and salience networks (parahippocampus and cingulate cortex regions). The global influence of craving (right insula) and reinforcement (left nucleus accumbens) was associated with higher nicotine dependence, but these trends were present only in male, not female, smokers. These data further support the concept that the mechanisms involved in maintaining nicotine addiction in male versus female smokers are different, and suggest that treatments targeting reinforcement and craving may be more efficacious in male smokers (PMID: 29059410).
- **Male smokers have greater brain reactivity to smoking cues than do women.** To address discrepancies in the literature regarding the reactivity to nicotine cues in male and female smokers, studies were conducted in two laboratories using different brain imaging and smoking cue methods to assess consistency in sex differences outcomes. Two brain imaging methods–arterial-spin labeling and BOLD fMRI–in laboratories at two different universities were used to assess brain responses to smoking cues versus non-smoking cues presented either as a short video or as still images. Correlations with craving following smoking cues were also assessed. In both studies, males showed greater brain reactivity to smoking cues compared to women in reward-related brain regions. Self-assessment measures of craving stimulated by the smoking cues were significantly correlated with activated areas for men but not for women. The study was an important replication of the observation that men have a stronger reactivity to smoking cues. These results are consistent with other studies of greater male brain reactivity for other drugs of abuse. Further, these results highlight the need for sex differences to be considered when studying the mechanisms of nicotine dependence and considerations for treatment (PMID: 28711813).
- **Adult sexual minorities have higher prevalence of current waterpipe smoking compared to their heterosexual counterparts in the US.** Several studies have established that sexual minority populations are at elevated risk of smoking compared to their heterosexual counterparts and that sexual minority women are more likely to smoke compared to their sexual minority men counterparts. While rates of cigarette smoking are declining within the general population, rates of use of other types of tobacco products are on the rise. Data from the 2012–2013 & 2013–2014 National Adult Tobacco Survey were pooled to determine the prevalence of waterpipe tobacco smoking (WTS) among sexual minority individuals. Results indicated that lesbian/gay and bisexual respondents reported higher prevalence of WTS compared to their heterosexual counterparts. These data indicate that novel interventions should be developed that target reducing WTS in this sexual minority population (PMID: 28601749).
- **Differences in puff topography, toxicant exposure, and subjective response between waterpipe tobacco smoking men and women.** Waterpipe tobacco smoking (WTS) exposes users to toxicants in much

greater amounts than a cigarette. Combined data from three WTS clinical laboratory studies revealed that men, compared to women, inhaled greater smoke volume and had greater post-WTS mean plasma nicotine concentrations. Women, on the other hand, had higher post-WTS scores for subjective measures of "nauseous," "dizzy," "nervous," "headache," and "heart pounding" compared to men (PMID: 30102062).

- **Sex (and other) differences in menthol smoking among individuals in substance use disorders (SUD) treatment.** Survey data were collected from 863 smokers sampled from 24 SUD treatment programs affiliated with NIDA's Clinical Trials Network. Overall, the prevalence of menthol was 53.3%. Smoking menthol versus non-menthol cigarettes was associated with being female, African American, Hispanic/Latino, and lower odds of having a college degree. Controlling for demographic factors, menthol smokers were more likely to report marijuana as their primary drug compared to alcohol. Lastly, menthol smokers were more likely to report interest in getting help for quitting smoking, although they were not more likely to report making a past year quit attempt. Regulatory policies targeting the manufacture, marketing, or sale of menthol cigarettes may benefit vulnerable populations, including smokers in SUD treatment (PMID: 29407684).

Drugs and Pregnancy Research

Research shows that substance use during pregnancy can lead to negative health consequences for unborn babies and infants. Many substances pass easily through the placenta–so anything that the pregnant woman ingests is taken in to some degree by the baby. The studies below describe research on opioid use in pregnancy, use of agonist therapies in pregnancy and nursing, and outcomes in children. Other studies are presented on cannabis, tobacco, and alcohol, their co-use in pregnancy, outcomes in children, and a promising intervention targeting pregnant women.

Opioids

- **Pregnant women in Appalachia face barriers to opioid treatment.** Opioid agonist therapies (OATs) are highly effective treatments for opioid use disorders, especially for pregnant women; thus, improving access to OAT is an urgent public policy goal. Investigators assessed whether insurance and pregnancy status were barriers to obtaining access to opioid agonist therapies OATs in 4 Appalachian states disproportionately impacted by the opioid epidemic. They found that OAT providers frequently did not accept any insurance and frequently did not treat pregnant women in an area of the country disproportionately affected by the opioid epidemic. Policymakers could prioritize improvements in provider training (e.g., training of obstetricians to become buprenorphine prescribers) to enhance access to pregnant women and enhance reimbursement rates as a means of improving insurance acceptance for OAT (PMID: 29949454).

- **Concentrations of buprenorphine and metabolites are low in human milk and maternal plasma.** Lack of conclusive data regarding the extent of the presence of buprenorphine and active metabolites in human milk makes the recommendation of breastfeeding for buprenorphine-maintained women difficult for many providers. In a recent study, breastfed infant plasma concentrations of buprenorphine were low or undetectable and metabolite concentrations undetectable at 14 days of infant age. There were significant correlations between maternal buprenorphine dose and maternal plasma and human milk buprenorphine concentrations. These data lend support to

the recommendation for lactation among stable buprenorphine-maintained women. However, the correlation between maternal dose and maternal plasma and human milk buprenorphine concentrations bears further study (PMID: 27563013).

- **Women who used multiple illicit substances during a pregnancy treated with buprenorphine had babies with more severe Neonatal Abstinence Syndrome.** Gestational illicit opioid use is on the rise in the US, with an attendant increase in the incidence of neonatal abstinence syndrome (NAS). Treatment of maternal opioid use disorders OUDs during pregnancy with either methadone or buprenorphine during pregnancy is the current standard of care. Buprenorphine has become more common as it provides major benefits, including greater birth weight, larger head circumference, less severe NAS, and shorter hospital stay when compared to methadone. In a recent study, researchers examined factors possibly associated with NAS severity in 41 infants of women maintained on buprenorphine during pregnancy at a comprehensive treatment facility for pregnant and parenting women. Fifty-nine percent of offspring exhibited NAS that required pharmacologic management. Both maternal buprenorphine dose, and prenatal polysubstance exposure, were independently associated with NAS expression. Polysubstance exposure was associated with more severe NAS expression after controlling for the effects of buprenorphine dose. Other exposures, including cigarette smoking and SRI use, were not related to outcomes. Maternal buprenorphine dose was positively associated with lower birth weight and length, although most infants were appropriately grown for gestational age at birth. In this sample of buprenorphine-exposed neonates, polysubstance exposure was the most potent predictor of NAS severity (PMID: 28869859).
- **Prenatal opioid agonist therapy is not deleterious to normal physical and mental development from birth to 3 years.** Questions about the long-term effect of prenatal exposure to maternal opioid agonist treatment and associated NAS have received new emphasis given the rising opioid epidemic and the significant increase in prenatal opioid exposure. Researchers addressed these questions using a sample of 96 infant-mother pairs who had participated in the MOTHER study which was a randomized controlled trial comparing methadone versus buprenorphine opioid-agonist pharmacotherapy during pregnancy. To assess possible deleterious effects of prenatal opioid agonist exposure they examined child growth parameters, cognition, language abilities, sensory processing, and temperament from 0 to 36 months of the child's life. Overall, they found that children prenatally exposed to buprenorphine or methadone were well within the range of normal development in those measures. Findings also strongly indicate no deleterious effects for NAS-requiring treatment children relative to those not-treated-for-NAS. The data reported in this paper are unique because they present findings on the largest and most comprehensive assessment of neonates prenatally exposed to agonist medications, with minimal to no additional drug exposure (PMID: 29413437).

Cannabis

- **Rising rates of cannabis use among young pregnant women.** Using data from the National Survey on Drug Use and Health, a January 2017 *JAMA* paper reported that past month use of marijuana self-reported by pregnant women, ages 18-44 increased from 2.37% in 2002 to 3.85% in 2014, representing a 62% increase. In 2014 use was greater in the age 18-25 group (7.47%) than in the age 26-44 group (2.2%). (PMID: 27992619). An accompany article by NIDA's director,

Dr. Nora Volkow, and others, entitled "The Risks of Marijuana Use During Pregnancy," summarized outcomes of animal and human studies investigating effects of prenatal cannabis exposure and use of cannabis to treat nausea in pregnancy. (PMID: 27992628). In a subsequent blog on the topic, Dr. Volkow stated: "Pregnant women and those considering becoming pregnant should be advised to avoid using marijuana or other cannabinoids either recreationally or to treat their nausea." In a December 2017 *JAMA* paper, researchers reported trends of prenatal marijuana use from 2009-2016 using data from Kaiser Permanente Northern California, a large California health care system with universal screening via self-report and urine toxicology. They reported that from 2009 through 2016, the adjusted prevalence of prenatal marijuana use based on self-report or toxicology increased from 4.2% to 7.1% and was higher based on toxicology than self-report each year. Use among females younger than 18 years to age 24 years increased the most, from 12.5% to 21.8%. In the recently published National Survey on Drug Use and Health, 7.1% of pregnant women reported past month marijuana in 2017. (NSDUH, 2017). These reports of rising rates of cannabis use in pregnancy and especially among young women are concerning. Along with studies such as those described in the section below, they point to a continuing need to advise against cannabis use in pregnancy or if considering becoming pregnant.

Tobacco, Cannabis and Alcohol

- **Cigarette smoking in pregnancy is associated with substance use severity.** Cigarette smoking is prevalent in pregnant substance users but receives low priority in substance use disorder treatment. A secondary analysis was conducted of the 145 pregnant women who smoked at baseline in a randomized, multisite trial of 200 pregnant substance users conducted by NIDA's Clinical Trial Network (CTN-0013, Motivational Enhancement Therapy to Improve Treatment Utilization in Pregnant Substance Users). Smokers in the trial had significantly greater substance use and approximately half of smokers wanted to quit. Those with a quit goal had significantly greater self-efficacy and lower perceived difficulty of quitting. These findings highlight the importance of addressing smoking in pregnant substance users. (PMID: 27802114).

- **Cigarette smoking and substance use in pregnancy.** In a cross-sectional study of 500 pregnant women recruited from two obstetric practices in Baltimore, MD, researchers used urine drug screening to assess the prevalence rates of substance use and the association between smoking and other drug use. Most participants were African-American (71.2%), never married (65.2%), employed (66.1%) and had high school or some college education (62.3%). Results indicated that current smokers were more likely than non-smokers to be never married, unemployed, African-American and had less than a high school education. They were more than four times more likely to have a positive drug screen in compared with nonsmokers. Half of current smokers were concurrently using cannabis, more than one in ten smokers also concurrently used opioids in pregnancy, and almost two thirds of current smokers were using some illicit drug. As has been shown previously, women were more likely to use tobacco and other drugs in the first trimester than in the second and third trimesters. (PMID: 29882032).

- **Infant small head circumference and birth defects more likely for pregnant women who use cannabis and tobacco.** In a follow-up study with the sample of women in the study reported above, the researchers

reported on birth outcomes associated with use of tobacco cigarettes, cannabis, and their co-use. The cannabis and tobacco cigarette co-use group had the highest odds of a small head circumference and birth defects compared with other use groups. The cannabis-only group had 12 times higher odds of a stillbirth or miscarriage. The prevalence of cannabis and tobacco cigarette co-use as well as the prevalence of cannabis only use was higher than the prevalence of tobacco cigarette only use, which is notable given the focus on tobacco cessation in clinical practice. Screening and interventions to address cannabis use and its co-use with tobacco use during pregnancy is needed. (PMID: 29883744).

- **Pregnant women who smoke both marijuana and cigarettes have a higher likelihood of smaller babies and increased maternal stress and aggression.** Pathways from prenatal risks–including maternal stress, anger, and use of tobacco and marijuana–to infant reactivity to environmental stimulation and regulation of those reactions (RR) at 9 months of infant age were examined in a low-income, diverse sample beginning in the first trimester of pregnancy, with fetal growth and postnatal stress/anger as potential mediators, and infant sex as a moderator. Participants were 247 dyads (173 substance-exposed infants). Consistent with existing literature, maternal co-use of tobacco and marijuana was associated with increased maternal stress and aggression, and with reduced fetal growth. There were no direct effects of prenatal risks on RR and no moderation by sex. However, there were significant indirect effects on RR via poor fetal growth and higher postnatal anger. The study adds to the literature on joint effects of tobacco and marijuana and highlights the role of fetal growth and maternal anger as important pathways from prenatal risk to infant RR. (PMID: 28383108).

- **A pilot brief intervention–health checkup for expectant moms (HCEM) –showed reduced reports of any alcohol or marijuana use.** A small cohort of 50 high-risk women were recruited at a prenatal clinic in a large inner-city hospital serving predominately low-income pregnant women. They were randomized to participate either in a computer delivered, single session brief motivational intervention plus booster session addressing both substance use and STI risk or participate in a control group for which the content of the computer sessions consisted of brief segments of popular television shows. Participants in the intervention group gave consistently high ratings of acceptability of the intervention and its helpfulness in having a healthy pregnancy. At the 4-month follow-up, those in the intervention group reported a significantly larger reduction (54%) in any marijuana or (heavy) alcohol use than participants in the control group (16%). There was also a non-significant trend toward higher reduction in condomless vaginal sex at follow-up in the health checkup for expectant moms (HCEM) group than in controls. The results of this pilot study are encouraging for the acceptability and preliminary efficacy of an intervention to reduce alcohol/marijuana use and condomless sex during pregnancy, and support testing the intervention in a larger sample (PMID: 28981379).

Treatment Research

Treatment research highlighted below encompasses studies of several substance use disorders, including opioids, nicotine, cannabis and cocaine as well as treatment research with general substance use disorder populations. This research is expanding our knowledge on differences in characteristics of men and women at treatment entry, factors affecting their

adherence to treatment, and differential treatment outcomes. These research findings hold promise for more gender-sensitive approaches to provide better treatment outcomes for women.

- **Gender differences in demographic and clinical characteristics of patients with opioid use disorder.** Baseline treatment entry data of men and women were compared in a randomized, controlled trial conducted by NIDA's Clinical Trial Network comparing extended-release naltrexone to buprenorphine among participants (N = 570) with opioid use disorder (CTN-0051). Women reported fewer lifetime drug treatments compared to men, however, no differences were detected on whether the current episode was a first treatment episode, whether a previous treatment episode was successful, or preference for buprenorphine or XR-naltrexone. Of the sample, 39.5% reported being treated with buprenorphine in the past, 31.8% with methadone, and 4.6% with XR-naltrexone, with no differences by gender. Results also showed that compared to men, women were younger, had greater psychiatric comorbidity, greater prevalence of histories of physical and sexual abuse, and demonstrated greater economic vulnerability, i.e., more likely to be unemployed despite similar education levels; dependent on someone else for their support; living with a sexual partner or with children alone; and living with someone also using illicit drugs. Women reported greater drug and sexual risk behaviors, including 25% of women reporting exchanging sex for drugs and sharing injection equipment. These findings underscore economic, psychiatric, and infection vulnerability among women with opioid use disorder. (PMID: 30106494).
- **Sex differences in opioid use and medical issues during opioid treatment.** A secondary analysis of data from NIDA's Clinical Trials Network was conducted to examine sex differences (men=347, women=169) in opioid-positive samples in a randomized clinical trial comparing 7-day vs. 28-day buprenorphine/naloxone tapering strategies (CTN-0003). Results indicated that during the clinical trial women were more likely than men to use opioids and that medical issues predicted opioid use for women but not men. These results suggest that complementary treatment for medical problems during opioid replacement therapy may benefit women (PMID: 29672167).
- **Cannabis-dependent women may present for treatment with more severe and impairing withdrawal symptoms and psychiatric conditions compared to cannabis-dependent men.** Recent evidence suggests that women may fare worse than men in cannabis trials with pharmacologic interventions. The current study compared baseline demographic, cannabis use, and psychiatric factors between women and men entering the Achieving Cannabis Cessation-Evaluating N-acetylcysteine Treatment (ACCENT) study conducted by NIDA's Clinical Trial Network (CTN-0053). Women reported greater withdrawal intensity and negative impact of withdrawal, predominantly due to physiological and mood symptoms. Women were more likely to have lifetime panic disorder and current agoraphobia and reported more days of poor physical health and cannabis-related medical problems. Women reporting chronic pain had greater mean pain scores than men with chronic pain. Identifying baseline clinical profiles of treatment-seeking cannabis-dependent adults could inform gender-specific treatment planning and development (PMID: 28152236).
- **Psychosocial relationship status and quality as predictors of exercise intervention adherence and substance use outcomes.** Limited research has

investigated how particular components of one's social environment—usual living arrangements, satisfaction with those arrangements, and global social and family discord—are related to substance use reduction and intervention adherence. These questions were investigated in 270 individuals receiving study intervention for stimulant abuse/dependence through the multi-site Stimulant Reduction Intervention Using Dosed Exercise (STRIDE) trial conducted by NIDA's Clinical Trial Network (CTN-0037). Using mixed effects modeling, results indicated that individuals with baseline social discord used stimulants on more days throughout the intervention period than those without social discord. An interaction between gender, usual living arrangements, and satisfaction with those arrangements indicated that women who lived alone and were dissatisfied with that arrangement reported greater days of stimulant use compared to several other groups. Finally, individuals who reported usually living with a non-partner over the past three years attended a greater percentage of intervention sessions compared to those usually living with a partner. These relationships between psychosocial factors and intervention adherence outcomes and suggest areas for future inquiry/intervention (PMID: 28525788).

- **Medications for smoking cessation have efficacy differences in women and men.** Converging clinical and biological evidence suggests that sex is a key factor when selecting a pharmacological intervention for smoking cessation. Researchers used network meta-analyses to estimate sex differences in the comparative efficacy of transdermal nicotine (TN), varenicline, and sustained release (SR) bupropion for smoking cessation. Data were from 32 studies and 14,389 smokers. For women, varenicline was more efficacious than TN and bupropion SR. For men, outcomes for those treated with TN and bupropion SR were similar to those treated with varenicline. These results suggest that clinicians should strongly consider varenicline as the first option treatment for women. (PMID: 27613893).

- **Phase 2 Multi-site Trial of AZD8529 for Smoking Cessation in Female Smokers.** This study evaluated the efficacy and safety of AZD8529, a potent and selective positive allosteric modulator of the metabotropic glutamate receptors, in female smokers seeking treatment for smoking cessation. AZD8529 showed positive findings in treatment for nicotine addiction in preclinical animal models. Due to toxicology findings related to the male reproductive system in animals, it was decided to evaluate the efficacy of this drug in a females-only exploratory clinical study. Unfortunately, no significant increase in smoking abstinence was detected in the intent to treat population. Subpopulation analyses are underway. (NCT02401022).

- **Women, but not men, with cocaine use disorder respond to guanfacine, which targets inhibitory control.** Currently, there are no approved medications for treating cocaine use disorder. Previous studies reported sex differences in responses to stress and drug cues, as well as in executive behaviors such as inhibitory control, cognitive flexibility and self-control. Deficits in these areas are associated with a higher risk of relapse. Inhibitory control, in particular, may represent an important process within the association between stress and the outcome of drug treatment. This study sought to test whether a pharmacologic agent that improves executive function, that is, the alpha-2 adrenergic agonist guanfacine, could rescue executive functions in cocaine dependent individuals. The investigators found that women who received guanfacine displayed

improved stress- and cue-related cognitive inhibitory performance on the Stroop task, compared with women receiving placebo. No effect by guanfacine was observed in men. Moreover, placebo treated women showed greater deficits in cognitive flexibility than the placebo treated men. Overall, these results suggest that inhibitory control may be an important target for medication development in cocaine dependent women (PMID: 28823835).

- **Women in intensive outpatient drug treatment had increased days abstinent with Mindful Awareness in Body-oriented Therapy (MABT).** Sensory information gained through interoceptive awareness may play a key role in goal-directed behavior and successful inhibition of drug use. Through mindful attention to the sensation of inhaling and exhaling during respiration and guided body scans, one may reduce symptoms of depression, stress and pain. A study conducted in women in intensive outpatient treatment for chemical dependency at 3 community clinics in the U.S. Pacific Northwest showed significant improvements in interoceptive awareness and mindfulness skills, emotion regulation, and days abstinent for the women who received MABT plus treatment as usual (TAU) compared with those who received women's health education plus TAU or who received just TAU. Findings that interoceptive training is associated with health outcomes for women in SUD treatment are consistent with emerging neurocognitive models that link interoception to emotion regulation. (PMID: 29949455).

IV. STEM Activities

As described below, NIDA-sponsored activities targeting junior investigators and aimed at nurturing their research careers have been very successful in attracting women. In addition, NIDA and the National Institute on Aging (NIA) have formed a partnership to support women intramural scientists at the NIH Biomedical Research Center in Baltimore, Maryland.

NIDA Intramural Research Program (IRP)

- **Women Scientist Advisors.** The mission of NIDA and NIA Intramural Research Programs' Women Scientist Advisors (WSAs) is to foster achievement and support career development among women scientists. Annual events include: 1) honoring women scientists from NIDA and NIA Intramural Research Programs by inviting them to talk about their research. This event is followed by a social. 2) sponsoring a 'Successful Women in Science' series, where informal discussions are held with incoming women seminar speakers. These speakers share information and advice on success at all stages of career development from a woman's prospective. 3) hosting a Winter Tea to promote communication among women scientists from different laboratories and to discuss ways in which WSA can serve the scientific community, 4) sponsoring Achievement Awards for Excellence in Scientific Research. These are competitive, highly distinguished awards that are given to a Senior Investigator, Staff Scientist, and Postdoctoral Fellow each year from both NIDA and NIA Intramural Research Programs.

- **Scientific Director's Fellowship for Diversity in Research (SDFDR).** The SDFDR is an Intramural Research Program (IRP) fellowship for under-represented post-baccalaureate and post-doctoral students. This mechanism promotes mentorship of young scientists from underrepresented populations by NIDA IRP scientists. Career development plans are customized to ensure each fellow's success in the pursuit of careers in science and medicine. Fellows

participate in research and present their findings at local and national meetings. Post-baccalaureate fellows are supported for two to three years and post-doctoral fellows are supported three to five years. In 2017 and 2018, one of three post-doctoral fellows and eight of fifteen post-baccalaureate fellows supported by this program were female. Estimated funding: $423,000.00

- **Recruitment & Training for Under-Represented Populations (RTURP) Program.** The RTURP is a NIDA intramural program that provides training opportunities for students from under-represented populations who are interested in the science of drug abuse and addiction. The program accepts students from high school to graduate school for 8-10 weeks of intense training. Activities such as lectures, seminars, weekly lunches, professional workshops and poster presentations are offered to students throughout the summer. In 2017 and 2018, 1 of 1 graduate students, 9 of 13 college students and 12 of 17 high school students supported by this program were female. Estimated funding: $83,000.00

NIDA Office of Diversity and Health Disparities (ODHD)

- **NIDA Summer Research Internship Program.** This program provides research internships for undergraduate students with a goal of enhancing underrepresented populations in biomedical research. Internships include a paid 8-week intensive, hands-on drug use and addiction research experience that provides students with the opportunity to gain an understanding of the research process. The experience may include laboratory experiments, formal courses, data collection activities, data analysis, patient recruitment, manuscript preparation, literature reviews, and library research. The program exposes students to drug use research and encourages them to pursue careers in biomedical and behavioral research. Internships are conducted with NIDA-funded investigators across the country. In 2017, NIDA awarded 66 internships, 46 (69%) of which were to women. In 2018, NIDA awarded 57 internships, 45 (79%) of which were to women.

- **Administrative Supplements to Enhance Diversity.** This diversity supplement program was established to enhance diversity in the biomedical research workforce by supporting and recruiting undergraduate students, pre-doctoral and postdoctoral fellows, and investigators from groups that have been shown to be underrepresented in science, including disabled individuals. In 2017, NIDA funded 20 diversity supplements, 15 (75%) of which were awarded to women. In 2018, NIDA funded 28 diversity supplements, 16 (57%) of which were awarded to women.

- **NIDA Diversity Scholars Network (NDSN).** The NDSN is a rigorous and comprehensive mentorship program aimed at improving the funding outcome of outstanding underrepresented early-stage investigators conducting drug use research, though all populations are eligible to participate. The NDSN program consists of two sessions and a research coach that support a cohort of scholars in gaining NIH grants or equivalent funding to build a sustainable independent research career. In 2017, 12 early-stage investigators participated in the NDSN program, 8 (66%) of whom were women. In 2018, 11 early-stage investigators participated, 9 (81%) of whom were women.

- **NIDA Diversity Scholars Travel Award.** NIDA's ODHD sponsors a travel award to help defray the costs of attending the annual Society for Neuroscience (SfN) meeting. As part of this award, recipients are required to attend the Frontiers in Addiction Research NIDA-NIAAA Mini-Convention held prior to

SfN. In 2017, 5 (45%) of 11 travel awards were made to women. In 2018, 14 (82%) of 17 travel awards were made to women.

NIDA Office of Research Training

- **NIDA Director's Travel Award at the College on Problems of Drug Dependence (CPDD) Annual Scientific Conference.** The NIDA Director's Travel Award program partially defrays the cost of travel for NIDA-supported National Research Service Award Fellows, trainees, NIDA diversity-supplement recipients and NIDA mentored career development awardees to attend the annual CPDD meeting. In 2017, 10 of the 20 (50%) awards went to women; in 2018, 16 of the 20 (80%) awards were made to women. [Objective: 4.5]

- **Grant Writing and Career Development Workshop at the CPDD Annual Scientific Conference.** NIDA's Grant Writing and Career Development Workshop, held in conjunction with the CPDD conference, capitalizes upon the expertise gathered for the CPDD meeting to provide young investigators with tools and resources necessary to become successful, independent substance use researchers. This workshop demonstrates NIDA's continued commitment to the next generation of these researchers. In 2017, 46 of 72 (64%) participants were women. In 2018, 37 of 57 (65%) participants were women. [Objective 4.5]

NIDA Women and Sex/Gender Differences Research Program

- **Women and Sex/Gender Differences Research Junior Investigator Travel Award Program at the Annual Scientific Conference of the College on Problems of Drug Dependence (CPDD).** To promote entry of junior investigators into drug use research on women and sex/gender differences, NIDA has sponsored a special travel award program to assist awardees in defraying the cost of attending the annual meeting of the CPDD since 2000. Award applicants (male or female) are required to be the first author on their research submission to CPDD, and the research must focus on women or include a sex/gender analysis of data. In 2017, 73% of the applicants were women, and in 2018, 83% were women. Twenty awards were made in each year of which 70% (2017) and 90% (2018) were awarded to women.

V. Other Activities That Support Implementation of the NIH Strategic Plan for Women's Health Research

NIDA Strategic Plan for 2016-2020

Throughout the planning process for NIDA's Strategic Plan for 2016-2020, a number of cross-cutting themes emerged that are relevant across multiple goals and objectives. NIDA is committed to working to ensure that these themes are addressed across institute programs and initiatives. Within the cross-cutting theme, *Supporting Health Equality*, a focus on women and sex/gender differences is prominently featured and discussed in the section, *Improving Outcomes by Considering Sex and Gender Differences*.

NIDA's Clinical Trials Network (CTN)

NIDA's CTN is a national consortium of drug abuse researchers and providers who conduct research to generate the evidence needed for the integrated management of patients with substance misuse/SUD at general medical settings and linked specialty care treatment settings. Currently, the CTN consists of 13

research Nodes (i.e. grantee institutions) affiliated with approximately 60 academic institutions and over 240 health care clinics (including hospitals, primary care settings, specialty clinics and Federally Qualified Health Centers) throughout the United States. The CTN has conducted approximately 116 trials since its inception in 1999. Study results from 41 multi-site clinical trials are posted at https://datashare.nida.nih.gov. NIDA encourages researchers (including early career investigators) to take advantage of these datasets for addressing gender-based questions. In addition, as new trials are planned, NIDA invites scientists to work with the trial investigators to plan ancillary or platform studies that can provide needed information on issues that can affect women in drug abuse treatment.

CTN established a Gender Special Interest Group which has played a key role in the overall gender research across the CTN studies and in identifying substance abuse research areas that could benefit from additional attention to gender-related outcomes. This group was involved in most of the gender-centered papers published from CTN studies, and in 2018 presented two symposia showcasing some of the recent findings from the CTN studies.

NIDA-Issued Funding Opportunity Announcements

- **Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence**, PA-18-603 (R01); PA-18-602 (R21); PA-18-601 (R03) issued January 29, 2018, expires May 8, 2021. The goal of these FOAs, issued by NIDA and NIAAA, is to advance research on male-female differences in drug and alcohol abuse and addiction and on factors specific to women. Both human and animal model research is sought.
- **Drug Abuse Dissertation Research**, PA-16-443. The goal of this NIDA FOA is to enhance the diversity of the drug abuse research workforce by providing dissertation awards on topics related to the study of basic and clinical neuroscience, development, epidemiology, prevention, treatment, services, or women and sex/gender differences as they relate to drug abuse. The FOA will expire January 8, 2020.
- **Pilot and Feasibility Studies in Preparation for Drug and Alcohol Abuse Prevention Trials (R34)**, PA-15-250 (R34) and grants.nih.gov/grants/guide/pa-files/PA-15-177.html. The purpose of this FOA, issued by NIDA and NIAAA, is to encourage pilot and preliminary research in preparation for larger scale services research effectiveness trials. Special emphasis is placed on taking a sex/gender-based research approach. The FOA expired May 8, 2018.
- **Drug Abuse Prevention Intervention Research**, PA-15-080 (R21); PA-15-081 (R03); PA-15-082 (R01). The purpose of these FOAs is to encourage grant applications for research that will employ rigorous scientific methods to test theoretically derived hypotheses to increase understanding of the science of drug use prevention within diverse populations and settings and across the lifespan. Special emphasis is placed on taking a sex/gender-based research approach. The FOA expired September 8, 2017.

NIDA Staff: Scientific Presentations

- "Sex as a Biological Variable in Addiction Research: What It Means for Women (and Men)." SAMHSA's Advisory Committee on Women's Services, Rockville, MD, February 1, 2017.
- "Sex as a Biological Variable (SABV) in Addiction Research and Practice: Why and Ways It Matters." Mid-Atlantic Phoenix House, Recovery Summit: Becoming Gender Sensitive: Changing the Model," Arlington, VA, March 15, 2017.

- "Sex as a Biological Variable (SABV): A Matter of Doing Good Science." American University, Washington, DC, April 10, 2017.
- "Women & Pregnancy: Marijuana and Other Drugs of Concern." Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders, NIAAA, Rockville, MD, April 13, 2017.
- "Sex as a Biological Variable (SABV) in Drug Addiction Research." American Psychological Association (APA) Division 50 Distinguished Scientist Plenary address, APA annual convention, Washington, D.C., August 3-6, 2017.
- "Factoring Sex (as a Biological Variable) into Drug Abuse Research: Why it Matters." NIDA Diversity Scholars Network Mock Review Workshop, NIDA Office of Diversity and Health Disparities, September 14-15, 2017.
- "Greetings from the National Institute on Drug Abuse." National Conference on Substance Use among Women and Girls: Advances in Prevention, Treatment and Recovery, Washington DC, October 26-27, 2017.
- "Male & Female Drug Addiction Data: Should You Mix 'n Stir or Should You Test for Differences?" NIDA's Division of Neuroscience and Behavior, November 3, 2017.
- "Factoring Sex into Drug Abuse Research: Why it Matters." NIDA Diversity Scholars Network Mock Review Workshop, Rockville, MD, September 14, 2018.
- "Factoring Sex (as a Biological Variable) into Drug Abuse Research: Does it Matter?" NIDA Intramural Research Program, Baltimore, MD, September 17, 2018.
- "Sex as a Biological Variable in the Opioid Crisis." FDA scientific conference, Opioid and Nicotine Use, Dependence and Recovery-Influences of Sex and Gender, Silver Spring, MD, September 27, 2018.
- "Sex Differences in the Intersection of Stress and Opioid Systems." FDA scientific conference, Opioid and Nicotine Use, Dependence and Recovery-Influences of Sex and Gender, Silver Spring, MD, September 28, 2018.
- "Sex Differences in the Convergence of Stress and Opioid System." Melbourne Brain Symposium 2018, Melbourne, Australia, October 31, 2018.
- "Interplay of Sex in Stress and Central Pain Modulation." Pain Medicine annual meeting, San Antonio, TX, November 16, 2018.

NIDA Staff: Scientific Symposia Organized

- *Sex as a Biological Variable (SABV): Research Findings from the NIH Office of Research on Women's Health (ORWH) & NIDA Center Grants — Ahead of Its Time or Long Overdue?* College on Problems of Drug Dependence annual meeting, Montreal, Canada, June 17-22, 2017.
- *Opioid Use Disorder in Women: Evidence from the NIDA CTN and the Implications for Treatment*. Clinical Trials Network annual steering and scientific meeting, Bethesda, MD, March 20-22, 2018.
- *Sex and Gender Implications for Emerging Drug Policy*. College on Problems of Drug Dependence annual meeting, San Diego, CA, June 9-14, 2018.
- *Sex Differences in the Nicotine Addicted Brain: Translational Implications*. American Psychological Association annual meeting, San Francisco, August 9-12, 2018.
- *Opioid Use Disorder in Women: Evidence from the NIDA CTN and the Implications for Treatment*. American Academy of Addiction

Psychiatry annual meeting, Bonita Springs, FL, December 6-9, 2018.

NIDA Staff: Service on NIH and HHS Conference Executive Steering and Scientific Planning Committees

- NIAAA scientific conference, *National Conference on Alcohol and Opioid Use in Women and Girls: Advances in Prevention, Treatment and Recovery Research*, Washington DC, October 26-27, 2017.
- FDA scientific conference, *Opioid and Nicotine Use, Dependence, and Recovery: Influences of Sex and Gender*, Silver Spring, MD, September 27-28, 2018.

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National Institute of Environmental Health Sciences

I. Executive Summary of NIEHS Women's Health and Sex Differences Research

"Your environment is your health." This statement summarizes why it is important to understand the ways in which our environment plays a role in our health and biology. The mission of the National Institute of Environmental Health Sciences (NIEHS) is to discover how the environment affects people's health and to promote healthier lives. NIEHS investigators conduct studies to understand better how women are affected by environmental exposures, how exposures and disease progression may impact women and men similarly or differently, and how an individual's sex and gender may influence both susceptibility to disease and the eventual outcome. The scope of women's health research has become a dynamic, multidisciplinary area of study within environmental health sciences. There are striking sex/gender differences in the prevalence, progression, and outcome of numerous conditions, including diabetes, obesity, cardiovascular diseases, substance use disorders, depression and brain disorders, infectious diseases, cancer, and autoimmune diseases.

Certain health conditions, including menopause and pregnancy, are unique to women; some diseases, such as endometriosis, ovarian cancer, and cervical cancer occur only in women; breast cancer is primarily found in women, and certain autoimmune diseases and osteoporosis occur to a great extent in women, compared to men. Many or most of these conditions and diseases may be environmentally mediated. These disparities between women and men are influenced by biological sex and gender identity, as well as by developmental, cultural, environmental, and socioeconomic factors. Women's health and sex differences research, therefore, encompasses not only clinical studies, but also a full spectrum of scientific investigations, such as molecular, genetic, and other basic and laboratory studies, as well as investigations into healthy lifestyles and behavior, risk reduction, and disease prevention. With this information in hand, women can better determine how to alter the lifestyle factors that lead to these exposures and diseases and provide better protection for themselves and their children. On a wider scale, society can better define standards that protect women from the environmental triggers of these diseases and develop better gender-specific and sex-specific interventions and therapies.

II. Accomplishments and Activities

Gata-2 Dependent Transcription Network Regulates Uterine Progesterone Responsiveness and Endometrial Function

Altered progesterone responsiveness leads to infertility and cancer in women, but little is known about how progesterone responsiveness is regulated. NIEHS intramural scientists and collaborators have gained insight into uterine progesterone responsiveness by studying a genetic mouse model whereby Gata2 was specifically deleted in cells expressing the progesterone receptor throughout the uterus resulting in infertile female mice. They employed cistromic (cis-acting targets of transcription

factors on a genome-wide scale) and transcriptomic analyses to show progesterone-regulated genes exhibited a cooperative relationship between the progesterone receptor and Gata2 in the transcriptional regulation of progesterone response genes. Specific ablation of Gata2 from the progesterone receptor expressing cells of the uterus resulted in altered morphology of the uterine cells and increased expression of TRP63, a gene thought to play a role in the developmental switch from epithelial cell fate to epidermal cell fate suggesting Gata2 may play role in postnatal uterine development (Rubel et al., 2016).

Relationship Between Obesity and Anti-Müllerian Hormone in Reproductive-Aged African-American Women

African-American women have the highest obesity rates amongst reproductive-aged women in the United States. NIEHS researchers examined the largest cohort of African-American women in their prime reproductive years where the relationship between obesity and Anti-Müllerian Hormone (AMH) has been studied and found a significant inverse association between obesity and AMH. An association between obesity as a late teen and decreased AMH in adulthood was also noted. AMH concentrations declined as current BMI increased, and AMH was significantly lower in participants with obesity compared to those who were underweight or normal. These data demonstrate that reproductive-aged women with obesity have lower AMH concentrations, suggesting that folliculogenesis is likely impaired as BMI increases, and supporting the notion that obesity may create an altered follicular environment (Bernardi et al., 2017).

3-D Model Simulates Female Reproductive Tract and Menstrual Cycle

A new miniature 3-D microphysiological model of the female reproductive tract and menstrual cycle, EVATAR, can be used to study the effects of chemicals and drugs on the female reproductive system. NIEHS grantees developed the model, which fits in the palm of the hand and mimics a normal 28-day hormone cycle. EVATAR, involves human tissue and 3-D models of the ovaries, fallopian tubes, uterus, cervix, vagina, and liver. A fluid and pumping method simulates the flow of blood between each of the organ systems. The organ models communicate with each other via secreted substances, such as hormones, replicating how organs work together in the body. EVATAR can be used to test secretion of hormones and interactions between organs during month-long experiments. EVATAR will also help scientists understand endometriosis, fibroids, cancer, infertility, and other hormone-related diseases of the female reproductive tract. Because human tissue is integrated into the model, the system could potentially offer reproductive models to test individual differences in responses to drug treatments and susceptibility to chemicals (Xiao et al., 2017).

Risk Communication About PFOA, an Environmental Risk Associated with Breast Cancer

Using a Heuristic Systematic Model, researchers investigated the ability, motivation, and systematic and heuristic processing of communications influence on the development of risk beliefs and attitudes about PFOA in 1,389 women, many of whom either have had breast cancer or know someone with breast cancer. This work suggests lower reading levels in risk communication messages improve outcomes for both low and high literacy individuals (Smith et al., 2017).

Season of Conception, Smoking, and Preeclampsia in Norway

Preeclampsia (PE) is a dangerous and unpredictable pregnancy complication. A seasonal pattern of risk would suggest that there are potentially preventable environmental contributors. NIEHS scientists and collaborators used harmonic analysis to show that risk of developing preeclampsia was related to season, with higher risk in spring conceptions

and lower risk in autumn conceptions. Parity, latitude, fetal sex, or smoking did not modify the effects. These findings suggest that there are potentially preventable environmental contributors responsible for the development of preeclampsia (Weinberg et al., 2017).

Association of Body Mass Index and Age with Subsequent Breast Cancer Risk

NIEHS scientists and colleagues examined data from 758, 592 premenopausal women found that increased adiposity is associated with a reduced risk of premenopausal breast cancer at a greater magnitude than previously shown and across the entire distribution of BMI and is most pronounced in early adulthood (Premenopausal Breast Cancer Collaborative et al., 2018).

Widespread Enhancer Activation Mediates Estrogen Response During Uterine Development

Little is known regarding how steroid hormone exposures impact the epigenetic landscape in a living organism. NIEHS scientists and colleagues investigated the effect of the environment on genomic and epigenetic regulation of reproductive tract development and examined the temporal window of early exposure to endocrine active compounds impacting development of the female reproductive tract. Using a global approach, the authors sought to understand how exposure to the estrogenic chemical, diethylstilbestrol (DES), affects the neonatal mouse uterine epigenome and gene expression program (Jefferson et al., 2018).

Exposure to perfluoroalkyl substances and associations with serum thyroid hormones in a remote population of Alaska Natives

NIEHS-funded research examined serum PFAS levels and thyroid function in a small population of Alaskan Natives of St. Lawrence Island, Alaska and showed increased levels of PFASs in the serum were correlated with increased levels of TSH. Sex-specific results showed increased PFOS and PFNA levels were associated with increased T3 in women, but not men. This work suggests PFAS exposure on thyroid hormone homeostasis may differ between men and women (Byrne et al., 2018).

Oxybenzone Alters Mammary Gland Morphology in Mice Exposed During Pregnancy and Lactation.

Hormones and endocrine-disrupting chemicals are generally thought to have permanent “organizational” effects when exposures occur during development but not adulthood. Yet, an increasing number of studies have shown that pregnant females are disrupted by endocrine-disrupting chemical exposures, with some effects that are permanent. NIEHS grantees researched the long-term effects of exposure to oxybenzone, an estrogenic chemical found in sunscreen and personal care products, on the morphology of the mammary gland in mice exposed during pregnancy and lactation. Their data indicates oxybenzone may alter mammary gland function and morphology at physiologically relevant doses (LaPlante, Bansal, Dunphy, Jerry, & Vandenberg, 2018).

Associations Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age

The utility of biomarkers of ovarian reserve as indicators of reproductive potential is controversial and lacking evidence. NIEHS scientists and their collaborators examined potential associations between biomarkers of ovarian reserve and reproductive potential among women of late reproductive age. The authors found that among women aged 30 to 44 years without a history of infertility who had been trying to conceive for 3 months or less, biomarkers indicating diminished ovarian reserve compared with normal ovarian reserve were not associated with reduced fertility. These findings do not support the use of urinary or blood follicle-stimulating hormone tests or antimüllerian hormone levels to assess natural fertility for women with these characteristics (Steiner et al., 2017).

Perinatal Lead Exposure Results in Sex and Tissue Dependent Epigenetic Effects

Studies indicate adult chronic disease is influenced by early life exposures via epigenetic changes. NIEHS funded research examined individual and global intracisternal A particle (IAP) retrotransposon methylation patterns after developmental exposure to lead in a mouse model and found exposure to physiologically relevant levels of lead preconception through day 21 of life results in sex-specific epigenetic changes in the adult brain (Montrose, Faulk, Francis, & Dolinoy, 2017).

Exposure to Magnetic Field Non-Ionizing Radiation and the Risk of Miscarriage: A Prospective Cohort Study

Magnetic field (MF) non-ionizing radiation is nearly ubiquitous and exposures occur with varying degrees across the population. NIEHS funded research examined a prospective cohort study of 913 pregnant women for an association between high MF exposure and miscarriage risk. Data revealed a link between exposure to MF and increased risk of miscarriage suggesting MF could have adverse health effects in humans and warrants further study (Li, Chen, Ferber, Odouli, & Quesenberry, 2017).

GATA3 Mutations Reprogram Breast Cancer Transcriptional Network

GATA3 is frequently mutated in breast cancer. In breast cancer, GATA3 expression is a prominent marker of luminal breast tumors, and loss of GATA3 expression is associated with aggressive tumor phenotypes. NIEHS scientists examined the impact of GATA3 mutations on breast cancer and demonstrated mutations in GATA3 found in clinical breast tumors result in loss of binding and function at a subset of genes and gain of function at genomic sites involved in epithelial to mesenchymal transition. This work begins to shed light on GATA3's influence on gene regulatory networks and tumor growth (Takaku et al., 2018).

Neonatal Genistein Exposure and Glucocorticoid Signaling in the Adult Mouse Uterus

Female reproductive tract development is sensitive to the endocrine-disrupting potential of environmental estrogens. Early-life exposure to the dietary phytoestrogen genistein impairs fertility and persistently alters the transcriptome in the oviduct and uterus of rodents. NIEHS scientists and colleagues examined whether early-life exposure to genistein disrupts glucocorticoid signaling in the mouse uterus, which may contribute to infertility. The authors discovered that neonatal exposure to the dietary phytoestrogen, genistein, altered the uterine transcriptome of adult mice and caused substantial changes to the transcriptional response to glucocorticoids. These findings suggest that disruption of glucocorticoid signaling due to early-life exposure to environmental estrogens may in part render the uterus unable to support implantation (Whirledge, Kisanga, Oakley, & Cidlowski, 2018).

PFAS and Changes in Body Weight and Resting Metabolic Rate in Response to Weight-loss Diets

The potential endocrine-disrupting effects of perfluoroalkyl substances (PFASs) have been demonstrated in animal studies, but whether PFASs may interfere with body weight regulation in humans is largely unknown. NIEHS funded scientists examined the associations of PFAS exposure with changes in body weight and resting metabolic rate (RMR) in a diet-induced weight-loss setting. This work examined the relationship between PFAS exposure, dieting, and weight gain and found people with higher PFAS blood levels who had recently dieted and lost weight, were more likely to experience a greater weight gain. This was particularly pronounced among women. In addition to increased weight gain, higher levels of PFAS were associated with a lower resting metabolic rate suggesting PFAS may perturb metabolic pathways involved in body weight regulation (Liu et al., 2018).

Prenatal Exposure to Unconventional Oil and Gas Operation Chemical Mixtures Altered Mammary Gland Development in Adult Female Mice

Unconventional oil and gas (UOG) operations, which combine hydraulic fracturing (fracking) and directional drilling, involve the use of hundreds of chemicals, including many with endocrine-disrupting properties. NIEHS funded scientists assessed unconventional oil and gas mixture exposures in pregnant mice that mimicked human exposures through drinking water consumption. They found pronounced changes to breast tissue in mice at in early adulthood that may have been precancerous suggesting the mammary gland is sensitive to exposure and this may pose a risk to women living in close proximity to fracking (Sapouckey, Kassotis, Nagel, & Vandenberg, 2018).

Women with Higher Exposures to Select Flame Retardants May Experience Less Successful IVF

Flame retardants are commonly used in polyurethane foam-containing products such as upholstered furniture and gym mats. NIEHS grantees published data indicating women with higher exposures to some organophosphate flame retardants had decreased probability of successful fertilization, implantation of the embryo, clinical pregnancy, and live birth suggesting their chances for a successful pregnancy may improve by limiting exposure to flame retardants (Carignan et al., 2017).

Soy Fed Infant Girls Exhibit Subtle Effects in Estrogen-Responsive Tissues

Soy formula contains high concentrations of isoflavones which have hormonelike activity. NIEHS scientists and collaborators examined potential effects of early postnatal exposure to soy formula in boys and girls and found soy fed infant girls displayed developmental perturbations in estrogen-responsive tissue suggesting postnatal exposures to soy formula may perturb estrogen-responsive tissue development (Adgent et al., 2018). Further research is needed to determine whether these effects lead to adverse health outcomes.

Agricultural Health Study

The Agricultural Health Study (AHS), funded by NIEHS, the National Cancer Institute, the U.S. Environmental Protection Agency (EPA), and the National Institute for Occupational Safety and Health, works to understand how agricultural, lifestyle, and genetic factors affect the health of farming populations. More than 50,000 farmers and greater than 30,000 spouses in Iowa and North Carolina have been involved in AHS since 1993. Several AHS reports of particular relevance for women's health were published during FY 2017–FY 2018, and the findings included the following:

- Pesticide exposure among female spouses of farmers in AHS had an increased risk of developing hypothyroidism or hyperthyroidism suggesting pesticides may play a role in thyroid disruption of female spouses of private pesticide applicators (Shrestha et al., 2018).
- Early life farm exposures, particularly in pregnant women, are strongly associated with reduced risk of atopy in adults suggesting farm exposures may have protective effects on allergies across the lifespan (House et al., 2017).

Transgenerational Inheritance of Health Effects

That National Toxicology Program's Office of Health Assessment and Translation conducted a state of the science review to examine the evidence for transgenerational inheritance of health effects associated with exposure to a wide range of stressors in humans and animals. The report systematically collected and categorized the literature to develop a systematic evidence map for transgenerational inheritance by broad health-effect categories, exposures, and types of evidence, and identified areas of consistency,

uncertainty, data gaps, and research needs. The review found relatively few bodies of evidence where multiple studies evaluated the same exposure and the same or similar outcomes. Evidence mapping illustrated that risk of bias, having generally few studies, and heterogeneity in exposures and endpoints examined present serious limitations to available bodies of evidence for assessing transgenerational effects. Targeted research is suggested to address inconsistencies and risk of bias issues identified, and thereby establish more robust bodies of evidence to critically assess transgenerational effects - particularly by adding data on exposure-outcome pairs where there is some evidence (i.e., reproductive, metabolic, and neurological effects) (Walker et al., 2018).

III. NIH Strategic Plan for Women's Health Research

NIEHS funds a large array of studies that explores variations due to sex as an integral part of the search for knowledge across the entire research spectrum, beginning at the most basic laboratory level. NIEHS research regarding sex differences encompasses diverse fields, including genetics, immunology, endocrinology, developmental biology, cell biology, epidemiology, microbiology, biochemistry, and toxicology, as well as in behavioral and social sciences. Below are examples of NIEHS research activities that further knowledge in this area. The activities support the implementation of the Office of Research on Women's Health (ORWH) Strategic Plan Goal 1: Increase Sex Differences Research in Basic Science Studies.

Endocrine Disruptors

NIEHS is funding numerous human studies examining the health effects on the developing fetus related to prenatal exposures to environmental chemicals. Many studies to date have reported small but significant changes as it relates to reported sexually dimorphic behaviors. In some studies, pregnant women exposed to a specific class of endocrine disruptors show changes in girls and not in boys as it relates to depression, but yet play behavior changes are reported in boys and not girls. Larger studies are being conducted to see if specific endocrine disruptors, such as phthalates and bisphenol A, may perturb the developing fetal endocrine system and increase the risk for behavioral disorders. This effect may be related to changes in the gestational sex steroid milieu as noted in animal studies. Outcomes to be addressed include, but are not limited to, visual and spatial abilities, and to determine whether males or females are more vulnerable to specific chemicals. An NIEHS grantee formerly funded through an ORWH Trans-NIH High Priority, Short-Term Awards (R56) has published five papers in 2017. This work examined the impact of phthalate mixtures on antral follicles from mice and found exposure reduces antral follicle growth, induces oocyte fragmentation, and decreases hormone production by adversely affecting the expression of cell cycle regulators, apoptotic factors, steroidogenic enzymes, and receptors (Zhou & Flaws, 2017). To test whether environmentally relevant phthalate mixtures impact female reproduction in mice, these scientists exposed pregnant mice to the same phthalate mixture that was found in pregnant women and tested fertility of female mice born to the exposed dam. They found prenatal exposure to the phthalate mixture significantly increased uterine weight and decreased anogenital distance on postnatal days 8 and 60, induced cystic ovaries at 13months, disrupted estrous cyclicity, reduced fertility-related indices, and caused some breeding complications at 3, 6, and 9months of age, suggesting an environmentally relevant phthalate mixture may adversely affect female reproduction in humans (Zhou, Gao, & Flaws, 2017b). Using this same phthalate mixture, scientists tested the effects of prenatal exposure on reproductive outcomes in second (F2) and third (F3) generation female mice. This work identified morphological and

functional perturbations across both generations suggesting prenatal exposure to the phthalate mixture induces multigenerational and transgenerational effects on female reproduction (Zhou, Gao, & Flaws, 2017a). *Supports ORWH Strategic Plan objectives 1.2, 1.7, and 1.8.*

National Toxicology Program

The general toxicology assessments conducted by the National Toxicology Program (NTP) usually involve exposures of rats and mice of both sexes to test articles for periods of 14 days or 13 weeks. Assessments almost always performed include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The NTP long-term toxicology and carcinogenesis studies (bioassays) in rodents generally employ both sexes of rats (Harlan Sprague Dawley) and mice (B6C3F1 hybrid), with three exposure concentrations plus untreated controls in groups of 50 animals for 2 years starting on gestational day 6. Both sexes are evaluated to determine if there are differences in outcome caused by gender differences.

The Office of Health Assessment and Translation (OHAT) within NTP serves as an environmental health resource for public and regulatory health agencies. OHAT conducts literature-based evaluations to assess the evidence that environmental chemicals, physical substances, or mixtures may be associated with adverse health effects. In the past, OHAT has produced evaluations relevant to women's health including cancer chemotherapy use during pregnancy and levels of organotin and total tin in reproductive-age Danish women. *Supports ORWH Strategic Plan objectives 1.2, 1.4, and 1.7.*

NIEHS Sister Study

The Sister Study is a landmark research effort created by NIEHS scientists to find causes of breast cancer. More than 50,000 women across the United States and Puerto Rico, who were between ages 35–74 and whose sister had breast cancer, joined this effort between 2004 and 2009. Because of their shared environment, genes, and experiences, studying sisters provides a greater chance of identifying risk factors that may help us find ways to prevent breast cancer and other adverse health outcomes. The Sister Study currently is tracking the health of women in the cohort.

Research in the Sister Study focuses on causes of breast cancer and other health issues in women, as well as on factors that influence the quality of life and outcomes after a breast cancer diagnosis. Results from the Sister Study have been accumulating every year. Several prominent studies appeared in 2017 and 2018:

- Vitamin D is an environmental and dietary agent with known anticarcinogenic effects, but protection against breast cancer has not been established. NIEHS scientists examined the vitamin D levels in a subset of women enrolled in the Sister Study and found that women with elevated risk, high serum 25(Premenopausal Breast Cancer Collaborative et al.)D levels and regular vitamin D supplement use were associated with lower rates of incident, postmenopausal breast cancer over 5 y of follow-up. These results may help to establish clinical benchmarks for 25(Premenopausal Breast Cancer Collaborative et al.)D levels; in addition, they support the hypothesis that vitamin D supplementation is useful in breast cancer prevention (O'Brien, Sandler, Taylor, & Weinberg, 2017).
- Indoor burning of fuel for heating or cooking releases carcinogens. Little is known about the impact of indoor air pollution from wood-burning stoves or fireplaces on breast cancer risk. NIEHS scientists evaluated the risk of breast cancer in relation to indoor heating and cooking practices in Sister Study participants. Data suggests having an indoor wood-burning stove/fireplace or natural gas/propane was associated with a higher breast cancer risk and the risk increased with

average frequency of use (White & Sandler, 2017).

- Using subjects in the Sister Study combined with a regression model for environmental exposure to particulate matter (diameter <10 µm, PM10; <2.5µm, PM2.5), nitrogen dioxide (NO_2), NIEHS scientists and colleagues show that PM10 exposure was related to chronic bronchitis prevalence. Among never-smokers, PM2.5 and NO_2 exposure was associated with chronic bronchitis and component symptoms. Results may have policy ramifications for PM10 regulation by providing evidence for respiratory health effects related to long-term PM10 exposure (Hooper et al., 2018).
- Many personal care products include chemicals that might act as endocrine disruptors and thus increase the risk of breast cancer. NIEHS scientists and collaborators examined participants in the Sisters Study to look for an association between usage patterns of beauty, hair, and skin-related personal care products and breast cancer incidence. Among white women, those classified as “moderate” and “frequent” users of beauty products had increased risk of breast cancer relative to “infrequent” users. Frequent users of skincare products also had increased risk of breast cancer relative to infrequent users. This work generates novel hypotheses about personal care product use and breast cancer risk (Taylor et al., 2018).

Supports ORWH Strategic Plan objectives 1.1, 1.2, 1.7, 1.8, and 1.9

Household Air Pollution and Cookstove Research

Chronic exposure to smoke from traditional cooking practices causes a range of health effects including heart disease, stroke, and acute respiratory infections. Most deaths occur in low- and middle-income countries (LMICs), with women and children disproportionately impacted. The NIEHS Household Air Pollution program takes a multi-pronged approach to understanding the global health impact of cookstoves, including research to assess exposures and determine health outcomes, as well as the support of improved cookstove design and intervention trials along with training and capacity building to support these efforts. NIEHS partners with the Fogarty International Center on the International Hubs of Interdisciplinary Research and Training in Global Environmental and Occupational Health (GEOHealth) funding program. GEOHealth supports paired consortia—led by an LMIC institution and a U.S. institution—to develop research, research training, and curriculum development activities that address and inform priority national and regional environmental and occupational health policy issues. GEOHealth Hubs in Bangladesh and Ethiopia support research on household air pollution and disease. The NIEHS-WHO Collaborating Centre for Environmental Health Sciences includes indoor air pollution associated with biomass burning as one of the five focus areas of environmental health concern. Global environmental health, including a focus on cookstoves and indoor air pollution, is identified as a priority research area for NIEHS in the 2012–2017 Strategic Plan. NIEHS is a lead NIH IC in the Global Alliance for Clean Cookstoves, an initiative that is using a specific gender strategy to empower women’s role in adopting clean cookstoves and fuels. *Supports ORWH Strategic Plan objectives 4.1, 4.2, 4.4, and 4.6*

Breast Cancer and the Environment Research Program

NIEHS and the National Cancer Institute co-fund the Breast Cancer and the Environment Research Program (BCERP), which supports the enhancement of our knowledge regarding environmental and genetic factors underlying breast cancer risk over women’s lifespans. Through the integration of experimental models

and human studies, the BCERP transdisciplinary research projects are studying how exposures during specific time periods over the life course may increase breast cancer risk. During these windows of susceptibility, such as puberty or during pregnancy, an individual may be particularly vulnerable to different chemical or dietary exposures. The BCERP program also includes studies that focus on targeted risk communication regarding breast cancer and the environment and validation of the effectiveness of existing materials developed for parents and caregivers, health care professionals, advocates and for the general public. The BCERP Coordinating Center serves as a hub for communication about priority research topics and scientific findings from the program that can inform prevention. Several prominent studies appeared in 2017 and 2018:

- In utero exposure to cadmium, an environmental metalloestrogen, stimulates expansion of the mammary progenitor cell population and increases express of estrogen receptor alpha. Research indicates these events are important steps in the development of estrogen receptor positive breast cancer. Given the ability of cadmium to cross the placenta and accumulate in the mammary gland in utero coupled with cadmium contamination in the environment, this work suggests in utero exposure to cadmium my increase the risk of developing breast cancer later in life (Parodi et al., 2017).
- Perfluorooctanoic acid (PFOA) is a potential environmental contributor to breast cancer. Research was conducted by NIEHS grantees to examine risk belief and attitude formation from translated scientific messages about PFOA. Using participants from the Dr. Susan Love Research Foundation's Army of Women, a Heuristic Systematic Model investigated what leads to risk beliefs and negative attitudes in women receiving translated scientific messages about PFOA. This work found more knowledge and lower literacy messages were associated with lower perceived risk. Greater involvement and ratings of heuristic cues led to greater perceived risk (Smith et al., 2017).
- Endocrine disruptor research often uncovers sex-specific effects. To address relationships of covariates with sex-specific outcomes, NIEHS grantees evaluated the performance of two traditional approaches for estimating sex-specific effects and identified a simple modeling alternative. They found bias was present when traditional approaches were used and results were unbiased, but less precise, when the modeling alternative was used. This work underscores the need for investigators to consider how their analytical approach may estimate sex-specific effects, particularly in endocrine disruptor research (Buckley, Doherty, Keil, & Engel, 2017).
- Increased expression of estrogen-related receptor α (ERRα) in certain ovarian, breast, and colon cancers has a negative prognosis, indicating an important role for ERRα in cancer progression. Identifying compounds that increase expression of ERRα would allow scientist to hone in on compounds that may act as endocrine disruptors through ERRα. After screening 8,311 unique compounds in the Tox21 10K chemical library, scientists narrowed down the chemical space to compounds that act as agonists of ERRα, including multiple novel agonists. While this work doesn't define human toxicity of ERRα agonists, it represents a high throughput method for surveying a large chemical space of and identifying compounds with the highest potential for toxicity in humans and prioritizing further testing on such compounds (Lynch et al., 2018).

Supports ORWH Strategic Plan objectives 1.7, 2.2, 3.1, 5.5

IV. NIEHS Inclusion Efforts

NIEHS supports very few clinical trials. However, NIEHS and NTP conduct a great deal of animal research, almost all of which is analyzed by sex. The NIEHS Clinical Research Unit currently actively recruits men and women for 27 clinical studies. Several of our studies have a specific focus on women's health. Researchers are studying the health effects of an herbal supplement taken by some women to treat hot flashes, cramps, or other symptoms in the Black Cohosh Study. To examine whether overweight girls are truly entering puberty before normal weight girls, researchers have recruited girls between the ages of 8–14 to participate in the Body Weight & Puberty Study. The NIEHS-EPA Pilot Study of Exposure to Chemicals in Consumer Products actively recruited healthy, stay-at-home women to improve the way data is gathered for studies that examine chemical exposure from consumer products. The Calorie Restriction, Environment, and Fitness: Reproductive Effects Evaluation Study recruited women participants to understand how nutrition, exercise, and the environment affect women's reproductive cycles. The Ovarian Health Study recruited women participants for developing assays to measure anti-Müllerian hormone in the urine as a promising biomarker for ovarian health.

V. NIEHS Science, Technology, Engineering, and Mathematics (STEM) Efforts

NIEHS Scholars Connect

The NIEHS Scholars Connect Program (NSCP) is designed to provide a unique opportunity to highly motivated STEM-focused undergraduate students to solidly connect with NIEHS and receive frontier-level training in biomedical research. Students in NSCP have an opportunity for hands-on mentored research experiences, as well as professional and personal development. The Program is committed to encouraging students to pursue careers in scientific investigation, both basic and clinical. NSCP also is committed to increasing diversity in environmental health science, and applications from underrepresented populations in STEM are strongly encouraged. In FY 2017–FY 2018, two African-American women, one Caucasian woman, one Latina woman, and one Asian Indian woman participated in the program comprised of ten total Scholars.

Female Tenure Track Investigators Program

The NIH Women Scientist Advisors Committee and the Intramural Committee of the NIH Working Group on Women in Biomedical Careers have developed a new program for basic and clinical tenure-track investigators and assistant clinical investigators. NIH program coordinators have agreed to help coordinate and develop a tenure-track investigators program at NIEHS. Female senior scientists serve as mentors for this program. As a result of the initiative, three new female tenure-track investigators started at NIEHS in FY 2017–FY 2018. As of January 2019, one additional new female tenure-track investigator started at NIEHS in FY 2019. There are currently nine female tenure-track investigators out of a total of twelve tenure-track investigators at NIEHS.

Office of Fellow's Career Development

The Office of Fellows' Career Development has undertaken a project to identify the career outcomes of all trainee alumni who left NIEHS within the past 15 years and to determine whether there are differences in career outcomes based on gender (Taylor et al., 2018). Determining whether gender-based career outcome differences exist is one of the first steps in evaluating the NIEHS training program to

Results: The overall composition of [males | females] was [54% | 46%] over the 15-year time period, with a trend towards equal gender composition when binned into 5-year increments. Upon closer examination of career outcomes, we found that 65 percent of tenure-track positions were held by men, while 35 percent were held by women—figures that mirror national statistics on the gender composition of new investigators. It should be noted, however, that these figures do not take into account the fact that a higher proportion of international fellows also enter into tenure-track positions, and males far outweigh females in this international population. Furthermore, analysis showed that females enter into science writing/communication careers at nearly four times the rate of men.

As part of this career outcomes project, we also conceived of and created a custom online interactive data dashboard for further investigating NIEHS postdoc alumni careers. We envision that other NIH ICs could build off of this foundation to readily create their own dashboards for highlighting career outcomes, especially to bring transparency to differences in career outcomes as a function of gender.

VI. Funding Initiatives, Workshops, and Conferences

Workshops and Conferences

NC Women of Color Research Network Annual Symposium

The Women of Color Research Network (WoCRn) (womeninscience.nih.gov/women-of-color) is a product of the NIH Working Group on Women in Biomedical Careers subcommittee on Women of Color in Biomedical Careers (www.womeninscience.nih.gov). The North Carolina Chapter of the WoCRn (NC WoCRn) is the second regional chapter. The Women of Color Research Network (WoCRn) was established to address challenges faced by all women and minorities entering and advancing in scientific careers. The mission of the NC WoCRn is to promote career advancement by broadening participation of women researchers and scientists of color, establishing collaborations and partnerships, multi-level mentoring, outreach, and professional networking. An annual symposium was held at NIEHS on May 31, 2018 featuring a networking event and research talks.

Women's Health Awareness Day: Transforming Communities by Enhancing Women's Health

NIEHS sponsored the 3rd and 4th Women's Health Awareness Day on April 8, 2017, and again on April 7, 2018, at North Carolina Central University in Durham, North Carolina. This was a community event that was free to the public, and more than 800 people participated in 2018 alone. The goal of this event was to promote healthier lives through disease prevention, control, and management by bringing health education and environmental health awareness and literacy to women in the area to ultimately develop healthier families, environmentally safer homes, and communities. Health information was disseminated on cardiovascular disease, diabetes, reducing cancer risk, protecting lung health, human sexuality, breast awareness, and reproductive and maternal health. Breakout sessions included information on women's preventive health care under the Affordable Care Act, health care services and challenges for women veterans, and how to make homes environmentally safe. Free health screenings were provided throughout the conference, including mammography, cardiovascular screening, diabetes screening, and lung capacity screening. Plans are underway for the event to be held in 2019.

VII. Health Disparities

Health Disparities from the 2010 Deepwater Horizon Gulf Spill

The NIEHS-led Deepwater Horizon Research

Consortia support community-university partnerships aimed at addressing the health effects stemming from the 2010 Deepwater Horizon Gulf spill to help improve community preparedness and response to disasters and minimize such disaster-related health impacts as stress, exposure to contaminants, and diet changes. Consortia studies that focus on women and children and involve minority or ethnic populations are being conducted at Louisiana State University and Tulane University:

WaTCH (5U01ES021497). Goal: Determine mid- and long-term physical, behavioral, social, and economic effects on women and children's well-being. Two substudies were conducted on resiliency (the association between resilience, social capital, and emotional health and association between subjects' exposure and their emotional and physical health) and a Child Impact Study. These studies included women from low-income communities, from Vietnamese subsistence communities, and among Houma Nation (Native American) communities. NIEHS-funded research studied 2,038 women in seven coastal Louisiana parishes following the Deepwater Horizon Gulf oil spill and found depressive symptoms among Louisiana coastal women had increased from Wave 1 (approximately 2-4 years after the oil spill) to Wave 2 (after 4-6 years of follow-up), whereas symptoms of mental distress had decreased in that same time period. Initial associations between economic and physical exposure to the oil spill and both mental health outcomes persisted up to 6 years after the spill, with women who were more highly exposed to the oil spill experiencing higher levels of depressive symptoms and mental distress at each time point (Rung et al., 2018).

Study of Environment, Lifestyle, and Fibroids

NIEHS intramural scientists are studying a variety of diseases that affect women. One epidemiological study, called the Study of Environment, Lifestyle & Fibroids (SELF), is being conducted among African-American women ages 23–34, in the Detroit, Michigan area (1ZIAES049013). Fibroids are more common in black women than in white women, and fibroids are the leading indication for hysterectomy. The reason for this health disparity is not known. This NIEHS study is a prospective cohort study with an enrollment of women before they are diagnosed with fibroids and with follow-up for at least 5 years to document new fibroid development with ultrasound examinations at intervals of about 20 months. Researchers will examine a wide range of potential risk factors for the condition to evaluate their associations with the appearance of new fibroids and growth of existing fibroids. Recent research used transvaginal ultrasound results and self-reported questionnaire data from participants in the SELF study to investigate the relationship between bacterial vaginosis (BV) and fibroids prospectively. This work uncovered a positive association between BV and the risk of developing fibroids, particularly when the first BV diagnosis was within 3-5 years prior to enrollment (Moore & Baird, 2017).

NIEHS scientists in the National Toxicology Program (NTP) Division have focused on defining the pathogenesis of disorders affecting the uterus and assessing the role of environmental and endogenous hormones and growth factors in these disorders. They have found that both positive and negative regulators of apoptosis are not differentially expressed in uterine fibroids, and that altered apoptosis does not appear to play a significant role in the development of these tumors. Their studies show that cell proliferation and extracellular matrix production may be the most significant contributors to fibroid growth. In studies addressing the role of growth factors in the pathogenesis of fibroids, receptor tyrosine kinases (RTKs) and their ligands are overexpressed in fibroids during the proliferative phase of the menstrual cycle, and many of the RTKs are activated, suggesting RTK signaling likely plays a role in uterine fibroid pathogenesis.

These studies will help to define some of the basic biological and molecular pathways important in fibroid growth, which can then be applied to developing alternative noninvasive treatment regimens for fibroids. *In vitro* model systems for studying fibroids are limited, but NTP scientists have overcome this obstacle by the development of human telomerase immortalized uterine leiomyoma and myometrial cell lines. These cells are being used to study leiomyoma tumorigenesis in a prospective manner. In FY 2017, NTP scientists published work describing the localization of estrogen receptor α in the uterine leiomyoma and myometrial cell lines suggesting estrogen receptor α is localized primarily in mitochondria and may play a pivotal role in non-genomic signaling and mitochondrial functions (Yan, Yu, Castro, & Dixon, 2017). If so, it may be a promising therapeutic target for treating fibroid tumors. Additional model systems continue to be explored, including the use of the miniature pig as a model of fibroids in women. In determining the role of environmental agents in fibroid development, scientists have found that prenatal and neonatal exposures of mice to diethylstilbestrol results in uterine leiomyomas similar to fibroids observed in women. Other exposures that have been evaluated include the phytoestrogen genistein and the environmental pesticide fenvalerate and metals, such as cadmium, all of which may increase the risk of uterine fibroid development.

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National Institute of General Medical Sciences

I. NIGMS/ORWH Executive Summary of Women's Health and Sex Differences Research

The National Institute of General Medical Sciences (NIGMS) supports basic research that increases understanding of biological processes and lays the foundation for advances in disease diagnosis, treatment, and prevention. NIGMS-funded scientists investigate how living systems work at a range of levels, from molecules and cells to tissues, whole organisms, and populations. Investments in such diverse and fundamental areas of biomedical research serve as the foundation for subsequent categorical or disease-specific discoveries and advances. Our ability to effectively treat, diagnose, manage, and ultimately cure diseases increases significantly with an understanding of their underlying mechanisms and biology. The Institute also supports research in certain clinical areas, primarily those that affect multiple organ systems. NIGMS also supports research training, career development, diversity, and capacity-building activities through a variety of programs at the undergraduate, graduate, postdoctoral, and faculty levels. The focus of these programs is to train the next generation of scientists, enhance the diversity of the scientific workforce, and develop research capacities throughout the country.

In FY 2017-2018, NIGMS supported research in a broad range of areas related to women's health and the interests of the Office of Research on Women's Health (ORWH). This includes projects increasing our understanding of basic biological processes that may lead to improved diagnosis and treatment of conditions specific to, or disproportionately affecting women. Key areas of research included maternal health during and after pregnancy, ovarian and breast cancer, and sex differences in reactions to anesthesia and postoperative pain treatment. Additionally, NIGMS supported projects aimed at improving women's STEM education, and identifying scientific workforce dynamics and barriers for women in biomedical and research careers. These projects align with several goals and objectives in the NIH Strategic Plan for Women's Health Research. For example, several projects align with goal 1 ("increase sex differences research in basic science studies"), including work on sex differences in anesthesia safety and post-operative pain regulation. A number of projects also align with goal 3 ("actualize personalized prevention, diagnostics, and therapeutics for girls and women"), including research on gestational weight gain and pregnant women's health, as well as work on early-stage breast cancer. Other projects align with goals 2 ("incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs") and 6 ("employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce).

Through the Trans-NIH Coordinating Committee on Research on Women's Health (CCWH), NIGMS awards supplemental funding to NIH-funded researchers to encourage the consideration of sex/gender factors in their ongoing research. In 2017, NIGMS participated in the Research on the ORWH FY17 Administrative Supplement for Health of Women of Understudied, Underrepresented and

Underreported (U3) Populations. NIGMS staff actively participates in the Think Tank for the Strategic Plan for Research on Women's Health, and in the NIH Working Group on Women in Biomedical Careers.

II. Accomplishments and Activities

Healthy Weight, Healthy Pregnancy: Incentives Targeting Gestational Weight Gain

Excessive weight gain during pregnancy is associated with adverse outcomes for both mothers and their children. Obese and overweight women are particularly prone to these effects, and individuals of low socioeconomic status are more likely to be obese or overweight. NIGMS-funded researchers are testing an intervention aimed at helping overweight and obese low-income women achieve healthy gestational weight gain. They are conducting a clinical trial in which participants receive either standard obstetrical care or an intervention combining financial incentives and weight management counseling. The group is measuring both gestational weight gain, as well as later health outcomes for mothers and babies (e.g., birth weight, rates of caesarian sections). This research can lead to low-cost strategies to improve mothers' and children's health, and addresses objectives 3.3, 3.4, and 3.8 of the NIH Strategic Plan for Women's Health Research.

Physical Activity During Pregnancy: Novel Pathways and Intervention Strategies for Improving Maternal and Neonatal Outcomes

Maternal obesity during pregnancy negatively impacts both a mother's and child's health. Through an NIGMS grant, a group of researchers have developed the Vermont Center on Behavior and Health, which is developing solutions to address maternal obesity and associated health risks for mothers and children. Recently, the scientists presented data demonstrating that after consuming high-fat meals, obese pregnant women showed smaller increases in lipid metabolism than lean women (Tinius et al., 2018). Currently, these scientists are also testing an intervention to increase physical activity during pregnancy and minimize gestational weight gain. This work supports objective 3.3 of the NIH Strategic Plan for Women's Health Research.

Effects of Perfluoroalkyl Substances (PFAS) on Gestational Weight Gain, Breastfeeding, and Early Life Growth

Perfluoroalkyl substances (PFASs) are synthetic chemicals that are used widely in food packaging, nonstick coating, and water-resistant clothing. PFASs have also been detected in drinking water in the United States. PFAS exposure during pregnancy could potentially be associated with excessive gestational weight-gain, shorter breastfeeding duration, and being overweight or obese during childhood. NIH supported-researchers are now investigating possible evidence for this link, using data from the New Hampshire Birth Cohort study to examine whether increased PFAS exposure during pregnancy is associated with these three negative outcomes. PFAS exposure is preventable, and thus, identifying any exposure-related health risks would inform policy that could reduce exposure and improve maternal and children's health. This work supports objective 3.3 of the NIH Strategic Plan for Women's Health Research.

Molecular Probes for Biomembrane Recognition

High-grade serous ovarian cancer (HGSOC) is the most common and deadly ovarian cancer sub-type and is responsible for approximately 80% of ovarian cancer cases and two-thirds of ovarian cancer deaths. A cell line collected from a 42-year-old ovarian cancer patient and found to be resistant to combination chemotherapy, OVCAR-4, was recently ranked as one of the most representative cell lines for HGSOC. Using this cell line, NIGMS-supported scientists

developed new fluorescent probes to selectively target these clinically relevant OVCAR-4 cells. Their results demonstrate extensive cellular uptake of the probes allowing for high-contrast molecular imaging and potentially more efficient drug delivery (Shaw et al., 2018). Further development of such probes could help clinicians to identify patients with integrin positive HGSOC, or other cancers, that should respond to integrin-targeted chemotherapy. This research supports objectives 2.5, 2.6 and 2.7 of the NIH Strategic Plan for Women's Health Research.

Behaviors, Chronic Disease, and Quality of Life after Ductal Carcinoma

Ductal carcinoma in situ (DCIS) is the earliest stage of breast cancer. While DCIS is not often fatal, being diagnosed and treated for DCIS can itself negatively impact a patient's health; patients for example often experience weight gain, increased antidepressant use, and physical declines. A group of NIGMS-supported researchers hypothesize that these negative health impacts may lead to greater long-term disease risk than cancer itself. To determine this, researchers are using data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, and the Wisconsin In Situ Cohort (WISC) study to measure how much disease burden (negative impact of a disease, such as quality of life declines and death) DCIS survivors experience, not due to cancer. Additionally, they are exploring the relationship between DCIS survivors' health-related behaviors, such as exercising, and their health and well-being outcomes – hypothesizing that positive health-related behaviors are protective factors for DCIS survivors. They are also exploring whether socioeconomic status is related to changes in health-related behaviors after DCIS diagnosis. Recently, the researchers published results indicating several links between health-related behaviors and health outcomes. For example, they found that DCIS survivors who engaged in moderate as opposed to no physical activity after diagnosis indeed had lower levels of mortality (Veal et al., 2017). Results of this study show potential for interventions to improve quality and length of life for DCIS survivors. This work supports objective 3.8 of the NIH Strategic Plan for Women's Health Research.

Understanding the Function of LBH in Normal Mammary Development and Breast Cancer Pathogenesis

A protein known as LBH is expressed during mammary gland development and is aberrantly overexpressed in aggressive breast cancer. To better understand the physiological functions of LBH, NIGMS-supported scientists previously investigated the in vivo role of LBH in normal breast development in postnatal mice and in normal human and mouse breast cells. Study results showed that LBH is a regulatory protein required in adult breast stem cells for their rapid expansion during puberty and pregnancy. In particular, LBH plays an essential role in the expansion and/or maintenance of mammary stem cells (MaSCs) as well as in the specification of breast cell type. Importantly, researchers found that excessive LBH is present in cancer-related dysfunction. This research has important implications for understanding the role of LBH in breast cancer pathogenesis and will inform efforts to develop novel therapeutic targets. This research supports objective 2.7 of the NIH Strategic Plan for Women's Health Research.

Testosterone's Role in Sex-Specific Outcomes after Early Anesthesia

Exposure to anesthesia in early childhood can cause changes to synapses and stem cells, brain cell death, and cognitive deficits. Some evidence suggests sex differences in these effects, but these differences and their underlying causes have not been studied. To address this knowledge gap, NIGMS-supported researchers are studying sex differences in cognitive deficits in rodents with early anesthesia exposure. They hypothesize that testosterone in male rodents causes a delay of the potassium-chloride transporter KCC2 expression. This delay slows down the transition

from excitatory to inhibitory GABAergic signaling in the hippocampus, which leads to neuronal spine loss and cognitive dysfunction. Their hypothesis could suggest that females have a different period of vulnerability to anesthesia than males, and the findings could lead to sex-specific recommendations on safety of early anesthesia exposure. This work supports objective 1.2 and 1.4 of the NIH Strategic Plan for Women's Health Research.

III. Additional Scientific and Organizational Activities

NIH Strategic Plan for Women's Health Research

Highlights: While NIGMS supports a large number of research projects and activities that advance the NIH Strategic Plan for Women's Health research, here we highlight two accomplishments that increase knowledge on pain research and the advancement of women in biomedical careers.

Prolactin Regulation of Postoperative Pain in Males and Females

Data suggest that there are sex differences in postoperative pain-medication responses, with women experiencing a lower degree of pain relief and a higher risk of medication abuse and addiction. NIGMS-funded researchers see an urgent need to create sex-specific pain-management plans and are studying sex differences in pain regulation. These researchers have found that after having surgical incisions, females but not males experience an upregulation of extra-pituitary prolactin (PRL) at the site of surgery and in the spinal cord. Blocking this response leads to reduced pain for males but not for males, further suggesting the role of PRL in postoperative pain sensitivity in females. Thus, the researchers are now exploring mechanisms—both spinal and peripheral—by which the prolactin (PRL) system regulates pain in female mice. This research has the potential to advance sex-specific pain management strategies and supports objectives 1.2 and 1.4 of the NIH Strategic Plan for Women's Health Research.

NIH Funding Longevity by Gender

Although over half of all Ph.D.s in the biological sciences have been awarded to women in recent years, women submit fewer than one-third of all first-time NIH applications. The success rate for those women who submit new applications is the same as that for men, but NIGMS staff wished to explore whether the funding longevity for women and men who receive a first major NIH grant is similar. Deputy Director Dr. Judith Greenberg and colleagues recently published a paper in PNAS (Hechtman et al., 2018) showing that once women receive their first NIH grant, their funding longevity is similar to, though slightly lower, than men's. A larger gap was present in the proportion of women entering the NIH funding pool to begin with (less than a third). This suggests a greater need for intervention before women obtain the first major NIH grant, rather than after, and helps clarify the points at which further retention efforts may be directed. This work supports objective 6.3 of the NIH Strategic Plan for Women's Health Research.

Other Activities: NIGMS actively participates in the Think Tank for the Strategic Plan for Research on Women's Health, Women in Biomedical Careers Team; the Trans-NIH Coordinating Committee on Research on Women's Health (CRWH); and the NIH Working Group on Women in Biomedical Careers.

Inclusion

NIGMS engages in several strategies to promote women's inclusion in clinical trials. Clinical research applications are judged based on the appropriateness of the proposed plan for inclusion by sex/gender and are barred from funding until acceptable inclusion plans are received. Program and grants management staff furthermore

oversee inclusion progress and inclusion documentation. NIGMS also ensures personnel are appropriately trained to monitor and document compliance with the NIH Inclusion Policy, providing annual staff trainings and individualized trainings.

IC Science Technology, Engineering, and Math (STEM) Efforts

Building a Classroom Game Economy to Improve Mathematical Reasoning and Prepare K-5 Students for Success in STEM Learning

Employment needs in STEM fields are rapidly growing, and yet women, minorities, and students of lower socioeconomic status are less likely to go into these fields. To address the need for increased elementary school STEM training, a group of NIGMS-funded researchers are creating educational technology to promote foundational mathematics skills and self-efficacy. They are creating a tablet game for K-5 students, in which students participate in a classroom economy (create stores, sell objects, engage in financial transactions, etc.) and in doing so, build basic math skills and learn higher levels of mathematical abstraction. Additionally, the technology will use artificial intelligence (AI) to identify the problem-solving strategies that students are using. The software will then provide this information to teachers to increase teaching effectiveness, and to identify at-risk students. The researchers hope that by producing AI that detects students' learning progress, teachers can intervene and ultimately build students'—including young girls'—foundational math knowledge and stronger self-efficacy. This work supports objective 6.3 of the NIH Strategic Plan for Women's Health Research.

Using Coauthor Network Metrics to Understand Faculty Advancement and Retention in Academic Medicine

The modern scientific workforce requires teams to solve the most critical problems that confront biomedical research. A network of productive collaborators is among the strongest predictors of research publications, productivity, retention, and advancement of academic faculty. Differences in the networks of women and minorities explain some of the disparities that exist in these subgroups with respect to research productivity and subsequent career advancement. Co-authorship of publication is evidence of a connection or collaboration between two or more authors. These publication-level relationships, when combined across the scientific literature, establish a coauthor network. NIGMS-funded researchers have previously explored network reach and its relationship to faculty promotion and retention. In a new line of work, NIGMS-supported scientists studied the network reach and NIH R01 award outcomes for female and male faculty at Harvard Medical School. The group found that individuals with broader network reach were more likely to obtain R01 awards, and there was no gender difference in R01 awards in this sample (Warner et al., 2017). These results further highlight network reach as an important predictor of academic outcomes and support objective 6.3 of the NIH Strategic Plan for Women's Health Research.

Funding Initiatives, Workshops, and Conferences

NIGMS actively participates in the Trans-NIH Coordinating Committee on Research on Women's Health (CCRWH) and has taken part in the funding opportunity announcements (FOA), "Administrative Supplements for Research on Sex/Gender Differences" in FY2017 and FY2018 (PA-17-078 and PA-18-658). This program provides supplemental funding to NIH-funded researchers to encourage the consideration of sex/gender factors in their ongoing research. Two NIGMS grantees were funded in both 2017 and 2018 under this FOA.

NIGMS participated in the ORWH FY2017 Administrative Supplement for Research on the Health of Women of Understudied, Underrepresented and Underreported (U3)

Populations (PA-17-101). This program supports administrative supplements to support research highlighting the impact of sex/gender influences at the intersection of race/ethnicity and other social determinants in human health and illness, including preclinical, clinical and behavioral studies.

Health Disparities

Several NIGMS-funded research in FYs 2017-2018 furthered knowledge of health disparities related to sex/gender. For example, as detailed above, research on prolactin regulation of postoperative pain in females may address women's specific reactions to postoperative pain medication—including lower degree of pain relief, and higher risk of abuse and addiction.

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National Institute of Mental Health

I. Executive Summary

Sex differences exist in the prevalence and clinical course of several mental disorders. For example, starting in childhood, sex differences begin to emerge such that girls have higher rates of anxiety disorders and eating disorders compared to boys, whereas boys are more likely to be diagnosed with autism spectrum disorder and attention deficit-hyperactivity disorder. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including post-traumatic stress disorder (PTSD). In adulthood, there are also differences in the course and severity of mental disorders between men and women. Additionally, some women are at increased risk of depression during certain times of reproductive change, such as in the perinatal and perimenopausal periods. Understanding sex differences in the mechanisms underlying mental disorders, including those in which rates do not differ for men and women, are critical for identifying key targets for intervention that may differ for the two sexes.

The National Institute of Mental Health (NIMH) funds research aimed at increasing scientific understanding of sex and gender differences in mental health and mental disorders. NIMH supports projects designed to advance knowledge of specific mental disorders that either affect women exclusively (e.g., perinatal depression), or predominantly (e.g., eating disorders).

In collaboration with the NIH Office of Research on Women's Health, NIMH fosters interdisciplinary collaboration and research to pave the way for improved diagnosis, treatment, and prevention of mental disorders in women. NIMH prioritizes initiatives in mental health disparities, global mental health, and training scientists in mental health disparities and global mental health research. These efforts lay the groundwork for interventions to meet the needs of women from diverse socioeconomic, racial, ethnic, and geographic backgrounds in a variety of treatment settings.

This report, spanning fiscal years (FYs) 2017 and 2018, highlights published findings from NIMH-funded research on sex and gender differences and women's mental health; specific workshops and initiatives to promote research on women's mental health; and, NIMH efforts to improve the mental health of diverse populations of women. Research highlights, initiatives, and workshops are organized below according to their alignment with specific objectives of the NIH strategic goals for women's health and sex differences research.

II. Accomplishments and Activities

Goal 1: Increase sex differences research in basic science studies

Sex differences in the prevalence, expression, and burden of certain mental disorders are demonstrated in population-based epidemiological studies of U.S. adults. For example, adult women experience major depression at almost twice the rate of adult men. Sex differences may be caused by a variety of factors, including the effects of sex-linked genes, reproductive hormones, and differences in environmental stressors that impact brain structure and function. Understanding the mechanisms underlying these sex differences may provide clues as to why men and women are differentially vulnerable to certain mental disorders. The following are examples of findings from NIMH-supported studies that illustrate the Institute's efforts in this area.

Studies of premenstrual dysphoric disorder (PMDD): PMDD affects approximately 5% of women, may present with symptoms such as anxiety and major depression, and is associated with differential sensitivity to circulating ovarian hormones. Investigators in the NIMH Division of Intramural Research Programs (IRP) evaluated the pharmacometabolomics (how a pharmaceutical compound is metabolized in the body) of Lupron, a drug that suppresses sex hormones. Specifically, they examined the metabolites of women with PMDD whose symptoms remitted in response to Lupron, but then returned during progesterone or estradiol replacement, and controls without pre-menstrual mood symptoms, who experienced no change in mood during the same period. Women with PMDD were found to process metabolites differently than women in the control group, such that they had lower levels of metabolites associated with inhibition of PMDD symptoms. (PMID: 28786978, PMID: 30184299). In addition, NIMH IRP investigators, working with the National Institute on Alcohol Abuse and Alcoholism (NIAAA), developed cell lines from women with and without PMDD to examine the ovarian steroid receptor. This in vitro experimental strategy attempted to recapitulate the endocrine events that trigger mood symptoms in women with PMDD. The results demonstrated that cells treated with ovarian steroids estradiol and progesterone from women with PMDD and from women without PMDD symptoms, manifested a cellular difference in function of a gene complex called ESC/E(Z). Dysregulation of ESC/E(Z) complex function could contribute to PMDD (PMID: 28044059). In collaboration with the Rockefeller Institute, NIMH IRP investigators also demonstrated overlap in the patterns of gene expression (including genes in the ESC/E(Z) complex) in both a mouse model for PMDD, and in the cells of women with PMDD. In this study, the mice that expressed a natural unique polymorphism that affects intracellular trafficking and secretion of brain-derived neurotrophic factor (BDNF) also demonstrated behavioral changes across the estrous cycle. These data suggest that the ESC/E(Z) family genes play a role in the expression of PMDD symptoms, and suggest a possible animal model for PMDD (PMID: 30356121).

Objective 1.1: Encourage genetic and epigenetic studies to identify sex differences in gene expression.

Objective 1.7: Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs. Apply this knowledge to sex differences in disease prevalence, symptoms, management, and outcomes in conditions such as lupus and cardiovascular diseases and to predominantly sex-specific diseases such as breast cancer and uterine fibroids.

Sex-dependent regulation of social reward by oxytocin receptors in the ventral tegmental area (VTA): Social reward is integral for social relationships; however, the characteristics of social interactions that are rewarding and sex-specific neural mechanisms that underlie this reward are not well understood. NIMH-supported researchers investigated whether the hormone oxytocin in the VTA, a brain region implicated in social reward, mediates the magnitude and valence of social reward. The results provide the first evidence in an animal model that same-sex social interactions may be more rewarding in females than in males and that activation of oxytocin receptors in the VTA is critical for social reward in both sexes. In addition, following social interactions, the researchers observed colocalization of FOS (a marker of activation) and oxytocin in sites that project to the VTA. Given the importance of social reward in both mental health and mental disorders, further studies examining sex differences in social reward processing may enhance understanding of the sex differences in the prevalence of certain mental disorders (PMID: 30467338).

Objective 1.2: Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

Objective 1.4: Include sex parameters in the design of experiments using animal models.

Objective 1.8: Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and wellbeing.

Sex differences in stressor effects on cognitive function: Habituation to stress may be disrupted in individuals with mental disorders, including post-traumatic stress disorder (PTSD) and panic disorder. Further, individuals with PTSD and panic disorder exhibit altered cerebrospinal concentrations of orexins and hypothalamic neuropeptides that regulate arousal, wakefulness, and appetite. Using rat models of repeated stress, NIMH-funded researchers explored whether orexins mediate effects of repeated stressors on cognitive function, finding that female rats have significantly diminished habituation to repeated stress and impaired cognitive flexibility following stress compared to male rats. These cognitive impairments were rescued by inhibiting orexin-expressing neurons in the lateral hypothalamus during stress. These results highlight the importance of considering differences in stressor effects due to sex, and a potential role for orexins in mediating these differences (PMID: 27955897).

Objective 1.2: Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs and physiological systems.

Objective 1.7: Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs.

Objective 1.8: Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being.

Largest genome-wide association study (GWAS) of PTSD yields sex differences in heritability: Understanding what genetic architecture may underlie PTSD is important to understanding why there are population level sex differences in the prevalence of the disorder. It has long been known that there are sex differences in the prevalence of exposure to different traumatic stressors; however, how biological factors may further contribute to the development of disease remains unclear. The NIMH-funded Psychiatric Genomics Consortium for PTSD combined genome-wide case-control molecular genetic data across 11 multiethnic studies, and reported the heritability estimate for females is substantially higher than males. These results parallel twin studies that showed moderate heritability for PTSD overall and higher heritability in females than males (PMID: 28439101).

Objective 1.1: Encourage genetic and epigenetic studies to identify sex differences in gene expression.

Sex differences in cognitive functioning and health behaviors in PTSD: PTSD has been linked to cognitive decline, but research in women is generally lacking. Using a sample from the Nurses' Health Study II, researchers analyzed the relationship between PTSD and cognitive functioning in middle-aged women. Findings suggested that symptoms of PTSD were associated with worse performance years later, on tasks of attention/psychomotor speed and learning/memory in women with PTSD as compared to those without PTSD. This association was not accounted for by adjustments for sociodemographic differences, depressive symptoms, nor other cognitive risk factors, though it appeared to be strongest among women with comorbid PTSD and depression (PMID: 28072503). Researchers also examined differences in peripheral blood cell telomere length in a subset of 116 women from the Nurses'

Health Study II. Telomeres are structures that protect chromosome ends from deterioration, and their erosion or shortening leads to cell death, accelerated aging, and increased risk of earlier development of chronic disease. Results showed that women with PTSD following civilian types of trauma had shorter telomere length than women without a history of trauma or without a history of PTSD following trauma—a finding comparable to that seen in male combat veterans with PTSD. These findings lend support to the interpretation that PTSD in women, as in men, appears to be linked with an acceleration of the biological aging process (PMID: 28380289).

Objective 1.5: Promote neuroscience research to study sex/ gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders.

Objective 1.8: Further understanding of sex/ gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and wellbeing.

Sex differences in the impact of schizophrenia on aging and functioning: Schizophrenia is linked with medical comorbidity and early mortality. These observations indicate possible "accelerated biological aging" in schizophrenia, although prior findings are mixed, and few studies have examined the role of sex. One putative marker of biological aging is leukocyte telomere length (LTL), which typically shortens with age. NIMH-funded researchers examined LTL as a marker of biological aging, finding that sex rather than diagnosis of schizophrenia was the major factor associated with LTL shortening in individuals aged 26 to 65 years. Overall, women had longer LTL than men with and without schizophrenia, and women with schizophrenia had shorter LTL than women without schizophrenia (PMID: 27835738). In a separate analysis, persons with schizophrenia were reported to have increased levels of inflammatory biomarkers and sleep disturbances compared to control participants. In particular, in people with schizophrenia, women had more inflammation and worse sleep quality than men (PMID: 30442531).

Objective 1.5: Promote neuroscience research to study sex/ gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders.

Objective 1.8: Further understanding of sex/ gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and wellbeing.

Estrogen-dependent mechanism associated with fear learning: NIMH-funded researchers analyzed DNA modification (via methylation) and its association with regulation of the HDAC4 gene, in a highly traumatized sample of women, who ranged in serum estradiol levels from childbearing, pregnancy, and menopause. HDAC4 is a gene known to be critical for learning and memory in mice. Researchers found more DNA methylation in HDAC4 among women with PTSD, and the lower level of HDAC4 gene activity was associated with differences in ability to recover from fear. Follow-up experiments in mice showed the HDAC4 gene was activated in the amygdala while the mice were undergoing fear learning, but only when estrogen levels were low. These results demonstrate an estrogenic influence of HDAC4 regulation and expression that provides insight into susceptibility to PTSD (PMID: 28093566).

Objective 1.1: Encourage genetic and epigenetic studies to identify sex differences in gene expression.

Objective 1.3: Study sex differences using a systems biology-based approach.

Objective 1.7: Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs.

Chronic peer victimization heightens neural sensitivity to risk taking: Although

behavioral and experimental studies have shown links between victimization and antisocial behavior, the neural correlates underlying this relationship are relatively unknown. NIMH-funded researchers tracked adolescents' reports of peer victimization experiences annually from the second through eighth grades, including a subsample of chronically victimized and non-victimized girls who completed a risk-taking task during a functional magnetic resonance imaging (fMRI) scan. Among the subsample of adolescent girls, chronic peer victimization was associated with greater risk-taking behavior during the task and higher levels of self-reported antisocial behavior in everyday life. At the neural level, chronically victimized girls showed greater activation in regions involved in affective sensitivity, social cognition, and cognitive control, which significantly mediated victimization group differences in self-reported antisocial behavior (PMID: 28393755).

Objective 1.5: Promote neuroscience research to study sex/ gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders.

Objective 1.8: Further understanding of sex/ gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and wellbeing.

Sex differences in network controllability as a predictor of executive function in youth: Executive function, which is a set of higher-order brain processes that regulate goal-directed behavior, attention, working memory, inhibition, and performance monitoring, emerges late in development and displays different developmental trends in males and females. Sex differences in executive function in youth have been linked to vulnerability to psychopathology as well as to behaviors that impinge on health, wellbeing, and longevity. Yet, the neurobiological basis of these differences is not well understood, in part due to the spatiotemporal complexity inherent in patterns of brain network maturation supporting executive function. NIMH-supported researchers are employing powerful network control theory and computational neuroscience to understand the network properties of brain circuits involved in executive function. Researchers tested the hypothesis that sex differences in impulsivity in youth stem from sex differences in the controllability of structural brain networks as they rewire over development. Results suggest that females have higher modal controllability in frontal, parietal, and subcortical regions while males have higher average controllability in frontal and subcortical regions. These neural differences correlate with behavioral differences on tasks involved in working memory and sustained attention (PMID: 30508681).

Objective 1.5: Promote neuroscience research to study sex/ gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders.

Objective 1.8: Further understanding of sex/ gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and wellbeing.

Goal 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs

Improvements in research methodology, instrumentation, and technology have driven advancements in biomedical services. NIMH is employing the use of complex modeling to better understand the factors that may promote or inhibit certain behaviors in women and girls. In addition, innovative research design techniques are being developed to improve women's mental health by improving drug delivery systems. Several NIMH-funded published findings focus on technologies and therapeutics aimed at improving treatment for mental disorders that differentially affect women and girls. The following are examples of findings from NIMH-supported studies that illustrate the Institute's efforts in this area.

Gene variation in functional neurocircuitry via ovarian steroid regulation: Preclinical evidence suggests that the actions of ovarian steroid hormones and brain derived neurotrophic factor (BDNF) are highly convergent on brain function. Multi-modal neuroimaging studies demonstrate that in healthy women, variations in genes regulated by ovarian steroids can impact functional neurocircuitry and gene expression. NIMH IRP investigators studied women carrying a unique polymorphism that affects intracellular trafficking and secretion of BDNF. Results demonstrated an interaction between ovarian hormones and BDNF that affects working memory-related hippocampal function, only in the presence of the hormone estradiol. These findings have clinical relevance for understanding the neurobiological basis of individual differences in the cognitive and behavioral effects of ovarian steroids in women, and may provide a neurogenetic framework for understanding mental disorders related to reproductive hormones, as well as illnesses with sex differences in disease expression and course (PMID: 28416813). These gene-hormone interactions in reward-responsive and resting state neural circuits are currently being examined (NCT00001259, NCT00001322).

Objective 2.6: Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery.

Advancing PTSD treatment for women: NIMH-funded researchers examined PTSD in women by focusing on the role of hormones in the formation of safety memories after fear extinction, which may be impaired in PTSD patients. Fear extinction (replacing strong fear related responses and thoughts associated with reminders of ones' trauma with less intense and more adaptive responses) is an important aspect of effective treatments for PTSD, and estrogens have been observed to influence the process of fear extinction. Women using hormonal contraceptives had poorer extinction recall (ability to maintain fear extinction) compared with naturally cycling women, and this effect was modified with administration of estradiol, enhancing participants' ability to recall extinction memories (PMID: 23158459). This research has led to a new clinical trial to evaluate the impact of estradiol, when administered in conjunction with exposure-based therapy, on the fear extinction brain network, on the ability to recall adaptive extinction memories, and on PTSD symptoms among women (R61MH111907).

Objective 2.5: Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.

Objective 2.6: Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery.

Objective 2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women

NIMH-supported research has provided a wealth of knowledge about mental health of women and NIMH also continues to support efforts to translate clinical knowledge into interventions and services that could have a measurable impact on improving mental health outcomes. In doing so, NIMH funds research focused on risk factors, etiology, and course of mental disorders to inform prevention, early detection, and therapeutic interventions for women and girls. The following are examples of findings from NIMH-supported studies that illustrate the Institute's efforts in this area.

Neurohormones may contribute to sex differences in schizophrenia: In individuals

with schizophrenia, there have been reports of sex differences in brain structure and function, cognition, emotion processing, and course of illness. Overall, schizophrenia tends to be less severe in women than men; women on average have a later age of onset, briefer and less frequent acute episodes of illness, less severe negative symptoms, better premorbid functioning, and a better treatment response to antipsychotic medication versus men. Two sex-dependent neurohormones, oxytocin and arginine vasopressin, effect cognition and emotion processing, and are associated with sex differences in schizophrenia. NIMH-funded researchers measured oxytocin and arginine vasopressin, and examined their relationship with resting brain activity and clinical associations in individuals with schizophrenia. They found that compared to male participants, female participants had lower oxytocin levels that were associated with cerebral and neuronal functioning in the frontal and cerebellar cortices and in the thalamus, which was associated with poorer emotional processing. The researchers found that alterations in these hormone levels are associated with resting brain physiology in a sex-dependent manner in schizophrenia, and this effect may contribute to sex differences in symptom severity and course of illness (PMID: 30539769).

Objective 3.1: Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affective women throughout the lifespan.

Depression during the menopause transition: Perimenopausal depression (PMD) is accompanied by decreased quality of life (QOL), decreased social adjustment, and impaired role functioning comparable to that seen in depression and anxiety disorders occurring at other stages of a woman's life. Preliminary data from a NIMH IRP longitudinal study of women transitioning through menopause helped to clarify this relationship. Investigators examined whether the changes in negative life events and declines in QOL measures observed in cross-sectional studies were antecedents of PMD or reflect the effects of the presence of depression. Compared to women who remained asymptomatic, during the four years prior to menopause, women with PMD reported significantly lower life satisfaction but did not report significant differences in overall QOL, marital satisfaction, experience of personal loss, or negative life events. Data suggest that negative life events and decreased QOL/marital dissatisfaction do not uniformly precede the onset of PMD. Further, the relative absence of antecedent social or environmental events in PMD suggests a more specific role for hormonal events in the triggering of PMD (PMID: 28000061). NIMH IRP investigators have also collaborated with investigators at UNC-Chapel Hill, with results demonstrating the efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition under double-blind, randomized conditions (PMID: 29322164).

Objective 3.1: Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions oh conditions affecting women and girls throughout the lifespan.

PMDD symptoms are triggered by change in ovarian steroid levels: PMDD is characterized by distressing mood and behavioral symptoms during the luteal phase of the normal menstrual cycle that disappear within a few days after menses begin. However, no abnormalities of ovarian hormone levels have been consistently identified that distinguish women with PMDD from women who experience no mood or behavioral symptoms during the luteal phase. NIMH IRP investigators have found that changes in levels of estradiol/progesterone hormones, and not the steady state levels, were associated with the onset of PMDD symptoms (PMID: 28427285). NIMH IRP investigators also completed a pilot

study evaluating the effects of a neurosteroid (allopregnanolone) that effects neurotransmitter function. Changes in neurosteroid levels have been found to precipitate mood symptoms related to PMDD. Investigators found that endogenous increases in allopregnanolone were associated with decreased PMDD symptoms (PMID: 26272051).

Objective 3.1: Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions oh conditions affecting women and girls throughout the lifespan.

Impact of low-weight severity and menstrual status on bone in adolescent girls with anorexia nervosa (AN): AN impacts approximately 0.8 to 1.7% of female adolescents. To date, the impact of low-weight and menstrual factors on clinical outcomes has not been assessed in adolescent girls. In this study, NIMH-funded researchers studied 262 adolescent girls with AN and 90 healthy controls (ages 12-20). The researchers found that girls with AN, even with mild AN, have lower bone mineral density (BMD), which increased their risk for fractures. Further, in terms of pubertal factors, girls with AN who had amenorrhea had lower BMD scores than those without, suggesting that the absence of menstruation, regardless of duration, is a severity marker for bone health in AN (PMID: 28152193).

Objective 3.5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

Maternal anxiety predicts attentional bias towards threat in infancy: Attention bias to threat has been linked with maintenance of anxiety-related symptomatology. NIMH-funded researchers examined this relationship in early infancy, and its association with temperament and maternal anxiety. Few studies have examined early risk factors for anxiety, particularly in terms of the role of attention bias in impacting factors associated with early anxiety-related processes. The researchers found that while infants' attention bias to threat was not associated with infant temperament, it was associated with maternal anxiety. These results highlight the role of maternal psychopathological factors on risk for negative infant mental health outcomes (PMID: 28206795).

Objective 3.5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

Goal 4: Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research

NIMH strives to create and maintain alliances and partnerships within NIH, HHS, other federal agencies, and with external women's health stakeholders to advance mental health research focusing on women and girls. The NIMH Office of Disparities Research and Workforce Diversity (ODWD) encourages program staff, including those in the Women's Mental Health Program and the Center for Global Mental Health (CGMH), to create and maintain alliances and partnerships to maximize the domestic and global impact of women's health research. The ODWD and CGMH are new organizational units that emerged from the reorganization of the Office for Research on Disparities and Global Mental Health (ORDGMH) within the Institute.

In FYs 2017-2018, NIMH supported initiatives to integrate knowledge and opportunities for women's health research with HIV/AIDS, mental health disparities research, and global mental health. Pregnancy, maternal, and child health research is relevant to each of these areas. Examples of these efforts are described in the following section.

Global research hubs: During FYs 2017-2018, the NIMH ODWD continued to fund the Collaborative Hubs for International Research on Mental Health, a set of five hubs in South Asia, Sub-Saharan Africa, and Latin America which

aim to reduce the mental health treatment gap in low- and middle-income countries. These hubs conduct research on task sharing for the delivery of mental health services in low- and middle-income countries; support mental health research capacity building in countries in their regions; and, will utilize the network they form to answer mental health services questions across different health systems. For example, the South Asian Hub for Advocacy, Research, and Education (SHARE) has developed an innovative, effective, and sustainable approach for the delivery of an established psychological treatment that reduces the burden of depression in mothers in South Asia (PMID: 29349268). A second hub, African Focus on Interventions Research for Mental Health (AFFIRM), is testing the effectiveness of a task-sharing model to provide counselling for depressed pregnant women by non-specialist health workers in a primary care setting in South Africa (PMID: 28666425).

Objective 4.6: Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries.

Collaboration and committees: NIMH staff in the Women's Mental Health Program worked with several trans-HHS committees in FYs 2017-2018, including the Federal Working Group on Women and Trauma and the Federal Working Group on Perinatal Depression. They also collaborated with the HHS Secretary's Office on Women's Health on the *Workshop on Women's Mental Health Across the Life Course and through a Sex-Gender Lens* that was convened on March 7, 2018. In addition, NIMH program staff continued to serve on the following NIH and NIMH committees and workgroups: the NIH Sexual Gender Minority Research Coordinating Committee; the NIH Coordinating Council for Research on Women's Health; the Trans-NIH Sex as a Biological Variable Workgroup; and, the NIMH Diversity and Re-entry Supplements Committee. These efforts contribute to NIH, HHS, and Federal coordination of women's mental health research issues and related policy.

Objective 4.2: Establish new ventures and initiatives with a wide cross section of partners, including NIH institutes, centers, and offices, academia; other Federal agencies, international organizations, private foundations and industry.

Bench-to-Bedside program: NIMH intramural and extramural investigators continue to collaborate with the international research group, the Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium (PMID: 27866476, PMID: 28476427). The PACT has developed and launched a research study aimed at examining the interaction of genes and environment in predicting which women are at risk of postpartum depression (PPD), and why some women experience PPD and postpartum psychosis, and others do not.

Objective 4.2: Establish new ventures and initiatives with a wide cross-section of partners, including NIH institutes, centers, and offices; academia; other Federal agencies; international organizations; private foundations; and industry.

Outreach to advocacy groups: The NIMH Office of Science Policy, Planning, and Communications (OSPPC) in the NIMH Office of the Director maintains a robust outreach effort to national mental health advocacy groups. This includes outreach to several women's mental health-related groups that participate in the annual NIMH Alliance for Research Progress (Alliance) and NIMH Professional Coalition for Research Progress (Coalition) meetings. Women's mental health-related groups that are members of the NIMH Alliance or Coalition and have participated in FYs 2017-2018 meetings include: Postpartum Support International; Black Women's Health Imperative; the Eating Disorders Coalition for Research, Policy and Action; the National Eating Disorders Association; Academy for Eating Disorders; Families Empowered and Supporting Treatment of Eating Disorders;

National Organization for People of Color Against Suicide; and, Treatment and Research Advancements for Borderline Personality Disorders.

Objective 4.4: Create solid partnerships by engaging in scientific briefings and ad hoc meetings with policymakers, elected officials, and advocacy groups.

Goal 5: Develop and implement new communication and social networking technologies to increase understanding and appreciation of women's health and wellness research

NIMH has responded to numerous requests from NIH, HHS, and Congress, as well as many requests from investigators, for expert information on women's health research opportunities. In addition to responding to these requests, NIMH utilizes new media technologies (e.g., Twitter, Facebook, YouTube, RSS feeds) to disseminate research findings and cultivate relationships with advocacy groups. Highlights of these activities are provided below.

Envisioning a conceptual model of sex and gender differences in health and disease: In May 2018, the NIMH ODWD sponsored a webinar featuring Chloe Bird, Ph.D., from RAND Corporation, who is an expert in women's health and determinants of sex and gender differences in health and health care. Dr. Bird shared her conceptual framework for researchers to incorporate sex and gender differences influences into research design to improve the rigor and reproducibility of scientific findings.

Objective 5.1: Serve as a key informational resource for Federal and State agencies, elected representatives, the media, health and advocacy organizations, and the public on women's health research issues.

Twitter chats on PMDD, PMD, and PPD: In addition, the NIMH OSPPC and IRP researchers from the Behavioral Endocrinology Branch held Twitter chats on PMDD, PMD, and PPD.

Objective 5.1: Serve as a key informational resource for Federal and State agencies, elected representatives, the media, health and advocacy organizations, and the public on women's health research issues.

Raising awareness about mental disorders affecting women and families: NIMH collaborated with the *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD) and partnered with Delta Sigma Theta Sorority, Inc. to launch the *Mental Health Across the Lifespan* initiative, which sought to raise awareness about mental disorders (e.g., PPD), and issues (e.g., bullying) affecting women and families across the lifespan. The initiative, which sunset in FY17, resulted in the development of new NIH/HHS resources.

Objective 5.1: Serve as a key informational resource for Federal and State agencies, elected representatives, the media, health and advocacy organizations, and the public on women's health research issues.

Goal 6: Employ innovative strategies to build a well-trained diverse, and vigorous women's health research workforce

To coordinate all extramural research training opportunities, NIMH established a Training Team, which comprises NIMH staff with both scientific and research training expertise from each extramural division (i.e., Division of Neuroscience and Basic Behavioral Science (DNBBS), Division of Translational Research (DTR), Division of Services and Intervention Research (DSIR), and Division of AIDS Research (DAR)) and ODWD. In addition, NIMH continues to fund diversity and re-entry supplements; expand efforts to provide additional training to early stage investigators who have received diversity supplements; and, conduct outreach to potential new and early stage researchers.

Objective 6.1: Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH.

III. NIH Strategic Plan for Women's Health Research

The NIMH Women's Mental Health Program is located organizationally in ODWD within the Office of the Director. The Women's Mental Health Program was established to ensure coordination of NIMH-funded research on women's mental health and on sex and gender differences. Other functions include serving as an organizational hub for women's mental health science communication and working with the NIH Office of Research on Women's Health (ORWH) and other governmental and nongovernmental organizations interested in women's mental health research. The program chief of the Women's Mental Health Program chairs the NIMH Women's Mental Health Team and serves on several NIMH, NIH, and other federal working groups and committees (detailed under Goal 4), to contribute to NIH and federal collaboration on women's mental health research.

The Women's Mental Health Team serves as the hub for coordination of NIMH scientific activities related to women's mental health and sex and gender differences research. Members of the team include representatives from all four extramural research divisions, including: DNBBS, DTR, DSIR, and DAR. The team also includes representatives from the IRP, the Division of Extramural Activities (DEA), the Office of Clinical Research (OCR), and OSPPC. Team members work together across disciplines to convene workshops, prepare/review scientific reports, and develop funding opportunities related to women's mental health.

IV. Inclusion Efforts

NIMH follows several steps to ensure compliance with inclusion guidelines for both extramural and intramural research. Grant applications are evaluated for the appropriateness of proposed plans for meeting sex, gender, racial, and ethnic minority enrollment goals, and how the investigator will meet these goals. For NIH-defined Phase III clinical trials, enrollment goals are further assessed for proposed analyses of intervention effects among sex, gender, racial, and ethnic groups. For extramural clinical research studies, OCR monitors the entry of inclusion data, performs quality assurance tasks, prepares aggregate reports for the National Advisory Mental Health Council and the NIH ORWH, and provides up-to-date training on procedures for ensuring the accuracy of inclusion data.

All NIH IRP clinical research studies require investigators to provide plans for the appropriate inclusion of women and minorities and/or a justification whenever representation is limited or absent, as part of their NIH protocol reviews. NIMH IRP investigators recruit girls and women throughout the greater Washington, D.C. area through a steady direct mail presence for active studies. Intramural institutional review boards review intramural research protocols for compliance with inclusion guidelines and conduct annual monitoring. The NIH Clinical Center's Office of Protocol Services (OPS) maintains centralized systems for capturing participant data including sex, gender, ethnic, and racial status. OPS coordinates annual reporting of demographic participant data to the NIH Office of Extramural Research (OER) and the NIH ORWH.

V. IC STEM Efforts

Diversity in the scientific workforce enhances excellence, creativity, and innovation. Thus, increasing diversity, including the number of

women, in the scientific workforce remains an important goal for NIMH.

In FY 2018, NIMH, along with other NIH partners, issued two program announcements in the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative's Advanced Postdoctoral Career Transition Award to Promote Diversity (PAR-18-814, PAR-18-813). The purpose of these awards is to enhance and maintain a strong cohort of new, talented, NIH-supported, independent investigators from diverse backgrounds in BRAIN Initiative research areas. The awards facilitate a timely transition of outstanding postdoctoral researchers to independent, tenure-track or equivalent faculty positions. Eligibility is limited to applicants from groups underrepresented in the biomedical, clinical, behavioral, and social sciences, including women.

VI. Funding Initiatives, Workshops, and Conferences

Funding Initiatives

NIMH funding opportunities related to the health of sexual and gender minorities: To encourage more research on sexual and gender minority mental health, NIMH is participating in the following sets of NIH program announcements: The Health of Sexual and Gender Minority (SGM) Populations (reissued in 2018; PA-18-037, PA-18-054, PA-18-040, and PA-18-210); Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations (reissued in 2018; PA-17-713); and, Research on the Health of Transgender and Gender Nonconforming Populations (reissued in 2018; PA-18-728, PA-18-729).

Understanding and addressing the multi-level influences on uptake and adherence to HIV prevention strategies among adolescent girls and young women in sub-Saharan Africa: The NIMH DAR supported funding announcements, which called for research on factors that influence HIV prevention strategies for use among adolescent girls and young women in sub-Saharan Africa (RFA-MH-17-550, RFA-MH-17-555, and RFA-MH-17-560). These funding announcements were a joint effort with the *Eunice Kennedy Shriver* NICHD and Fogarty International Center (FIC). Eleven grants were funded.

Workshops and Conferences

Autism in girls and women: In September 2017, the NIMH ODWD, the NIMH Women's Mental Health Team, and the NIMH Office of Autism Research Coordination (OARC) hosted a scientific symposium to highlight recent research findings on sex specific characteristics of autism in girls and women with respect to screening, diagnosis, and treatment. The video of the symposium is available on the Interagency Autism Coordinating Committee website.

Addressing the mental health needs of immigrant, refugee, and asylum-seeking women in the U.S.: In November 2017, NIMH convened an expert workshop at the American Public Health Association Annual Meeting in Atlanta, Georgia, which highlighted the unique challenges that mental health providers face as they address and meet the mental health needs of immigrant, refugee, and asylum-seeking women. Participating researchers shared promising evidence-based practices and mental health interventions tailored for these women.

VII. Health Disparities

The NIMH ODWD is focused on understanding the causes and examining ways to address inequities in mental health care. Some racial and ethnic groups of women bear a greater burden of certain mental health issues. In addition, there are often barriers to mental health care for certain populations of women that may be related to racial and ethnic differences, sexual

orientation or gender identity, geographic location, socioeconomic status, or the presence of serious mental disorders. In addition to research findings described elsewhere in this report, an example of NIMH's efforts in this area is below.

Intimate partner violence (IPV), suicide ideation, and the mental health of young Asian American women: NIMH-sponsored researchers used data collected from Chinese, Korean, and Vietnamese American women (ages 18-35) who were screened for eligibility to participate in the development of an efficacy study of Asian American Women's Action for Resilience and Empowerment (AWARE). Researchers measured the prevalence of IPV, life suicidal ideation/intent, and childhood abuse, and examined the association between IPV and lifetime suicidal ideation/intent among study participants who completed the screening assessment. The results indicated that seven out of ten women in the sample experienced lifetime suicidal ideation/intent, and that psychological aggression was the most commonly reported form of IPV, followed by sexual coercion and history of physical and sexual partner violence. Results suggested that suicide prevention and intervention programs for Asian American women should not only address childhood abuse but also incorporate culturally adapted behavioral health approaches to identify and target physical and sexual partner violence (PMID: 30467448).

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National Institute on Minority Health and Health Disparities

I. Executive Summary

The mission of the National Institute on Minority Health and Health Disparities (NIMHD) is to lead scientific research to improve minority health and to reduce health disparities. To accomplish its mission, NIMHD plans, coordinates, reviews, and evaluates NIH minority health and health disparities research and activities; conducts and supports research on minority health and health disparities; promotes and supports the training of a diverse research workforce; translates and disseminates research information; and fosters innovative collaborations and partnerships.

Minority health refers to the distinctive health characteristics and attributes of a racial and/or ethnic group who is socially disadvantaged and/or subject to potential discriminatory acts. Minority health research is the scientific investigation of distinctive health characteristics and attributes of minority racial and/or ethnic groups who are usually underrepresented in biomedical research to understand population health outcomes. Racial and ethnic minority populations included in this definition are defined by the Office of Management and Budget Directive 15 (American Indian or Alaska Native, African American or Black, Asian, Native Hawaiian or Other Pacific Islander, Hispanic, or Latino).

A health disparity is defined as a health difference that adversely affects disadvantaged populations, based on one or more specified health outcomes:

- Higher incidence and/or prevalence of disease and/or disorders;
- Premature and/or excessive mortality in diseases where populations differ;
- Greater burden of disease demonstrated with metrics such as disability-adjusted life years
- Poorer daily functioning or reduced quality of life using observed or self-reported measures, or
- Worse behavioral risk factors and/or biomarkers associated with clinical outcomes

Health disparities research is a multi-disciplinary field of study devoted to gaining greater scientific knowledge about the influence of health determinants, understanding the role of different pathways leading to disparities, and determining how findings translate into interventions to reduce health disparities. Health disparity populations include OMB defined racial and ethnic minorities, rural residents, individuals of less privileged socioeconomic status (SES), and sexual and gender minorities (SGM).

This report presents select examples of NIMHD-funded minority health and health disparities research and research findings to address women's health. It also highlights some of the diseases or conditions that disproportionately impact women from different racial and ethnic populations, and research efforts that are taking place or necessary to improve women's health or reduce women's health disparities. Breast and cervical cancer are among the leading cancers affecting some racial and ethnic minority populations. African American women have the highest rate of mortality from breast cancer, while Hispanic or Latina women have the highest incidence of cervical cancer. Research and research-related activities supported by NIMHD are examining predictors and factors that contribute to triple-negative breast cancer (TNBC) diagnosis and survival and exploring the potential

of precision medicine in addressing the biology of TNBC. The human papillomavirus (HPV) vaccine has shown potential to prevent cervical cancer. NIMHD supports research to increase awareness about HPV vaccination and to understand the disparities in HPV vaccination among Hispanic or Latina women.

African Americans have a higher rate of new HIV diagnoses, while the highest rate of undiagnosed HIV infection and new cases of HIV are seen among African American youth. Gender differences in HIV risk factors and behaviors persists. One NIMHD-funded study aimed at increasing HIV testing and raising awareness about one's HIV status, analyzed data from a HIV evidenced-based safer sex behavioral intervention to identify any gender differences in attitudes, knowledge, and risk behaviors among young African Americans towards HIV testing. Men reported a higher number of sexual partners in the past three months and more negative HIV testing attitudes compared to women. Lower HIV testing among men was associated with negative attitudes about HIV testing, however, this was not a predictor of HIV testing among women. Older age was significantly associated with higher past HIV testing among women but not among men. Understanding gender differences to predict HIV testing can provide important information for prevention and management to increase rates of HIV testing among young African American adults.

II. Accomplishments and Activities

Amigas Latinas Motivando el Alma (ALMA): A Randomized Control Trial of an Intervention to Reduce Mental Health Disparities in Mexican Immigrant Women

Studies suggest that 30 percent of Hispanic or Latina immigrants are living with clinically significant depressive and anxiety symptoms. Hispanic or Latina immigrants are particularly vulnerable to depression and anxiety due to the many social and economic stressors they face, including high levels of poverty, low levels of education, family obligations, language barriers, and social isolation. They are also less likely to access and utilize quality mental health care, due to lack of health insurance, few culturally and linguistically competent providers, and stigma associated with seeking mental health care. The ALMA intervention is a randomized control trial (RCT) of an eight-week intervention offered in a group format to teach women coping strategies and enhance their social ties and social support to prevent and reduce their depression and anxiety. The RCT measured recruitment, retention, fidelity, and participant satisfaction through observations and in-depth interviews, as well measured efficacy by comparing changes in women's depressive and anxiety symptoms. [1R01MD012230-01]

Biopsychosocial Mechanisms Linking Gender Minority Stress to HIV Comorbidities

Despite a high prevalence of HIV among some sexual and gender minority women, very little is known about HIV comorbid conditions among this population. While there is a high rate of HIV prevalence among transgender women, some research also suggests a higher prevalence of HIV among lesbian and bisexual women when risk associated factors such as having multiple sexual partners and substance use are present. This study enrolled 200 participants in a 24-month, mixed-methods, prospective intervention to measure stigma, biomarkers of chronic stress, sex hormones, mental health, and cardiovascular disease risk. The specific aims of the project are to quantify the longitudinal relationship of stigma to chronic stress biomarkers; identify pathways linking chronic stress biomarkers to HIV comorbidities;

and examine the role of chronic stress in pathways linking stigma, sex hormones, and HIV comorbidities. [1R01MD013498-01]

Breast Cancer Screening: Priorities and Attitudes of Diverse Women Under 50

Breast cancer screening mammography guidelines for women aged 40-49 years may be controversial. Conflicting recommendations focus on when to initiate screening, how often to be screened and what sources to trust. Women from diverse racial and ethnic groups and those with limited health literacy, are particularly vulnerable to misunderstanding screening recommendations. This project compared the intersections and differences between how Hispanic or Latina, African American or Black, and White women consider the benefits and harms associated with breast cancer screening mammography. The goal is to create decision support tools for Hispanic or Latina, African American or Black, and White women under age 50 with varying levels of health literacy who may be considering breast cancer screening. [1K99MD011485-01A1]

Epigenetic Mechanisms of Prenatal Environmental Stressors and Off-Spring Obesity Risk

Childhood obesity is a major public health problem with widening racial and ethnic gaps and health consequences across the life course. Racial inequalities in childhood obesity occur during early infancy, signifying the prenatal period as a potential window during which differences in environmental exposures may promote early disparities. Critical research gaps exist regarding the effects of exposure to adverse prenatal social environments and air pollution on offspring obesity risk. This study will investigate whether prenatal neighborhood psychosocial stressors and air pollution exposure are associated with offspring risk of obesity due to genetic modifications. [1K99MD012808-01]

Influence of Prenatal Psychosocial Stressors on Maternal and Fetal Circulating miRNAs

The environment in which a developing fetus grows can have profound impact on their health outcomes throughout life. Epigenetic mechanisms are critical mediators of the environment's impact on children's health. MicroRNA (miRNA) represent one epigenetic mechanism that controls the stability of messenger RNA (mRNA) and the translation of proteins. Psychosocial variables also influence the pattern of expression of maternal and fetal miRNA. This study used state-of-the-art technologies to characterize the full repertoire of miRNA in the Maternal and Developmental Risks from Environmental and Social Stressors (MADRES) pregnancy cohort, which focuses on low-income Hispanic women in Los Angeles county. The main aims of the proposal are to: 1) examine how maternal psychosocial stress impacts the pattern of expression of miRNA in maternal blood during pregnancy; 2) delineate how maternal circulating miRNA impact newborn health outcomes including birth weight and small-for-gestational birth; and 3) examine the relationship between patterns of expression of miRNA in the placental tissue and in cord blood to those in maternal serum. [1R01MD011698-01]

Linking Pre- and Post-natal Psychosocial Determinants, DNA Methylation, and Early Developmental Health Disparities

Despite improvements in access and quality of health care, children from socioeconomically disadvantaged and/or racial and ethnic minority families experience elevated risks for impaired cognitive and social-emotional development. Maternal adversity and protective factors (i.e., maternal psychosocial experience) across the life-course contribute to offspring cognitive and social-emotional developmental disparities

through genes DNA methylation (DNAm) along multiple biologic pathways. This study combines retrospective assessment and prospective data collection on 375 mother-infant dyads enrolled in five study visits spanning pregnancy through 18 months postnatal. The goals of this study are to determine the association between the life-course maternal psychosocial experience and the change in infant DNAm during the first year of life; characterize the association between postnatal maternal psychosocial experiences in the infant's first year of life and infant DNAm at one year; and determine the impact of DNAm at two time points (1 month and 12 months) of infant development across the first 18 months. [1R21MD013652-01]

Maternal Exposure to Vicarious Structural Racism and Newborn Health Disparities in Michigan: The Flint Water Crisis

The effects of structural racism negatively affect the health of mothers and their offspring via stress-related mechanisms. Residents of Flint, Michigan, a predominantly African American community, were directly harmed by exposure to lead-contaminated water, also known as the Flint Water Crisis (FWC). Some argue FWC is the result of structural racism. The proposed transdisciplinary, mixed- methods research examined whether there were negative effects on the well-being and the health of infants of African American women in Michigan communities outside of Flint, who witnessed the structural racism of the FWC that African American women in Flint experienced. By identifying multi-level sources of resilience to vicarious structural racism, the proposed study will provide information necessary for the development of evidence-based policies and interventions to reduce the harmful intergenerational effects of vicarious structural racism on the health of African Americans in the U.S. [1R21MD012683-01]

Multilevel Mediation Analysis to explore Racial Disparities in Breast Cancer Recurrence and Survival using CDC Special Studies

Breast cancer is the most common cancer and the second leading cause of cancer death among American women of all races. Despite overall improvement in survival rates, and decreases in recurrence of breast cancer, significant differences between White and African American or Black women remain. Previous studies have found that more advanced and aggressive tumors and less than optimal treatment may explain the higher recurrence and lower survival rates for African American or Black women compared to White women. This study correlated individual level information such as treatment history and tumor characteristics, with provider characteristics, and physical and social environmental information. The study uses CDC-funded Special Studies data, including Patterns of Care study, Enhancing Cancer Registry Data for Comparative Effectiveness Research (CER), and the Patient Centered Outcomes Research (PCOR), to examine the determinants of racial disparities in breast cancer survival and recurrence using a novel Multilevel Mediation Analysis. This study will provide knowledge that could significantly contribute to efforts by public health officials and health care agencies to develop efficient intervention strategies to reduce the disparities. [1R15MD012387-01]

Pathways to Cardiovascular Disease Prevention and Impact of Specialty Referral in Underrepresented Racial and Ethnic Minorities with HIV

There is an urgent need to determine pathways to cardiovascular disease (CVD) prevention for underrepresented racial and ethnic minorities with HIV and elevated cardiovascular risk. This project will retrospectively analyze patient-level data from electronic health records from institutions in

the U.S. Southeast "HIV-belt" and "Heart Attack belt," using PCORnet's Common Data Model. The study aims to measure the association between cardiology referral and CVD outcomes in underrepresented racial and ethnic minorities with HIV; identify the individual and health system-level factors that impact CVD outcomes for underrepresented racial and ethnic minorities, and ultimately develop a qualitative framework for an intervention to improve CVD outcomes for people living with HIV (PLWH). The project's goal is to generate evidence-based recommendations for the management of CVD risk for PLWH to inform clinical care guidelines and health system interventions. [1R01MD013493-01]

Pharmaco-epigenomics of Recurrent Preterm Birth in African American Women

African American women are twice as likely as women of other races to deliver preterm. A progestin known as 17-alpha hydroxyprogesterone caproate (17P) prevents recurrent spontaneous preterm births (SPBs) in some women, but is less effective for African American, compared to White women. The objective of this research is to quantify the role of nitric oxide pathways in the functional changes associated with recurrent spontaneous preterm term birth (SPTB) among African American women receiving 17P. The goal is to identify African American women at risk for 17P non-response and provide them with alternate therapies to prevent SPBs. [1R01MD011609-01]

Secondary Analysis to Identify HPV Vaccination Disparities across Hispanic Subpopulations in the United States

Hispanic or Latina women have the highest cervical cancer incidence rate of any racial and ethnic group in the country. This study will analyze data from the 2012-2016 National Immunization Survey-Teen (NIS-Teen) to identify existing HPV vaccination disparities across Hispanic or Latina subpopulations. The NIS-Teen is considered the gold standard of U.S. vaccination data, and analyses will include a large, national sample of Hispanic or Latina adolescents. Specifically, this project aims to determine how Hispanic or Latina subgroups differ in terms of current HPV vaccine coverage among adolescents; identify multi-level correlation of HPV vaccine coverage and potential barriers to parents vaccinating their children against HPV. The study seeks to understand how HPV vaccination outcomes differ across Hispanic or Latina subpopulations that could inform the development of strategies to increase vaccine coverage among this population. [1R21MD012800-01]

Vaginal Microbiome and Racial Disparity in Preterm Delivery

Preterm births have been associated with the presence of ascending infections. Understanding the barriers to ascending infections include the study of the production of lactic acids and the susceptibility following the introduction of organisms that can cause disease. The Pregnancy, Infection and Nutrition (PIN) study is a landmark longitudinal investigation of the causes of prematurity among African American women and Whites. This study explores the factors that create physiological barriers in a diverse cohort of women enrolled in the PIN. Specifically the study will: 1) examine the associations of the vaginal microbiome with spontaneous preterm birth (sPTB), and explore whether these associations differ by maternal race; 2) examine the influence of innate sPTB risk factors, such as maternal polymorphisms in innate immunity genes and maternal psychosocial stress and depression, on vaginal microbiome profiles overall and stratified by race; and, 3) examine the influence of external risk factors for sPTB on vaginal microbiome profiles, such as maternal nutritional patterns, maternal smoking, and other health behavior. [1R01MD11504-01]

Understanding Socioeconomic Disparities in Perinatal Risk: The Role of Epigenetic and Transcriptional Regulation in the Placenta

Evidence suggest a strong association between socioeconomic status (SES) and children's health outcomes, however how it influences biological processes such as brain maturation is still unknown. This study hypothesized that women in a lower SES will show epigenetic and transcriptional patterns indicative of lower fetal tolerance, greater immune activation, and slower organ maturation. The study recruited an economically diverse sample of 700 women during pregnancy and characterized the multiple dimensions of their life course socioeconomic conditions to study associations with gene regulation. Data for gene regulation analyses was gathered from the placenta collected at delivery, to later assay patterns of DNA methylation (DNAm), and expression of microRNA (miRNA) and messenger RNA (mRNA). Analyses will explore the connections between features of neighborhoods (economic deprivation, violent crime, residential segregation, social capital), families (job instability, financial duress, relationship qualities), and individuals (depressive symptoms, pregnancy anxiety, lifestyle factors), and characterize the strength and nature of their associations with dimensions of placental gene regulation, i.e., DNAm, miRNA, and mRNA. [1R01MD011749-01]

We Are Here Now -A Multi-level, Multi-component Sexual and Reproductive Health Intervention for American Indian Youth

American Indian (AI) communities are disproportionately affected by sexual and reproductive poor health outcomes compared to other populations. This study titled: "Nen ŨnkUmbi/EdaHiYedo" or "We are Here Now," utilizes a culturally tailored ecological intervention to address sexual and reproductive health (SRH) issues and prevent risky sexual behaviors among AI youth that may lead to sexually transmitted infections (STIs), HIV, and teen pregnancy. The primary outcome of the project is to increase condom use. In addition, the study aims to delay onset of sexual intercourse, reduce the number and frequency of sex partners, promote consistent use of birth control and avoidance of alcohol and/or drug use. Researchers will also focus on increasing parent/legal guardian-child communication about SRH topics, increasing understanding of cultural values related to traditional AI beliefs, and increasing use of SRH services. "We are Here Now" recruited 456 AI youth ages 15 to 18 years old and their parent/legal guardian. Participants worked collaboratively with the research team to refine and tailor the components of the study to test the efficacy of We are Here Now in five high schools in Fort Peck, MT. [1R01MD012761-01]

Why Adolescent Latinas Attempt Suicide More than Other Females

Adolescent Hispanics or Latinas suicide attempt rates are much higher than any other group of American adolescents. Little is known about the reasons for Hispanics or Latinas' propensity to suicidal behavior. This study examines the influence of family dynamics on suicidal behavior among Hispanics or Latinas and contrast the reports of Hispanics or Latinas with White, and African American or Black women using in-depth interviews with the girls and their primary female caregiver. Twenty adolescent-caregiver dyads in racial and ethnic groups were recruited to explore the psychological vulnerability of teenage suicide attempters in three racial and ethnic groups and the life contexts that influence suicidal behaviors; and describe the life histories and trajectories of family dynamics that influenced the attempt for each racial and ethnic group. [1R21MD012338-01]

III. Other Sub-headings

NIH Strategic Plan for Women's Health Research

NIMHD supports the implementation of the NIH Strategic Plan for Women's Health Research through its programs and activities including collaborations and partnerships with other NIH Institutes and Centers. In addition, NIMHD provides staff representation to the Coordinating Committee on Research on Women's Health led by the Office of Research on Women's Health. Below are examples of projects and research findings from NIMHD-funded research that align with goals and objectives of the strategic plan.

Accelerated Placental Aging in Early onset Preeclampsia Pregnancies Identified by DNA Methylation

Adverse pregnancy outcomes including preeclampsia remains a major public health concern. The goal of this project is to determine if DNA changes that occur in the placenta can predict gestational age during pregnancy. A predictive tool to measure gestational age of the placenta was created using DNA regions. DNA data revealed that early onset of preeclampsia is associated with acceleration of placental age. These findings reveal that DNA can predict gestational age during pregnancy, which may provide insight into mechanisms to mitigate and/or prevent pregnancy disorders (Mayne et al., 2017) [Goal 3, Objectives 3.3, 3.4, 3.6]. PMID: 27894195

A Mobile Framework to Measure Ejection Fraction by Automated Non-invasive Analysis of Cardiac Signals

Heart disease is the leading cause of death among women and men in the U.S., although African American women are 30 percent more likely to die from heart disease compared to White women. Decreased ejection fraction is a marker of left ventricular systolic dysfunction, the most common type of heart failure. This project aims to develop a novel mobile framework to measure left ventricular ejection fraction as a marker for systolic dysfunction using automated non-invasive analysis of cardiac signals. Researchers will use a specially engineered sensor system combined with the novel algorithm technology accessible via a smartphone or tablet, to provide a low-cost and portable tool for providers in community settings to diagnose systolic dysfunction in underserved populations. [2R44MD009556-03] [Goal 2, Objectives 2.5]

Improving Hospital Quality to Reduce Disparities in Severe Maternal Morbidity and Mortality

Significant racial and ethnic disparities in maternal morbidity and mortality exist in the United States. African American or Black women are three to four times more likely to die a pregnancy-related death compared to White women. This project examined how improvements in hospital quality, including implementing standard protocols, checklists, simulation trainings, coordinated care and staff trainings addressing health disparities can improve patient outcomes, by lowering mortality and morbidity rates. Implementing quality initiatives aimed at standardizing delivery of healthcare, will likely improve care at all hospitals and especially the lowest performing hospitals, which serve a disproportionate number of racial and ethnic minority women (Howell & Zeitlin, 2017) [Goal 3, Objectives 3.3, 3.4, 3.9]. PMID: 28735811

Older African American and White Breast Cancer Survivors Perspectives on Physical Activity

This project evaluated the perspective of older breast cancer survivors, from diverse racial and socioeconomic backgrounds, toward physical activity to inform the design of a physical activity program that fosters acceptability. Project findings reveal that among older breast cancer survivors,

physical activity preferences are shaped by cancer experience, rather than by race and socioeconomic status. Physical activity programs should focus on addressing cancer treatment-related concerns and developing physical activity programs that are acceptable to older breast cancer survivors to reduce their cancer disparities (Owusu et al., 2018). [Goal 5, Objectives 5.4, 5.5] PMID: 29306608

Promoting Optimal Native Outcomes by Understanding Women's Stress Experiences

Stress is associated with various chronic diseases and mental illness. Current scales to measure women's stress do not adequately capture daily stressors of low-income rural women. The Promote Optimal Native Outcomes (PONO) project examined psychosocial stressors among women living in a rural Hawaii community with a large Native Hawaiian and Other Pacific Islander population. Specifically, the study explored the attitudes, beliefs and feelings of women regarding stressors, perceived intensity of stressors, and the effect on women. Seven stressor themes were identified: *1) intimate relationships within the context of lack of partner assistance, different values, and gender stereotype; 2) family and home life as it relates to feeling like an outsider and lack of respect; 3) childrearing pertaining to finding quality and affordable childcare, and conflicting discipline styles; 4) time for self and the feeling that duties are never-ending and feeling too tired to relax; 5) neighborhood environment and concerns about neighborhood safety or not feeling part of the community; 6) workplace issues such as workload and transportation obstacles; and 7) finances in terms of making ends meeting and having arguments about money.* The goal is to use the findings of this study to develop a culturally and community-appropriate scale to assess perceived stress, that could help to inform the development of innovative interventions for this population (Okihiro et al., 2017) [Goal 3, Objective 3.9] PMID: 27995538

Reducing Cervical Cancer Health Disparities among African American Women: An mHealth Approach to Improving Prevention and Treatment Outcomes

African American women in the United States continue to be disproportionately burdened by cervical cancer. The incidence rate is 41 percent higher among African American women than White women, who are also twice as likely to die from the disease and experience a lower 5-year survival rate. This project aims to increase HPV vaccination coverage, promote safer sexual practices, increase cervical cytology, and improve follow-up clinical adherence to abnormal Pap results among African American women using mobile technology. Users received three types of texts: reminders for screenings and follow-ups, educational, and supportive messages, accompanied by web-based video components with scripted vignettes, unscripted peer narratives, and educational instruction. The usability of the interventions will focus on efficiency, accuracy, and subjective satisfaction [Goal 5, Objective 5.5] [1R43MD011581-01].

SLC9B1 Methylation Predicts Fetal Intolerance of Labor

Fetal intolerance of labor is a common complication during caesarean section deliveries in pregnant women. Fetal intolerance during labor was investigated in women using novel methods to identify DNA regions associated with fetal intolerance. Four DNA regions in gene SLC9B1, predicted fetal intolerance of labor, consistent with previous findings by other researchers. This novel method can accurately predict fetal intolerance of labor between 24-32 weeks of pregnancy. The identification of pregnant women at elevated risk for fetal intolerance of labor may allow for the development of targeted treatments or management plans to reduce and/or prevent fetal intolerances of labor in women (Knight et al., 2018) [Goal 3, Objective 3.3]. PMID: 29235940

IV. Inclusion

Two NIMHD staff members represented the Institute on the NIH Inclusion Across the Lifespan Planning Committee to provide expert input and support activities associated with reviewing, revising and expanding the NIH policy on inclusion of women, minorities, and children. In accordance with the 21st Century Cures Act, the revised policy, the NIH Policy on the Inclusion of Individuals Across the Lifespan, was broadened to include research participants of all ages in clinical research studies.

V. NIMHD STEM Efforts

In FY 2017 and 2018, NIMHD provided fellowship awards to women from racial and ethnic minority populations in the early stages of their research careers, through the Ruth Kirschstein Predoctoral Individual National Research Service Award. The program supports mentored research training during the dissertation research phase for promising predoctoral students seeking to become productive, independent research scientists. Examples of the women's health research conducted by candidates receiving NIMHD-funded fellowship awards included:

Developing Evidenced-Based Health Messages to Increase HIV Testing among African-American Young Adult Women

African American young adults have the highest rates of new and undiagnosed HIV infection in the United States. Over half of new HIV infections among young adults result from individuals uninformed of their positive HIV status. Limited research has examined mechanisms to increase HIV testing among African American women. The specific aims of this proposal are to: 1) identify barriers and facilitators related to HIV testing among young African American women, and 2) develop and test evidence-based health messages to increase HIV testing among this population. The project aims to reduce rates of HIV transmission that happen inadvertently by making more HIV positive young adults aware of their status; reduce the likelihood of transmission by linking HIV positive individuals to healthcare; and promote HIV testing as a HIV reduction strategy among young adults and African Americans. [1F31MD011278-01]

Evaluating Racial & Geospatial Disparities and Factors in Triple-Negative Breast Cancer

The overarching goal of this study is to advance the field of population-based research in breast cancer disparities through innovative statistical techniques. The objective is to address racial and geospatial disparities in triple-negative breast cancer diagnosis and survival to examine potential predictors of both diagnosis and survival. Descriptive epidemiologic analysis allowed for comparison in incidence of triple-negative breast cancer across racial and age groups at multiple geographic levels. Exploratory spatial data analysis will be used to create descriptive maps and evaluate patterns of geospatial clustering and underlying community characteristics while multilevel modeling with latent variables will be utilized to explore predictors of triple-negative breast cancer diagnosis and survival. [1F31MD012752-01]

VI. Funding Initiatives, Workshops, and Conferences

NIMHD develops funding initiatives to support research that aligns with its mission to improve minority health and/or reduce health disparities which may include research on women's health or sex and gender influences. There were no specific funding opportunity announcements in FY 2017 or FY 2018 that were exclusive to

research on women's health or sex and gender influences. Below is an overview of a scientific conference grant that NIMHD funded during the reporting period related to triple-negative breast cancer:

First International Triple Negative Breast Cancer Conference: Illuminating Actionable Biology

NIMHD provided conference grant funding for the "First International Triple Negative Breast Cancer Conference: Illuminating Actionable Biology," held on September 18-20, 2017 in Atlanta, Georgia. The long-term objective of the conference was to help realize the promises of precision medicine for people with triple-negative breast cancer (TNBC). Patients with TNBC are more likely to be of African ancestry, and more likely to relapse or have the cancer spread within five years of diagnosis. The aims of the conference were to present the latest research on actionable biology in TNBC; provide a forum for labs across the world to present their latest research findings on TNBC; and host an engaging, innovative and participant-led "Talk It and Chalk It" brainstorming session to generate new research ideas. The conference included domestic and international speakers and diverse participants such as TNBC survivors, leading breast cancer researchers, medical students and fellows, clinicians, translational researchers, epidemiologists, and biostatisticians. Areas for future research and action to address TNBC through precision medicine that emerged from the conference included: 1) integration of classical pathology and the next generation of "omics" technologies (genomics, proteomic, transcriptomic, metabolomic); 2) increasing access to quality healthcare; 3) improving healthcare delivery systems; 4) clinical trials exploring promising novel targeted treatments; and 5) elucidating and actively addressing potentially modifiable risk factors through education and community engagement.

Health Disparities

The projects and research findings highlighted throughout this report represent examples of NIMHD-funded minority health or health disparities research related to women's health. Additional examples include:

Effects of Marriage Recognition on Substance Abuse and Health for Sexual Minority Women

Sexual minority women (SMW) which includes lesbian or bisexual women, experience substantial health disparities, including significantly higher rates of hazardous drinking, depression, and poor self-reported health compared to heterosexual women. This project explored minority stress, intersectionality, social-ecological frameworks and mixed-methods research designs to examine the relationships between psychosocial factors associated policies and marriage recognition among SMW and three health outcomes: hazardous drinking, depression and general health. Using a sample of 32 diverse SMW this project developed new measures to assess factors that underlie the impact of marriage recognition, to later assess psychometric properties of these new measures among approximately 500-600 SMW, using item analysis and confirmatory factor analysis. Finally, this project will examine the predictive value of these novel SMW-specific measures on hazardous drinking, depression and self-reported health, with specific focus on racial and ethnic differences. [5R03MD011481-02]

Healthy Lifestyle Intervention for High-Risk Minority Pregnant Women

Evidence suggest that pregnant racial and ethnic minority women experience significant anxiety and emotional distress during pregnancy. This randomized controlled trial (RCT) evaluated the efficacy of an intervention designed to decrease health disparities in pregnant, emotionally distressed racial and ethnic minority

women. Through six sessions, the RCT tested cognitive behavioral skills building prenatal care intervention, known as COPE-P, at sites in New York and Ohio. Specifically, the project evaluated the short and long-term efficacy of the COPE-P program to improve healthy lifestyle behaviors (nutrition and exercise), psychosocial health, and birth and post-natal outcomes in pregnant emotionally distressed women. In addition, the project examined the role of cognitive beliefs and perceived difficulty in leading a healthy lifestyle in mediating the effects of the COPE-P program on healthy lifestyle behaviors and psychological symptoms in racial and ethnic minority pregnant women. [1R01MD012770-01A1]

Social Adversities, Epigenetics, and the Obesity Epidemic

Over the last three decades racial and ethnic disparities in obesity rates have widen. Social adversity is a risk for obesity in youth and a potent predictor of negative social, educational, vocational, and health outcomes later in life. This research intends to learn how to positively influence health trajectories, modify disease risk in racial and ethnic minorities, and reduce health disparities, by assessing the impact of mothers' prenatal stress on measures of DNA methylation in human umbilical vein endothelial cells (HUVEC). The project focuses on predicting growth trajectories and measures of obesity at 24 months of age; and examining moderating factors, including maternal Adverse Childhood Experiences (ACE), maternal social supports, maternal postnatal psychosocial distress, postnatal offspring ACE, genetic variants, and relevant confounding variables. The mediating role of inflammatory markers will also be explored, and saliva DNA specimens will be collected on the full cohort at 24-months and on 50 children at birth, allowing for tests of comparability of DNA methylation between HUVECs and saliva, and the stability of markers over time. [1R01MD011746-01]

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National Institute of Neurological Disorders and Stroke

I. Executive Summary

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. This burden is borne by every age group, every segment of society, and people all over the world. Most disorders of the nervous system affect men and women equally, but some have specific health implications for women or disproportionately affect women. NINDS supports basic, translational, and clinical research to understand sex differences in neurological disorders and in normal development and function of the nervous system. In addition, NINDS supports efforts to increase the inclusion of women in research and their representation in the biomedical research workforce.

Much of the research supported by NINDS focuses on how sex-specific mechanisms influence both normal neurological functioning as well as the burden or manifestation of various disorders. In some conditions, such as chronic pain, investigators are trying to understand the reasons for the higher burden observed among women and how sex hormones may play a role in disease mechanisms. Diseases associated with aging, such as stroke and AD, are associated with higher burden in women due in part to the longer life expectancy among women, and researchers are working to understand how sex interacts with age and other biological and social factors to influence risk and outcomes of the disease. Other conditions that have both social and biological differences related to sex include spinal cord and traumatic brain injury, and investigators are working to understand factors that lead to different rates and symptoms of injury as well as how sex influences injury recovery and outcomes. Women with epilepsy face special problems during pregnancy due to potential effects of anti-seizure medications on the fetus, and during phases of the menstrual cycle. Women with epilepsy also experience lower birth rates than women without epilepsy, and NINDS-funded investigators are working to understand underlying factors that lead to these differences. NINDS also supports research relevant to women in its rare disease portfolio. Researchers are exploring mechanisms and potential therapeutic targets for Rett syndrome, which is only observed in females because it is caused by a mutation on the X chromosome, and boys with the mutation do not have another X chromosome with a normal version of the mutated gene. Finally, NINDS supports research to understand disparities, most notably in stroke, among racial and ethnic minority populations and some of this work also explores differences by sex and how these relate to race and ethnicity to influence risk and outcomes. Examples of research in these areas are described in the following section.

II. Accomplishments and Activities

Basic Neuroscience

Differential Effects of Past Experiences on Female and Male Nervous Systems. Female and male brains show differences across the animal kingdom, from molecular mechanisms to anatomical features. Investigators are exploring how past experiences can regulate sexually dimorphic anatomy, gene expression and function in the nervous system (NS096863). Earlier reports have indicated that early-life stress can

have long-lasting effects in vertebrates, including both behavioral effects and some molecular effects, but it has been difficult to correlate specific molecular changes to behavior outcomes. This recent study shows that starvation stress during juvenile stages results in lasting circuit and behavioral effects in adult male, but not hermaphrodite, nematodes by affecting serotonin levels during sexual maturation. The researchers discovered that serotonin acts as a cue for male-specific synaptic pruning. The results revealed how temporary early-life stress can lead to lasting changes to the nervous system and how stress can intersect with sexual maturation, resulting in different effects between females and males (PMID: 30150774, Bayer and Hobert, 2018).

Chronic Pain

Sex-Specific Mechanisms in Chronic Pain. NINDS-funded investigators are exploring cellular and molecular mechanisms involved in chronic pain in female and male rats to understand the marked sexual dimorphism that exists for many chronic pain syndromes (e.g., migraine, endometriosis, and microvascular [syndrome X]) (NS084545). Previous findings from this group showed that an interaction between estrogen and a novel ryanodine receptor in female rats increases the susceptibility of sensory nerve cell activation, such that a significantly smaller stimulus can activate nerve cells. They demonstrated that estrogen plays an important role in the regulation of nerve cell activation, which contributes to the mechanisms underlying sexual differences in chronic pain. They further identified a molecular pathway by which the activation of ryanodine receptors is regulated by estrogen receptor α in female rats, that leads to changes in sensory neurons and could potentially contribute to hypersensitivity to pain stimuli. Outcomes from this study contribute to our understanding of sex differences in chronic pain syndromes (PMID: 28115480, Khomula at al., 2017).

Stroke

Role of pregnancy and child births on stroke in females. Epidemiologic evidence suggests that pregnancy increases later stroke risk. This study examined the role of child births on stroke outcome. Mice with multiple births were more sedentary, had higher body weight and lipid levels, and had increased risks of stroke compared to mice that had never been pregnant. However, mice with multiple births demonstrated decreased inflammatory response, smaller regions of damaged brain tissue, and better behavioral recovery. These results show that reproductive experience has complex effects on stroke and neurovascular health. This study will contribute to our understanding of the life-long patterning of stroke risk in women (PMID: 28645895, Ritzel et al., 2017).

Sex Differences in Moyamoya Syndrome (MMS). MMS is an unexplained change in the cerebrovasculature that leads to the formation of aberrant new blood vessels and subsequent stroke. The female-to-male ratio of MMS prevalence is about 2:1 and investigators are working to improve our understanding of the pathophysiology of MMS (NS097763). In this study, investigators utilized innovative brain imaging methods to test fundamental hypotheses about the relationship between organ function, mechanisms regulating blood flow, and stroke onset. They used X-ray and noninvasive MRI to examine blood flow and established a new classification system for patients with MMS. This system may provide a measure of hemodynamic severity in MMS, which could be useful for making clinical decisions and evaluating patients' responses to treatments (PMID: 26967789, Ladner et al., 2017).

Sex and Age Differences in Adipose Immune Cells and Risks of Stroke. The risks of stroke and the prevalence of cardiovascular disease have increased among middle-aged women in the U.S. Previous studies have shown that abdominal obesity, which is often found to be more

common in women, may contribute to a higher risk for ischemic stroke in women than in men. Researchers observed that middle-aged female mice have elevated pro-inflammatory T cells and decreased anti-inflammatory regulatory T cells in fat tissue, which may promote an enhanced systemic pro-inflammatory environment and lead to a greater risk for stroke in middle-aged females (NS098628) (PMID: 29670627, Ahnstedt et al., 2018).

Alzheimer's Disease (AD)

Interaction of Sex and Genotype in AD. AD is a neurodegenerative disorder and the most commonly diagnosed cause of dementia. The E4 allele of the apolipoprotein E (APOE4) gene is a known genetic risk factor for AD. The APOE gene provides instructions for making a protein called apolipoprotein E, which combines with fats in the body and helps carry them through the bloodstream. Importantly, female APOE4 carriers have a greater lifetime risk for developing AD, an increased rate of cognitive decline, and accelerated accumulation of Aβ (the main component of amyloid plaques found in the brains of AD patients), compared to male carriers. The link between APOE4 and AD risk remains poorly understood, and the increased risk for APOE4-induced AD in females remains virtually unexplored. As most AD is sporadic and with age as the key risk factor, investigators are using a novel preclinical mouse model to investigate the interactive effects of aging, APOE genotype, and sex on AD progression, establishing a foundation for testing mechanistic-based therapeutic interventions (NS100127).

Spinal Cord Injury (SCI)

Understanding Sex Differences in SCI Mediators. SCI traditionally has been most prevalent in young males, due in part to risk-taking lifestyle choices. There is a changing demographic, however, with an increasing age of injury and increasing prevalence of older, active women experiencing injuries from falls. Some studies suggest that women have better recovery than men with similar injuries, and this may be due to estrogen or non-estrogen-dependent mechanisms. This project seeks to understand the role of variations in inflammatory cell types and activation states on recovery after SCI (NS091582). The interaction of sex, age, and treatment on the inflammatory response and recovery in rats following SCI will be directly tested to better understand the mechanisms behind differences among men and women following spinal cord trauma.

Traumatic Brain Injury (TBI)

Sex Differences in Female and Male Athletes. A mounting body of evidence now suggests that the incidence of and recovery rate from concussion differs between men and women. Female athletes are at greater risk than male athletes for more severe symptoms after acute traumatic brain injury, including concussion. For example, in soccer, it is believed that women are at risk for having more frequent and severe physical and cognitive symptoms both following concussion and from the accumulation of hitting the ball with their heads (headers) (PMID: 30063172, Rubin et al., 2018). NINDS is funding a study to characterize sex differences following soccer-related concussion and the accumulation of headers in amateur adult soccer players (NS082432). Beyond comparison of the sexes, this study investigates whether hormonal variation contributes to differences in cognitive functional changes and potentially in post-concussive symptoms. The researchers have examined the role of sex in abnormal white matter structure after soccer heading by using brain imaging techniques. They found that with similar exposure to heading, women show more widespread alteration of microstructural white matter than men, indicating sex differences in brain response to repetitive trauma (PMID: 30063172, Rubin et al., 2018).

Gaining a Better Understanding of TBI Across Clinical Populations. The role of sex differences in response to moderate and severe TBI is being investigated in two large comparative effectiveness clinical trials supported by NINDS. The first is a pediatric observational trial in severe TBI – The Multiple Medical Therapies for Pediatric TBI – A Comparative Effectiveness Approach trial (NS081041). This trial is studying the effectiveness of first-line therapies for treatment of severe TBI in children, including intracranial hypertension strategies, secondary injury detection, and metabolic support. The second trial—Transforming Research and Clinical Knowledge in Traumatic Brain Injury—is an observational TBI trial focused on patients across the TBI severity spectrum that present to the emergency room (NS086090). This trial is enrolling 3,000 patients and will compare differences in outcomes across the severity range and between sexes. The results of these trials will help to inform both current clinical care and future clinical trials.

Epilepsy

Epilepsy's Impact on the Underlying Mechanisms of Reproductive Endocrine Disorders. Both men and women with epilepsy have higher risks of reproductive endocrine disorders, and researchers are exploring the neural mechanisms linking epilepsy and these comorbidities (NS103029). In one study using a mouse model of temporal lobe epilepsy, researchers reported changes in the function of gonadotropin-releasing hormone neurons (GnRH), a type of neuron that controls fertility. GnRH neurons from female mice with epilepsy showed aberrant activity dependent on estrous cycle stage and the severity of cycle disruption. In contrast, the impact of epilepsy on GnRH neurons in males were less severe. These results demonstrate that the effects of epilepsy on the neural regulation of reproduction are dynamic across the estrous cycle and are sex-specific (PMID: 30255128, Li et al., 2018).

Effects of Epilepsy on Fertility and Birth Outcomes in Women Seeking Pregnancy. Previous studies have reported lower birth rates for women with epilepsy, and researchers are working to differentiate the biological and social factors that play a role (NS038455). In this study, the investigators compared fertility data from women with epilepsy and women without epilepsy who were seeking pregnancy. The group of women with epilepsy showed similar likelihood of achieving pregnancy, time to pregnancy, and live birth rates compared to the women without epilepsy, providing evidence that epilepsy does not affect pregnancy outcomes (PMID: 29710218, Pennell et al., 2018).

Rett Syndrome

Investigating the Underlying Mechanisms of Rett Syndrome. Rett syndrome is a genetic brain disorder in females and is characterized by coordination and language problems, repetitive movements, seizures, and autism spectrum behavior. The symptoms typically become apparent after 6 to 18 months of age in females. Rett syndrome is caused by mutations in the MeCP2 gene located on the X chromosome and can occur sporadically or from germline mutations. As MeCP2 may be a potential therapeutic target for Rett syndrome, several research groups are investigating the role of MeCP2 in regulating neuronal gene expression (NS048276, NS093066) or cellular and circuit dysfunction (NS057819, NS092216) to better understand the pathways that may be targeted with therapeutic interventions.

NIH Strategic Plan for Women's Health Research

Several of the NINDS-supported research projects described in this report address one or more goals of the NIH Strategic Plan for Women's Health Research. Highlights are listed below.

Goal 3.1 Conduct developmentally framed research to understand the role of hormonal changes and reproductive transitions on conditions affecting women throughout the lifespan

- Epilepsy patients, including both men and women, have been shown to have higher risks of reproductive endocrine disorders. Using a mouse model with epilepsy, researchers demonstrated that epilepsy has significant impacts on a type of neuron that controls fertility (gonadotropin-releasing hormone (GnRH) neurons) in females. In males, on the other hand, the effects of epilepsy on GnRH neurons were less prominent (PMID: 30255128, Li et al., 2018).
- Reports have shown lower birth rates for women with epilepsy, though the exact contributions of biological and social factors are unclear. This study collected data from women with and without epilepsy who were seeking pregnancy. The results indicated that epilepsy did not affect the pregnancy success rates, nor the live birth rates (PMID: 29710218, Pennell et al., 2018).

Goal 2.2 Develop novel animal, in vitro, and computational (virtual) models to study sex differences in diseases and conditions

- Earlier studies suggested that abdominal obesity may contribute to the higher risks of stroke in middle-aged women in the U.S. NINDS-supported investigators studied middle-aged female mice and observed an activated systemic pro-inflammatory environment in adipose tissue and lower levels of anti-inflammatory molecules compared to age-matched males, which may explain the increased stroke risk in middle-aged females (NS098628) (PMID: 29670627, Ahnstedt et al., 2018).

Goal 4.5 Partner with professional societies to include women's health research issues in national scientific meetings and conferences, including issues involving career and training development.

- While TBI is a major public health concern, little is known about TBI in females. NINDS, along with the National Center for Medical Rehabilitation Research (NCMRR), the Office of Research on Women's Health (ORWH) and the Defense and Veterans Brain Injury Center held the "Understanding Traumatic Brain Injury (TBI) in Women Workshop" in December 2017 to discuss the current research and identify new directions.

Inclusion

NINDS uses several approaches to facilitate and monitor inclusion of women in clinical research. During the peer review process for grant applications, the inclusion plan for clinical research is examined. Phase III clinical trials are required to have inclusion analysis plans to inform enrollment targets. Peer reviewers assess the inclusion plans, and prior to each NINDS Advisory Council meeting, program directors examine the reviewers' comments on unacceptable inclusion goals and resolve issues in writing with the investigators. Program directors also review enrollment data submitted in the annual progress reports and determine whether the enrollment targets for gender inclusion are scientifically appropriate. NIH monitors inclusion through a centralized system and allows access to Institute-specific records and cumulative reports, enabling program staff to track enrollment data.

Science, Technology, Engineering, and Mathematics (STEM) Efforts

NINDS has actively participated in several outreach activities to foster interest in neuroscience among girls and young individuals from backgrounds that are underrepresented in biomedical research. In December 2018, Flowers High School and NINDS coordinated an outreach program to provide young girls the chance to learn and experience the importance of neuroscience research. The students will explore

topics of neuroscience research at Flowers High School, as well as visit the NIH Main Campus to conduct hands-on experiments in different NINDS labs. These outreach activities aim to attract young individuals from diverse backgrounds to the field of neuroscience.

NIH BRAIN Initiative Advanced Postdoctoral Career Transition Award to Promote Diversity (K99/R00) PAR-18-814. This program aims to help outstanding postdoctoral researchers from diverse backgrounds, including women and underrepresented racial and ethnic groups, to complete their mentored training and transition into independent investigators. The BRAIN Initiative Diversity K99/R00 program hopes to foster diversity in the scientific workforce and encourage new and talented investigators to conduct research in BRAIN Initiative areas.

NINDS Ruth L. Kirschstein National Research Service Award (NRSA) for Training of Postdoctoral Fellows (F32) PAR-16-458. The purpose of this award is to support a diverse pool of highly promising junior scientists who are just beginning their postdoctoral training. The early applications preclude preliminary data and encourage creative, innovative ideas that address significant questions. The NINDS F32 helps to promote retention and advancement of women scientists and supports six-month extensions for fellows who have children while supported by this award.

III. Funding Initiatives, Workshops, and Conferences

Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (PA-18-592). This research grant continues the program for supporting individuals with high potential to re-enter an active research career after interruption for family responsibilities or other qualifying circumstances. This program is sponsored by the ORWH and many NIH Institutes and Centers.

Traumatic Brain Injury (TBI) Workshop. Little is known about the differential outcomes following TBI in males and females. To address this knowledge gap, NINDS, along with NCMRR, ORWH and the Defense and Veterans Brain Injury Center held the "Understanding TBI in Women Workshop" in December 2017. The principal goal of the workshop was to bring together researchers and clinicians to better understand the studies that focus on sex differences within the field of TBI. Deliverables from the workshop included a white paper (https://www.ninds.nih.gov/sites/default/files/tbi_workshop_summary_-_december_18-19_2017_508c_0.pdf) describing the conference, state of the science, and future directions for research in women with TBI.

Neurodevelopmental Disorders Biomarkers Workshop. Investigators studying neurodevelopmental disorders, including, e.g. Rett syndrome, tuberous sclerosis complex, and fragile X syndrome, are striving to develop and validate biomarkers for use in clinical trials. NINDS, together with NICHD, NIMH, NCATS, and several disease foundations organized the "Biomarkers to Enable Therapeutics Development in Neurodevelopmental Disorders Workshop" in December 2017. The aim of the meeting was to allow researchers and professionals working in related fields to share and discuss biomarkers that have potential for translational success (Sahin et al., 2018).

IV. Health Disparities

Health Disparities and Cognitive Impairment RFA-NS-17-012. NINDS partnered with NIA to invite research projects that test approaches for detecting cognitive impairment, including dementia, in primary care clinical settings across the U.S. The research funded through this program will focus on utilizing tools strategies that can be implemented in primary care and other

clinical settings and among diverse populations, including identification of obstacles that lead to delay or lack of detection of cognitive impairment in health disparities population. NINDS funded three projects through this initiative in FY2018: NS105562, NS105557, and NS105565.

Sex-Specific Stroke Incidence Over Time in the Greater Cincinnati/Northern Kentucky Stoke Study. While recent reports have suggested that stroke incidence is decreasing over time, it is unclear whether the extent of decrease differs between men and women. Researchers in this study collected data from the Greater Cincinnati/Northern Kentucky Stoke Study, which consisted of a largely biracial population of approximately 1.3 million people (NS030678). Their results showed that the overall decrease in stroke incidence is mainly driven by a decrease in ischemic stroke in men and that the change in women over the same time period was not significant. This group's current findings, together with their past work demonstrating that stroke incidence is not decreasing to the same extent in black and white participants (Kleindorfer et al., 2010), indicate that targeted stroke preventions efforts are required to effectively eliminate stroke risks across all demographics (PMID: 28794254, Madsen et al., 2017).

Risk of Stroke Among Women in a Large Biracial Cohort. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study is a national study exploring risk factors for stroke and dementia among 30,000 African American and white adults living within and outside of the Stroke Belt region of the southeastern U.S. (NS041588). REGARDS investigators studied sex differences in stroke onset for black and white individuals. They found that for both races, women aged 45 to 64 were at lower risk for stroke compared to men. At age 65 through 74 years, white women were at lower stroke risk than white men, while there was no difference between the stroke risk of black men and women. Moreover, white women had larger associations between key risk factors and stroke risk than white men, but this difference was not observed between black women and men. Their observations suggest that while optimal stoke prevention and management of stroke risk factors are universally required, understanding differences by sex and by race may point to the need for more tailored interventions in demographic subgroups (PMID: 30535250, Howard et al., 2018).

Disparities in Stroke Care Among Women and Race/Ethnic Minorities in Puerto Rico and Florida. Reports have shown that women and race/ethnic minority groups less frequently receive tissue-type plasminogen activator treatment and other life-saving interventions compared with men and white patients. A project funded through the NINDS Stroke Prevention-Intervention Research Program established a stroke registry in Florida and Puerto Rico to address race, ethnic, sex and regional differences in type and quality of stroke care (NS081763). More than 65,000 patients from years 2010 to 2015 were included in this study, called the Florida-Puerto Rico Collaboration to Reduce Stroke Disparities. Analysis of the registry data revealed that stroke treatment within an hour (a treatment time window for acute stroke that is associated with improved outcomes) is lower in women compared with men. A separate analysis comparing Medicare beneficiaries in hospitals participating in the registry with hospitals not participating in quality improvement programs found that disparities in post-stroke risk of mortality and readmission were more common in registry hospitals. These studies identify a need to understand and address sex, racial, and ethnic disparities in health care among diverse populations (PMID: 28706119, Oluwole et al., 2017; PMID: 30587062, Gardener et al., 2019).

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National Institute of Nursing Research

I. Executive Summary

The mission of the National Institute of Nursing Research (NINR) is to promote and improve the health of individuals, families, and communities. To achieve this mission, NINR supports clinical and basic research on health and illness that spans and integrates the behavioral and biological sciences. From low birth weight infants, to adolescents living with chronic illness, to elderly people and their caregivers coping with dementia, nursing research develops the science to help people strengthen the quality of their health and lives. Across all of its scientific programs, NINR's research addresses disease prevention, elimination of health disparities, and promotion of health equity.

NINR promotes the study of women's health and sex/gender influences on health and disease through research on health topics across the lifespan, among a variety of communities, regarding a wide range of topics, and with a commitment to advancing the careers of women scientists. The institute supports research on women's health across its entire research portfolio. As defined by the NINR Strategic Plan, these areas include symptom science, self-management of chronic conditions, wellness, and end-of-life and palliative care.

NINR supports many research efforts relevant to women's health, with specific attention to issues surrounding pregnancy, management of chronic conditions, promotion of wellness, identifying and ameliorating health disparities, and caregiving. Through these efforts, NINR seeks to strengthen research specific to women, whether as patients, caregivers, or community members. The Institute actively ensures that research it supports includes a diversity of women and that health disparities experienced by women in urban, minority, rural, and other underserved communities are addressed. Throughout 2017-2018, NINR continued its long-time practice of supporting research in women's health and sex/gender differences. Finally, NINR primarily funds female scientists across the span of their careers through extramural grants, intramural grants, and training programs, due to the demographics of the nursing field, and the Institute remains dedicated to the growth of current and future nurse scientists.

II. Accomplishments and Activities

NINR is committed to supporting research on women's health and sex/gender influences on health and illness through investigator-initiated research and through specific NINR-sponsored funding opportunities. NINR-supported research spans a range of topics that affect women, as well as the role that sex and gender may play in the health of women differently from men whether through biological, environmental, or societal influences. The following listing serves as an overview of NINR's in women's health and sex/gender differences, organized by topic area.

Pregnancy, Childbirth, and Perinatal Health

Women's health research naturally has a focus on the reproductive cycles of women and the impact of the dynamic nature of this biological system on women's health. From the onset of puberty, to pregnancy, child birth, and menopause, many of the unique aspects of women's health is influenced by biological sex. Furthermore, women's roles as mothers significantly impact not

only the mother but also the fetal development and the health of their children.

Healthy First-Time Mothers Have Different Birth Experiences Depending on Clinician

In a retrospective study of births at an academic medical center between 2005 and 2012, researchers supported by NINR and other organizations examined over 3,000 low-risk full-term births by first-time mothers. First time mothers were found to have more unplanned caesarean sections and labor interventions, including oxytocin use, regional anesthesia use, and delivery with the use of forceps or vacuum, when treated by an obstetrician versus a nurse-midwife. Understanding the differences in labor management style between different groups of clinicians is essential to helping lower caesarean rates among first-time, low risk mothers and improve outcomes for the mothers and their offspring (Carlson et al., 2018).

Human Milk Consumption Improves Short and Long-Term Health Outcomes in Very Low Birth Weight Infants

An observational study of very low birth weight infants and the impact of consumption of human milk found that every additional 10mL/kg/day consumed in the first 14 days of life was associated with fewer hospitalizations in the first year of life and fewer specialized pediatric therapies used at 2 years of life. The study concluded that human milk consumption in the first two weeks of life can significantly improve health and well-being of very low birth weight infants (Johnson et al., 2018).

Pregnant African American Women's Nutritional Intake Found to be Lower Than Recommended for Fiber, Protein, and Micronutrients

A study of pregnant African American women in a larger study of preterm birth examined nutritional intake in the second and third trimesters of pregnancy. The women reported lower than recommended intake of protein, fiber, and micronutrients, as well as lower than recommended intake of fruit and vegetables. This research indicates that further work is needed during prenatal care to improve information and access to adequate nutrition during pregnancy. (Myles et al., 2017)

In addition to these advances, in FY2017-2018, NINR supported several grants in this topic area, including the following:

- K01NR016984: Metabolomics of Labor Dysfunction in African American Women
- K01NR016971: The Subgingival Microbiome in Non-Hispanic Black Women: Relationship to Periodontal Inflammation, Systemic Inflammation, and Preterm Birth
- K01NR017903: The Microbiome of Pregnant African American Women with Group B Streptococcus Infection Colonization and the Influence of Prenatal Antibiotics
- R00NR015106: Preventing Perceived Insufficient Milk: Development of a Text Message-Based Intervention
- R01NR014540: RCT of a Tailored Walking Program to Reduce Stress among Pregnant Women
- R01NR014831: Supporting AI/AN Mothers and Daughters in Reducing Gestational Diabetes Risk
- R01NR017602: Longitudinal Changes in Weight and Biology in the Pregnancy-Postpartum Period and Subsequent Cardiometabolic Risk
- R01NR018115: Group Antenatal Care: Effectiveness for Maternal/Infant and HIV Prevention Outcomes and Contextual Factors Linked to Implementation Success in Malawi
- R01 NR013661: Maternal Stress, Obesity, and Influenza Virus Vaccine Immunogenicity in Pregnancy

- R01 NR017020: Severe Maternal Morbidity: An Investigation of Racial-Ethnic Disparities, Social Disadvantage & Maternal Weight
- R21NR016352: Development of a Group Prenatal Care Intervention to Address Maternal and Child NCD Risk in American Samoa
- R15 NR017092: Behavioral and physiological responses to oral feeding in infants with complex congenital heart disease

Symptom Science

Symptom science focuses on understanding the biological mechanisms underlying symptoms and in the development of improved, personalized strategies to treat and prevent the adverse symptoms of illness across diverse populations and settings. The following advances in women's health research underscore the importance of understanding how symptoms cluster together to better develop treatments that target symptoms as a group rather than in a singular fashion.

Breast Cancer Symptom Clusters Vary Over Time During Chemotherapy

Researchers identified two distinct and dynamic symptom clusters in women undergoing chemotherapy for breast cancer. The identified symptom clusters were associated with gastrointestinal systems or were treatment-related. The researchers also found that symptom clusters change dynamically over the course of, and after, treatment for breast cancer (Albusoul et al, 2017).

Three Distinct Symptom Clusters Identified in Women with Fibromyalgia

In a study of the variability of pain and fatigue in fibromyalgia patients, researchers identified three distinct symptom clusters including low symptom variability, high symptom variability, and mixed symptom variability groups. These groups also varied in how changes in their symptoms affected their mood and daily living. The ability to identify differences between how fibromyalgia affects individuals over time is an important step in clinical treatment of varying experiences of pain and fatigue in these patients. (Bartley, Robinson, and Staud, 2017)

A Multi-Ethnic Study of Adult Women Identified Symptom Clusters Prior to, During, and After Menopause

In a study that is part of the Study of Women's Health Across the Nation (SWAN), researchers surveyed women to determine their symptom experiences at midlife, during menopause, and after menopause. The study identified 6 sets of symptom clusters that remained stable over time and found an association between perceived quality of health and symptom severity. The patterning of symptom clusters could point to underlying mechanisms that could be treated systematically. (Harlow et al., 2018)

Symptom Survey Helps Predict Heart Events in the Short Term in Women Without Known Coronary Disease

In a study of women without known coronary heart disease, the administration of the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAP-MISS) identified key symptoms that could help predict cardiac events in the short-term (within 90 days). The study identified arm pain or discomfort and unusual fatigue as symptoms associated with future cardiac events. (McSweeney et al., 2017)

In addition to these advances, in 2017-2018 NINR provided support for the following grants in this area:

- R01NR017635: Testing Adaptive Strategies to Improve Physical Activity for Sedentary Women
- R01 NR013507: Technology Enhanced Community Health Nursing to Reduce Recurrent STIs after PID

- K99NR016484: A Personalized Behavioral Intervention to Improve Physical Activity, Sleep, and Cognition in Sedentary Older Adults
- R01NR015495: Elucidating causes of vaginal symptoms using a multi-omics approach
- K01NR017664: The Persistence of Cardiometabolic Dysregulation in Postpartum African American Women: The role of the gut microbiome and the lipidome

Self-Management of Chronic Conditions

The science of self-management examines strategies to help individuals with chronic conditions and their caregivers better understand and manage their illness and improve their health behaviors. NINR-supported research helps individuals from diverse backgrounds and their families live with chronic illness by developing effective approaches to self-management that can improve quality of life.

An Internet-based Intervention Improves the Recognition and Treatment of Teen Mothers' Postpartum Depression

Untreated postpartum depression is detrimental to a mother's relationship with their child, her functioning at work and school, and her development as a mother and that of her child. An inexpensive, Internet-based intervention for adolescent mothers was found to be effective at changing attitudes, perceived control, and intention to receive and actual treatment for depressive symptoms in adolescent mothers (Logsdon et al., 2017).

Telenursing Intervention Helps Rural, Low-Income Pregnant Women

The Baby Behavioral Educational Enhancement of Pregnancy (Baby BEEP) study found that nurses were able to provide much needed psychosocial support to a vulnerable and hard-to-reach population of low-income, rural women during pregnancy. The telenursing intervention had high levels of retention and was well-received by the target population throughout the intervention and built strong provider-patient relationships. (Evans and Bullock, 2017)

Wellness

In focusing on wellness, nursing science seeks to promote health and prevent illness across health conditions, settings, the lifespan, and in minority and underserved populations. NINR supports research to understand the physical, behavioral, and environmental causes of illness, assess behaviors that lead to healthy lifestyle choices, and develop evidence-based interventions to promote wellness. In 2017-2018, NINR supported a number of interventions aimed at improving and promoting women's health.

Interventions Improve Custodial Grandmother's Parenting Skills for their Grandchildren

A randomized controlled trial was conducted in four states with over 300 custodial grandmothers with the goal of improving parenting skills, limiting custodial grandparents' psychological distress, and improving the psychological well-being of the custodial grandchildren. The trial tested a behavioral parent training (BPT) intervention and a cognitive-behavioral training (CBT) intervention, comparing both to a control group receiving information-only, and found that both BPT and CBT had positive effects as measured by an improvement in parenting practices and reduced psychological distress in the custodial grandmothers and improved psychological well-being in their grandchildren (Smith et al., 2018).

Intervention Promoting Oral HIV Testing and Education in Domestic Violence Shelters Found to be Acceptable, Feasible, and Effective

Women who experience intimate partner violence may also be at risk for sexually transmitted infections, including HIV, due to lack of knowledge and ability to negotiate safe sexual practices, as well as being at higher risk for PTSD and

substance use disorders. Shelters for IPV victims often do not offer HIV testing or strategies for risk reduction. A trial of rapid HIV testing and a risk education intervention in domestic violence shelters was found to be feasible, acceptable, and effective in reducing risk behaviors. (Johnson et al., 2017)

In addition to these important advances, in FY2017-2018 NINR supported the following research projects focused on wellness:

- R00NR015473: Mindfulness-Based Stress Reduction to Improve Cognitive Function During Aromatase Inhibitor Therapy
- R01NR013507: Technology Enhanced Community Health Nursing to Reduce Recurrent STIs after PID
- U01NR004061: Study of Women's Health Across the Nation (SWAN V): Michigan Site
- R01NR014851: A Novel Pregnancy Prevention Intervention for Latino Middle School Girls
- R01NR017635: Testing Adaptive Interventions to Improve Physical Activity for Sedentary Women
- R01 NR015029: Bone Loading Exercises versus Risedronate on Bone Health in Post-Menopausal women

III. NIH Strategic Plan for Women's Health Research

NINR actively collaborated in the development of the NIH Strategic Plan for Women's Health Research, and many of NINR's efforts in women's health research are targeted toward the implementation of this plan. In particular, NINR's focus on complications associated with preterm birth and research training serve to address specific goals in the Strategic Plan.

Overarching Goal: Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women

Strategic Plan Goal 3.4-Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.

Beginning in FY2013, NINR supported a funding opportunity (RFA-NR-13-002: The Influence of the Microbiome on Preterm Labor and Delivery) that supported several projects on pregnancy and the microbiome of mother and infants that have led to advances in our understanding of these complex interactions on the health of the mother and child, as well as the prevention of problems arising from preterm birth and pregnancy complications. The supported projects were funded through FY2017 and have resulted thus far in 40 publications.

Overarching Goal: Employ vigorous strategies to build a well-trained, diverse, and vigorous women's health research workforce

Strategic Plan Goal 6.1: Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at NIH.

Strategic Plan Goal 6.2: Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs; encourage the evaluation of mentoring practices.

NINR has long focused a significant percentage of its appropriated resources to training and career development initiatives for nurse scientists and interdisciplinary training. Given that the nursing field and nurse scientist workforce are primarily female, the vast majority of NINR training and career development grants train female scientists and promote the advancement of women in science. These initiatives include trainee-initiated projects (F31 and F32), institutional training programs (T32), and career

development activities for early and mid-career mentored training opportunities (K awards). A key component of all training and career development grants is the mentoring provided by experienced nurse scientists who have also secured NIH funding. All grantees and mentees also develop individual development plans for their training and career development projects. Given the demographic profile of nurses, who both comprise the largest group of clinicians and are predominantly female, by supporting the training of nurse scientists and interdisciplinary scientists, NINR is helping to improve the number of women in research careers.

In addition to extramural grants to individual investigators and institutions, NINR is also committed to training opportunities through its Division of Intramural Research. Training activities include its annual week-long Methodologies Boot Camp, which focused on "Precision Health: From 'Omics' to Data Science" in 2017 and "Precision Health: Smart Technologies, Smart Health" in 2018. Another training opportunity is the Graduate Partnerships Program (GPP) for nursing students who are currently enrolled in a PhD program. Students can apply to the NINR for doctoral-level research training opportunities within research programs at laboratories across NIH and conducted by leading scientists and clinical investigators. Finally, NINR sponsors the Summer Genetics Institute, a tuition-free month-long training program that provides participants with a foundation in molecular genetics appropriate for use in research and clinical practice. The program seeks to increase the research capability among graduate students and faculty and to develop and expand clinical practice in genetics among clinicians.

IV. Inclusion

NINR actively supports research that examines the effect that sex/gender differences have on health, especially in symptom science, as symptom experiences often differ between men and women with the same disease or condition. Additionally, NINR supports research on sex/gender differences in response to treatment. Finally, understanding how both symptoms and treatment responses vary over time and across the lifespan is also an important area of study.

In Women Living with HIV, Menopause Contributes to a Higher Symptom Burden

As an increasing number of people living with HIV (PLWH) are living longer under combined anti-retroviral therapy, there is limited information on symptom burden and characteristics that they experience. In a sex-based analysis of symptom burden in people living with HIV (PLWH), researchers used an online survey to study symptoms in PLWH; they also undertook a secondary survey of female PLWH. The researchers found that women living with HIV report a higher symptom burden of fatigue (including higher frequency and bother) and muscle aches/pains than men living with HIV, and this is exacerbated after menopause. (Schnall et al., 2018)

Gender Differences in Heart Treatment, Rates of Transplants, and Rejection Exist

An observational study of heart transplant recipients found that men were older, more ill, and more likely to receive a heart transplant than women, who were often treated less aggressively for their heart failure. Women were also more likely to be hospitalized for acute rejection and experience moderate or severe rejections. There is a compelling need for future research to examine why these clinical and gender differences persist (Hickey et al, 2017).

V. NINR STEM Efforts

Training future nurse scientists is of great importance at NINR; as the majority of nurse scientists are women, NINR promotes the development of these female scientists in many topical areas, including in women's health research. NINR promotes pre- and post-doctoral

trainees through the F31 and F32 mechanisms, and supports mentored career development through the K01, K23, and K99/R00 mechanisms. NINR also supports an institutional training grant on "Research on Vulnerable Women, Children and Families" (T32NR017100), in addition to other institutional grants that include women's health topics.

VI. Funding Initiatives, Workshops, and Conferences

PA-18-776: Maternal Nutrition and Pre-pregnancy Obesity: Effects on Mothers, Infants and Children (Clinical Trial Optional)-This Funding Opportunity Announcement encourages applications to improve health outcomes for women, infants and children, by stimulating interdisciplinary research focused on maternal nutrition and pre-pregnancy obesity. Maternal health significantly impacts not only the mother but also the intrauterine environment, and subsequently fetal development and the health of the newborn. (Open Date: September 5, 2018, Expiration Date: September 8, 2021)

Health Disparities

NINR supports health disparities research in women's health through basic and clinical research in a variety of contexts. These include studies to: identify disparities in diseases and conditions in women; determine the factors that combine to produce a disparity; and test interventions that could reduce or eliminate a health disparity. Health disparities research conducted by NINR-funded grantees often is focused on developing culturally appropriate interventions to help reduce health disparities, including in women's health.

Non-Hispanic African American Women at Higher Risk of Co-Morbidity of Diabetes and Hypertension

A nationally representative study of women of reproductive age who were not pregnant found that over a third of women with diabetes had comorbid hypertension. The study found that non-Hispanic African American women had a higher chance of having both conditions, and if found to be co-morbid, they were less likely to have been originally diagnosed with diabetes. These disparities could threaten maternal and child health among women with diabetes. (Britton, et al., 2018)

Community Members Lead a Culturally Tailored Physical Activity Intervention Promoting Physical Activity

Researchers developed and tested a culturally appropriate physical activity intervention using Latina community members as partners and promotors. The community-based participatory research study found that the promoters were successful in their efforts, leading to increases in aerobic fitness, muscle strength and flexibility, and daily physical activity levels (D'Alonzo, Smith, and Dicker, 2017).

Group Antenatal Care Empowers Pregnant Women in Some Cultural Contexts

A randomized controlled pilot research trial focused on providing group, rather than individualized, antenatal care was conducted in Malawi and Tanzania. Depending on the sociodemographic context, some women scored higher on a scale measuring pregnancy-related empowerment when they received group antenatal care. These findings highlight the importance of understanding cultural context when determining appropriate forms of antenatal care in different populations. (Patil, et al., 2017)

In addition to these advances, NINR supported the following projects in 2017-2018.

- R01NR017626: Paternal Role in Adverse Birth Outcomes in Black Families
- R21NR016905: Testing an Intelligent Tutoring System Intervention to Enhance Genetic

Risk Assessment in Underserved Blacks and Latinas at Risk of Hereditary Breast Cancer

- R21NR017154: Social Network Analysis of Puberty, Activity Behaviors, and Health Disparities
- R01NR01463: Intergenerational Impact of Genetics and Psychological Factors on Blood Pressure

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Fogarty International Center

I. Executive Summary

The Fogarty International Center (FIC) seeks to advance the mission of the National Institutes of Health (NIH) by supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the United States and abroad, and training the next generation of scientists to address global health needs. The Office of Research on Women's Health (ORWH) is among the many NIH Institutes and Centers (ICs) that collaborate with FIC to support this mission. Although FIC does not have any programs that are designed to specifically address women's health issues, several FIC efforts support research and research training related to conditions that disproportionately or exclusively affect women or girls. FIC programs also enhance understanding of sex as a biological variable and gender differences. Scientific areas of focus include violence against women, mental health—including postpartum depression and post-traumatic stress disorder—cervical cancer, HIV/AIDS, pregnancy, and other reproductive health/contraception issues.

FIC accomplishments and activities particularly relevant to women's health and highlighted in this report include the following:

- The International Research Scientist Development Award (IRSDA) supports early-career U.S. scientists to pursue independent research careers in global health.
- The Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries (mHealth) Program funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology.
- The Chronic, Non-Communicable Diseases and Disorders Across the Lifespan (NCD Lifespan) program is a collaborative research training program that supports training of scientists to conduct research on chronic, non-communicable disease and disorders in LMIC contexts.
- The Global Health Program for Fellows and Scholars supports 1-year mentored clinical research experiences for postdocs, medical students, or graduate students in the health sciences at 27 LMIC research sites.
- The International Tobacco and Health Research and Capacity Building (TOBAC) program provides opportunities for scientists to engage in locally relevant observational, intervention, and policy research and build research capacity related to tobacco consumption in LMICs.
- The Fogarty HIV Research Training Program strengthens the human capacity to contribute to the ability of institutions in LMICs to conduct research on the evolving HIV-related epidemics in their country to provide training in infrastructure development in support of the research programs and maintenance of grants and to compete independently for research funding.
- The Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institution program strengthens their capacity to participate in and carry out locally relevant research that contributes to improved human health and fosters the next generation of faculty researchers in Africa.

- The Global Brain and Nervous System Disorders Research Across the Lifespan program supports collaborative research and capacity-building projects relevant to LMICs on brain and nervous system disorders throughout life.
- The Fogarty Emerging Global Leader Award provides research support and protected time for career development activities to a research scientist from an LMIC who holds an academic junior faculty position or research scientist appointment at an LMIC academic or research institution.
- The **Global Infectious Disease (GID)** program addresses research training needs related to infectious diseases that are predominantly endemic in or impact upon people living in developing countries. The ultimate goal is to build a critical mass of researchers and support staff to conduct independent infectious disease research in developing country institutions.
- Reducing Stigma to Improve HIV/AIDS Prevention, Treatment and Care in Low- and Middle-Income Countries (Stigma) seeks to stimulate new and impactful research towards the development of stigma reduction interventions leading to better outcomes for the prevention and treatment of HIV/AIDS and on the quality of life of People Living with HIV/AIDS (PLWH) in LMICs.
- Fogarty's Global Health Research and Research Training eCapacity Initiative (eCapacity) aims to support innovative research education programs to teach researchers at LMIC institutions the knowledge and skills necessary to incorporate Information and Communication Technology (ICT) into global health research and research training.
- The Global Environmental and Occupational Health (GEOHealth) program supports the development of institutions in LMICs serving as regional hubs for collaborative research, data management, training, curriculum and outreach material development, and policy support around high-priority local, national and regional environmental and occupational health threats.
- FIC—in partnership with other NIH ICs, key Federal agencies, and the Global Alliance for Clean Cookstoves—hosts the Clean Cooking Implementation Science Network (ISN) to advance the science of uptake and scale-up of clean cooking technology in the developing world.
- The Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA) aims to enhance the effective use of evidence and help overcome implementation challenges related to prevention, screening, and treatment of HIV among adolescents (ages 15 to 24) in sub-Saharan Africa by catalyzing collaboration and communication among implementation scientists, program implementers, and policymakers.

II. Accomplishments and Activities

The FIC portfolio includes a variety of programs and projects related to research that disproportionately or exclusively affects women and/or girls. Several of these are in areas of expressed Congressional interest, including neuroscience, cardiovascular disease and stroke and inclusion of women in clinical research. FIC's programs fall under several of ORWH's strategic goals, primarily Goal 4, "Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research," and Goal 6, "Employ innovative strategies to build a well-trained, diverse, and vigorous health research workforce." Highlights of these programs and projects are provided below.

International Research Scientist Development Award (IRSDA)

IRSDA supports U.S. postdoctoral biomedical, epidemiologic, clinical, social, and behavioral scientists in the formative stages of their careers in pursuing careers in research on global health and preparing them for independent research by engaging in a mentored career development experience. Current IRSDA investigators are studying prevention of intimate partner violence in India, promoting mental and sexual health among young pregnant women in Liberia, evaluating family smoking cessation starting with pregnant women in Romania, identifying risk factors for sub-optimal breastfeeding among working mothers in Kenya, and mental health and understanding pre-exposure prophylaxis cascade in pregnant and breastfeeding women in South Africa.

With support from IRSDA, Dr. Maria Kim evaluated the implementation of Malawi's national PMTCT program Option B+ (B+).[28] While the program theoretically provided a simplified approach to PMTCT, there were no published studies evaluating its efficacy. Dr. Kim proposed a three-prong study to both evaluate and optimize the implementation of B+. Through this research opportunity, Dr. Kim gained expertise in areas such as implementation research in resource-limited settings. advanced study design and biostatistical methods. and intervention design and evaluation. After her mentored research experience, she was awarded an R01 in 2018 testing an intervention to improve retention and adherence to ART among pregnant and breastfeeding women.[29]

Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries

The mHealth program funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology. The overall goal of the program is to contribute to the evidence base for the use of mobile technology to improve clinical outcomes and public health. mHealth researchers are developing and testing mobile phone interventions that could assess hemoglobin for anemia detection and improve diagnosis of surgical site infections post-cesarean delivery in rural Rwanda.

In response to high number cervical cancer deaths in Peru, one mHealth grantee is evaluating the efficacy of an mHealth-supported telecolposcopy approach in communities within Lima Province, Peru.[30] During the study, midwives conducting community-based screening will acquire cervical images using a low-cost ultraportable colposcope and receive remote feedback from expert colposcopists using a mobile device. The central hypothesis is that access to expert colposcopists using an mHealth-supported telecolposcopy approach will improve the quality and timeliness of patient triage in community-based settings, increasing the proportion of women who receive a diagnosis, and adhere to treatment. The study will use telemedicine to allow women to receive colposcopic evaluations in the communities where they live, precluding need for additional and distant clinical visits for diagnosis of cervical lesions.

Chronic, Non-Communicable Diseases and Disorders Across the Lifespan (NCD-Lifespan)

NCD-Lifespan is a collaborative research training program that pairs high-income and LMIC institutions to train LMIC scientists to conduct research on chronic, non-communicable diseases and disorders with the goal of implementing evidence-based interventions relevant to their countries. This program covers areas of particular

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Congressional interest, including cardiovascular disease and stroke, through research on tobacco control among women in Antioquia, Colombia, household air pollution in Ghana, and predicting early cardiovascular risk among HIV-infected and uninfected Kenyans.

One current NCD-Lifespan award is focusing on building research capacity to identify antenatal causes of NCDs and treat those with NCDs in Bolivia. The project consists of a series of workshops aimed at engaging leading Bolivian practitioners, researchers, and policy makers to update and standardize diagnostic criteria and treatment strategies for hypertensive pregnancy complications, along with establishing a centralized, online perinatal database with the goal of enabling improvements in clinical practice and health policy likely to reduce the frequency of cardiopulmonary diseases for both mother and child in Bolivia.

Global Health Fellows and Scholars

The Fogarty Global Health Program for Fellows and Scholars, in partnership with NIH ICOs including ORWH, supports 1-year mentored clinical research experiences for postdocs, medical students, or graduate students in the health sciences at 95 LMIC sites across 35 countries. The most recent gender-based clinical research include topics such as violence against women and children in Eastern Europe, trauma exposure and injury prevention in South Africa, and maternal and child health in Asia and Africa.

One Fogarty Fellow is currently studying how socio-ecological, physical, inflammatory, and cultural, factors influence physical activity and health in Samoan women (Rivara, 2018). Dr. Anna Rivara will also identify unique risks of obesity co-morbidities in Samoan women by analyzing biomarkers of inflammation and anemia in adults and conducting interviews, home visits, and focus groups with women, community leaders, and health workers to identify obstacles to female health improvement.

International Tobacco and Health Research and Capacity Building Program (TOBAC)

With support from TOBAC, scientists engage in locally relevant observational, intervention, and policy research and build capacity in epidemiologic and behavioral research, prevention, treatment, communications, health services, and policy research related to tobacco consumption in LMICs. One program will also identify variables that are spatially associated with tobacco points-of-sale that are non-compliant with WHO Framework of Tobacco Control Research, such as brands for women.[31]

Fogarty HIV Research Training Program

Fogarty has provided over 25 years of support to HIV research through two HIV research training programs: the AIDS International Training and Research Program (AITRP) and the International Clinical, Operations and Health Services Research Training Award for AIDS TB program (ICOHRTA AIDS TB). In 2013, Fogarty consolidated these two programs into the new Fogarty HIV Research Training Program[32]. This program seeks to strengthen the capacity of LMIC investigators and their institutions to conduct HIV-related research on the evolving HIV-related epidemics in their countries and to compete independently for research funding. Mentored research training projects conducted under this program include addressing AIDS-related cervical cancer (screening, exploring disease mechanisms, and identifying treatment strategies) and the treatment as prevention and PMTCT of HIV.

One HIV Research Training Program grantee is building capacity around the intersection of HIV and women's reproductive health in Zambia.[33]

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The project will leverage connections between the University of North Carolina at Chapel Hill. the University of Zambia, and the University of the Witwatersrand. It will support both doctoral and postdoctoral training for Zambian investigators and professional development of current faculty at the University of Zambia in order to develop a cadre of UNZA faculty researchers who are independently funded to conduct collaborative, multidisciplinary research in HIV and women reproductive health.

Medical Education Partnership Initiative (MEPI) Junior Faculty Research Training

To support grantee institutions in strengthening their research culture, FIC supports Junior Faculty Research Training in Africa through MEPI. The Research Training for Career Development of Junior Faculty program strengthens capacity to participate in and carry out locally relevant research that contributes to improved human health and fosters the next generation of faculty researchers in Africa. It is expected that increased research opportunities can add to the sustainability and quality of the original MEPI program to strengthen medical education, promote faculty retention, and lead to the acquisition of new knowledge that contributes to improved human health.

The *UZCHS-Promote Excellence in Research and Faculty Enhanced Career Training (PERFECT Program)*,[34] which receives funding from FIC, the National Heart, Lung, and Blood Institute, National Institute of Nursing Research, and ORWH, conducts research training in the following scientific areas: (a) HIV/AIDS (b) Cardiovascular Diseases (c) Mental Health (d) Women's Health. These target scientific areas have been selected because of their national and institutional importance/ interest and the opportunity to address cross cutting issues among them and to be able to use past and current research strengths at the University of Zimbabwe College of Health Sciences (UZCHS) to implement a viable training program. To date, 8 of their trainees have worked on projects related to women's research, including indoor biomass smoke exposure and respiratory health outcomes in adult women from rural and urban communities in Zimbabwe; musculoskeletal health status in HIV infected women of reproductive age; and incidence of hypertensive disorders of pregnancy.

Global Brain and Nervous System Disorders Research Across the Lifespan Program

The Brain program supports collaborative research and capacity-building projects that are relevant to LMICs on brain and nervous system disorders throughout life. Grantees have developed innovative, collaborative research programs that contribute to the long-term goal of building sustainable research capacity in nervous system function and nervous system impairment.

A group of researchers, with funding from the Brain program, is assessing mother-to-child transmission of chikungunya virus in Grenadian pregnant mothers.[35] They will compare the neurodevelopment of 2-year-olds who have been exposed at different trimesters *in utero* to chikungunya virus to that of unexposed children and assess the burden of confounding factors. Working with a local university, the group will build local capacity for arboviral and neurodevelopmental testing.

Fogarty Emerging Global Leader Award

The purpose of the Fogarty Emerging Global Leader Award is to provide 3 to 5 years of research support and protected time for career development activities to an early-career research scientist from an LMIC who holds a junior faculty position at an LMIC academic or research institution. Along with other NIH ICs signed on

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to the Funding Opportunity Announcement, including ORWH, FIC expects this intensive, mentored research career development experience to lead to an independently funded research career at an LMIC institution.

ORWH and the Office of the Director co-funded an FIC grantee who will improve care, screening, and outcomes for Kenyan women with a history of gestational diabetes mellitus (GDM) and hypertensive disease in pregnancy (HPD) by focusing on metabolic syndrome, a direct predictor of cardiovascular disease.[36] Over the course of 5 years, the grantee will work with mentors from the University of Nairobi and the University of Washington to conduct a prospective cohort study to estimate the burden and characteristics of metabolic syndrome in Kenya following GDM and HPD. The study findings will inform use of high attendance of maternal health clinics in sub-Saharan Africa and may inform maternal health and primary care linkages and development of screening and monitoring strategies of women with HDP, GDM, and metabolic syndrome in resource-constrained settings.

Global Infectious Disease (GID) Research Training Program

Sustainable infectious disease research capacity is known to require a critical mass of scientists and health research professionals with in-depth scientific expertise and complementary leadership skills that enable an institution to conduct independent, internationally-recognized infectious disease research relevant to the health priorities of their country. GID supports collaborative research training programs that strengthen the capacity of an LMIC institution to conduct infectious disease research that focuses on major endemic or life-threatening emerging infectious diseases, neglected tropical diseases, infections that frequently occur as co-infections in HIV infected individuals, or infections associated with non-communicable disease conditions of public health importance in LMICs. The training programs include a variety of research training options to match the needs of the LMIC institution.

One GID grant will focus on infectious diseases in mothers and children in Bangladesh, with the goal of reducing morbidity and mortality associated with childhood infectious diseases in the country.[37] They will recruit, train and provide career support to Bangladeshis who will staff local centers of excellence in childhood infectious diseases research in Bangladesh. Training will include subjects such as epidemiology, biostatistics, infectious diseases of childhood, nutrition and infection, behavioral science and responsible conduct of research. The program will foster a sustainable research environment in LMICs and build alliances for global health research and training.

Clean Cooking Implementation Science Network (Clean Cooking ISN)

In collaboration with other NIH ICs, key Federal agencies, and the Global Alliance for Clean Cookstoves, FIC launched the Clean Cooking ISN, which aims to advance collaborative efforts and understanding among researchers and implementers to accelerate successful adoption and use of clean cooking technologies, with the goal of scaling up sustained and exclusive use. Half of the world's population relies on elemental stoves for cooking or heating. Those using cookstoves usually burn dung, wood, soft coal, or rice husks, all of which produce harmful emissions of particulate matter and noxious gases. In many cultures, women traditionally do the majority of the cooking and, therefore, are disproportionately impacted by this exposure. The resulting household air pollution is estimated to cause between 2.2 and 4.3 million premature deaths per year, largely from pneumonia in children under five years of age, but also from adult morbidities such as chronic respiratory

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disease, lung cancer, stroke, and cardiovascular disease.

The primary goal of the ISN is to develop an implementation science platform to advance the understanding of how to improve the uptake and sustained use of evidence-based clean cooking interventions to maximize their benefits on the health and longevity of populations in LMICs. In 2018, the Clean Cooking ISN funding cycle focused on one-year research projects, as well as workshops and analytical tools to extend the learning of the network to the broader HAP community. Nine projects are currently being supported. ISN also has supported four research projects on clean cooking adoption and sustained use in the context of active implementation programs. One such project implemented a conditional cash transfer program focusing on newly married and newly pregnant women in the northern Pune district of Maharashtra, India. To encourage the use of improved, liquefied petroleum gas stoves, a specially modified stove use monitor ("Pink key") was installed to track the stove's use. When a pregnant woman brings the Pink Key to her antenatal health visits, she would receive a small cash payment for each meal prepared using the stove. The effect of the program on stove use is being evaluated using SUMs tracking on improved stoves and traditional stoves, air pollution monitoring, and time-activity tracking.

Reducing Stigma to Improve HIV/AIDS Prevention, Treatment and Care in Low- and Middle-Income Countries (Stigma)

Reducing Stigma to Improve HIV/AIDS Prevention, Treatment and Care in Low- and Middle-Income Countries seeks to support research on novel stigma reduction interventions, reducing the impact of stigma on adolescent or youth health, strategies to cope with stigmatization, and improved stigma measurement. Proposed collaborative exploratory research is expected to help build the capacity for full research programs by improving the research environment and strengthening LMIC individual and institutional research capabilities in the proposed research areas. Areas of study include peer support to mitigate impact of stigma in HIV-positive pregnant women in South Africa,[38] stigma reduction at time of entry into antenatal care to improve PMTCT services in Tanzania,[39] and reducing HIV/AIDS-related stigma among providers for pregnant women in Haiti.[40]

One Stigma grantee is evaluating the role of layered stigma on engagement in care among HIV positive women who use drugs in Ukraine.[41] Layered stigma refers to the multiple stigmas that women often face due to HIV status, drug use, and gender, among others; layered identities interact with each other and cannot be understood in isolation or in a purely additive way. This study will use Latent Class Analysis and qualitative, in-depth interviews to empirically characterize patterns of HIV, drug use, and gender-based stigma among women living with HIV who use drugs in order to provide a more sophisticated perspective on the intersection between layered stigmas, mental health, and engagement in HIV care.

Global Health Research and Research Training eCapacity Initiative

Fogarty's Global Health Research and Research Training eCapacity Initiative aims to develop innovative educational approaches that enhance research capacity at LMIC institutions by expanding the use of information and communication technology (ICT) in global health research and research training. Programs build on established research programs and increase the ability of researchers to use, adapt and

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integrate ICT approaches, establishing electronic capacity (eCapacity) at LMIC institutions. One grantee, based in Costa Rica, is developing a mentored training program for applied research teams throughout Latin America to learn about ICT applications in maternal health.[42] Their program includes testing specific team ICT innovations in field settings to demonstrate feasibility and appropriateness for local context; creating a collaboratory where stakeholders share developing material, comment on plans, and provide support for trainees in the innovation process; and stimulating development of a professional network of ICT, medical, public health professionals with students, faculty, researchers, and practitioners devoted to supporting ICT for Maternal Health in Latin America.

Global Environmental and Occupational Health (GEOHealth)

The GEOHealth program supports the development of institutions in LMICs serving as regional hubs for research and policy support around regional environmental and occupational health threats. GEOHealth Hubs are supported by two coordinated linked awards to 1) a LMIC institution for research and 2) a U.S. institution to coordinate research training. Together they form the GEOHealth Network, a platform for coordinated environmental and occupational health research and research training activities.

In response to Suriname's high perinatal mortality, environmental contamination, and a lack of environmental policies, the Research Center at the Academic Hospital Paramaribo and the Faculty of Medical Sciences at the University of Suriname is partnering with Tulane University`s School of Public Health and Tropical Medicine to form a GEOHealth Network. Together they will offer tailored training, mentoring, and Caribbean-wide professional development and policy workshops in order to build research capacity related to neurotoxicant exposures and their impact on maternal and child health in Suriname.

Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA)

AHISA convenes a forum that enables the exchange of ideas, insights and experiences in understanding factors that drive uptake and adherence to adolescent HIV prevention and treatment strategies. Comprised of program implementers, policymakers, and NIH-funded scientists, the group aims to enhance the use of evidence and help overcome implementation challenges related to prevention, screening, and treatment of HIV among adolescents (ages 15 to 24) in sub-Saharan Africa. AHISA currently has 26 teams composed of NIH-funded scientists conducting relevant implementation research; and in-country partners including key in-country government representatives, in-country research collaborators, and other stakeholders. Their research addresses topics including HIV treatment targeting adolescent girls in Zambia, cost-effective scale-up of cervical cancer prevention in Sub-Saharan Africa, and gender-based violence and HIV risk.

Launched in September 2016, AHISA is a collaboration with OGAC, the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), other NIH ICs, and multilaterals that will (1) provide a platform for cross-fertilization and exchange of ideas and information among implementation scientists and other stakeholders focusing on different aspects of HIV in adolescents, (2) enable the research to be better informed by programmatic challenges and questions, (3) inform policymakers of promising evidence and encourage use of the data in decision making, and (4) extend the reach and impact of implementation science related to adolescent HIV prevention and treatment.

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III. NIH Strategic Plan for Women's Health Research

FIC's work maps closely to ORWH/NIH Strategic Plan Goal 4, "Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research," and Goal 6, "Employ innovative strategies to build a well-trained, diverse, and vigorous health research workforce."

As mentioned above in Accomplishments and Activities, ORWH supports the Fogarty Emerging Global Leader Award and reviews applications for their ability to directly fulfill Goals 4 and 6. In the first round of reviews, ORWH co-funded one award. FIC participation in ISN supports ORWH/NIH Goal 4, primarily Objective 4.6, "Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries," and, secondarily, Objective 4.4, "Create solid partnerships by engaging in scientific briefings and *ad hoc* meetings with policymakers, elected officials, and advocacy groups." FIC's research training portfolio generally addresses Goal 6 by supporting scientists' career development. Many grants involve a significant mentorship component. In addition, FIC's MEPI Junior Faculty and Global Health Program for Scholars and Fellows address Goal 6, primarily, Objective 6.1, "Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH," and, secondarily, Objective 6.2, "Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs, and encourage evaluation of mentoring practices."

MEPI Junior Faculty[43] funds foreign institutions in sub-Saharan African countries to strengthen their capacity to carry out locally relevant research that contributes to improved human health, and to foster the next generation of faculty researchers in Africa. The recent Limited Competition: Research Training for Career Development of Junior Faculty in MEPI Institutions states, "Support for increased engagement of female junior faculty and mentors in research activities in any relevant health area is also highly desired." FIC also promotes the careers of emerging young global health leaders through the Global Health Program for Scholars and Fellows. Following their year abroad, many female scholars and fellows successfully compete for a FIC IRSDA career development award (see Accomplishments and Activities) and acquire a faculty position at an academic institution and compete successfully for independent research funding (e.g., NIH R01).

In addition, as mentioned above, AHISA is a collaboration of researchers, program implementers, and policymakers in the United States and sub-Saharan Africa, as well as representatives from multilateral organizations, that aim to improve communication among these stakeholders. This Alliance seeks to catalyze partnerships to enhance the evidence base for translating effective interventions into community- and population-level services, programs, and strategies at scale.

IV. Inclusion

FIC has incorporated the following language in its research training announcements to encourage research training activities related to sex and gender differences: "Where appropriate, the design of training-related research projects should take into account potential sex and gender differences that may affect the questions asked and the analyses performed. These might include different responses to and impacts of health interventions, differences in physiology, and different behavioral bases for disease prevention strategies."

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V. Science, Technology, Engineering, and Mathematics Efforts

The Fogarty Global Health Program for Fellows and Scholars is a 1-year mentored clinical research experience

in 95 LMIC sites in 35 countries for postdocs, medical students, or graduate students in the health sciences. The most recent gender-based clinical research topics include maternal and child health, dolutegravir use in women and adolescent girls, and PrEP delivery in antenatal care clinics. Over the last 2 years, 29 Fellows and scholars have participated in Women's Health Research.

VI. Funding Initiatives, Workshops, and Conferences

Several funding initiatives are relevant to women's health or the influence of sex on disease in this reporting period. The Fogarty Emerging Leader Award[44] provides research support and protected time for career development activities to an LMIC research scientist from an LMIC academic or research institution. The mHealth program funds exploratory research studies on the development or adaptation of innovative mHealth technology specifically suited for use in LMICs and health-related outcomes associated with implementation of the technology.[45] The NCD Lifespan program is a collaborative research training program that pairs high-income and LMIC institutions to train LMIC scientists to conduct research on chronic, non-communicable diseases and disorders with the goal of implementing evidence-based interventions relevant to their countries.[46]

The annual Fogarty Global Health Program for Fellows and Scholars supports 1-year mentored clinical research experiences for postdoctorates, medical students, or graduate students in the health sciences at 44 LMIC sites. The Fogarty HIV Research Training Program seeks to strengthen the collaborations in the LMIC with U.S. partners and local researchers to increase capacity to conduct HIV-related research on the evolving HIV-related epidemics in their countries; to obtain the technical expertise, administration and financial management skills to support research grants; and to compete independently for research funding.[47]

The Brain program supports collaborative research and capacity-building projects that are relevant to LMICs on brain and nervous system disorders throughout life.[48]

In addition to funding initiatives, several FIC-sponsored workshops and conferences have been relevant to women's health or the influence of sex on disease. In FY2016-2017, the ISN supported four two-year field research projects on various aspects of clean cooking adoption, taking place in Cameroon, Ghana, and India. The ISN also recently supported the development of eleven case studies of clean cooking implementation programs around the world, published in October 2018 as a Special Issue: Scaling Up Clean Fuel Cooking Programs in the Journal Energy for Sustainable Development. In FY2018, the ISN is supporting nine one-year activities that build upon the knowledge developed through the network's activities thus far. Some of these are research projects, for example investigating how to better understand the sources of women's exposure to pollution through source apportionment modeling of air pollution data. Others of the activities focus more on training: for example, a workshop on community-based system dynamics is being held in Udaipur, India next month, to train local

44 PAR-19-051; PAR19-098

45 PAR-18-242

46 PAR-17-097; PAR-18-901

47 D43, PAR-18-717; D71, PAR-16-281; G11, PAR-16-280

48 PAR-18-836; PAR-18-835

researchers in a method that engages women and other community members in building conceptual model of the effect of clean fuel availability and cost, as well as peer influences, one their cooking behaviors, and the associated health outcomes.

As well, FIC hosts the Adolescent HIV Prevention and Treatment Implementation Science Alliance. This novel platform brings together researchers, program implementers, and policymakers in the United States and sub-Saharan Africa, as well as representatives from multilateral organizations. The Alliance aims to improve communication among these stakeholders and catalyze collaboration to enhance the evidence base for translating effective interventions into community- and population-level services, programs, and strategies at scale. In the reporting period, the Alliance held two meetings, the first in May 2017 and the second in January 2018.

VII. Health Disparities

Health disparities work is embedded in a variety of FIC programs and projects. For example, one NCD-Lifespan project is studying attitudes and perceived norms regarding IPV and exploring potential culturally-appropriate IPV prevention strategies in Pakistan.[49] Recognizing that women are disproportionately affected by IPV and IPV-related physical injury and psychological harm, this project aims to facilitate an understanding of the perceived barriers to and opportunities for community-based IPV prevention strategies in rural Pakistan, with relevance for other, comparable settings in which patriarchal norms are still strongly entrenched and programmatic attention to IPV is historically limited.

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49 R21TW010443

National Center for Advancing Translational Sciences

I. NCATS Executive Summary

The National Center for Advancing Translational Sciences (NCATS) was established to catalyze a transformation in the way health interventions are developed and to bring more treatments to more patients more quickly. Translation is the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public. Translational science is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process. Translational scientists share their expertise and work collaboratively to more effectively develop and deliver interventions that benefit the health of the public. These efforts support more efficient and effective intervention development for the prevention and treatment of all diseases.

II. Accomplishments and Activities

Tissue Chips for Drug Screening

Approximately 30 percent of promising medications fail in human clinical trials because they are found to be toxic despite promising pre-clinical studies in animal models. About 60 percent of candidate drugs fail due to lack of efficacy. NCATS' Tissue Chip program is an extramural program that demonstrates the promise of translational science. Tissue chip devices are designed as accurate models of the structure and function of human organs, such as the lungs, liver and heart. Once developed and integrated, researchers can use these models to predict whether a candidate drug, vaccine or biologic agent is safe or toxic in humans.

Tissue chips raise the exciting possibility to model both sexes, and to study sex-specific diseases. In 2016, NCATS issued a series of funding opportunities around tissue chip initiatives and projects, including the Tissue Chips for Disease Modeling and Efficacy Testing initiative designed to support development of models of human disease and pathology. The funding opportunity included language encouraging the study of sex differences in disease onset, progression, and response to therapy, as well as the use of primary cells or induced pluripotent stem cells representative of gender, genetic variations, and demographics. ORWH signed on as a participating organization for this exciting program.

One of the awardees of this program, Dr. Teresa K. Woodruff at Northwestern University is leading the project "Polycystic Ovary Syndrome (PCOS) and Androgen-Related Disease Modeling and Drug Testing in Multi-Organ Integrated Microfluidic Reproductive Platform." PCOS is a highly prevalent human health crisis for women in their reproductive years, but there are no good animal models of the disease. This project team has created a next-generation platform technology that will support the translation from mouse to human models of the female reproductive system (ovaries, fallopian tubes, uterus, cervix, adipose, liver and pancreas). The human model has demonstrated capability of mimicking a 28-day menstrual cycle (Xiao et al, 2017) and will be utilized to test drugs to treat PCOS. The project was funded by NCATS, NIEHS, and the NIH Office of the Director.

Zika Virus Repurposing Screening

In the midst of the recent global health emergency posed by the Zika virus outbreak and its link to microcephaly and other neurological conditions in babies born to infected women, NCATS scientists worked in collaboration with Johns Hopkins University and Florida State University to rapidly identify compounds that potentially can be used to inhibit Zika virus replication and reduce its ability to kill brain cells. The research team screened a library of approximately 6,000 compounds, including approved drugs, clinical trial drug candidates, and other pharmacologically active compounds for activity against Zika virus infection. Combination treatments using one compound from each category (neuroprotective and antiviral) further increased protection when tested on human neural cells.

Results of the study were rapidly published to enable these compounds to be studied by the broader research community to help combat the Zika public health crisis. A company is now sponsoring an early phase clinical trial to establish safety of one drug (niclosamide) identified by the investigators. These results demonstrate the benefits of this screening strategy to rapidly translate the potential of candidate drugs into Zika virus therapeutics.

Rare Diseases

NCATS also supports a number of research studies in rare diseases in women through the Rare Diseases Clinical Research Network (RDCRN). Protocols focus on women's health through either enrollment and/or disease(s) focused on women. Studies on pregnancy or reproductive systems are also included in the RDCRN. Research areas include: autonomic inflammatory reflex, pregnancy in Osteogenesis Imperfecta registry, trials using Sirolimus in Lymphangioleiomyomatosis, and reproductive health in women with vasculitis.

Clinical and Translational Science Awards (CTSA) Program

The NCATS Clinical and Translational Science Awards (CTSA) Program strengthens and supports clinical and translational research from scientific discovery to improved patient care and leverages the expertise and resources from a network of high-performing biomedical research institutions across the United States. Several programs within the CTSA program support aspects of women's health research.

- Collaboration & Engagement Domain Task Force of the CTSA Program

The CTSA Program contains several trans-CTSA workgroups that focus on short- and long-term needs of the Program, with the goal to enable translational science and to advance translational research. One of these workgroups, the Collaboration & Engagement Domain Task Force, focuses on:

- Engaging stakeholder communities so they contribute meaningfully across the translational sciences spectrum.
- Enabling team science to become a major academic model.
- Ensuring that all translational science is performed in the context of collaborative team science and that shared leadership roles are the norm throughout the entire translational science process.

One their current activities is determining which CTSA institutional strategies are most effective at engaging community partners. Best practices will be disseminated across the entire CTSA Program (Skinner et al, 2018).

- CTSA Program Trial Innovation Network: Recruitment Innovation Center

The Trial Innovation Network is a collaborative initiative composed of three key organizational partners: three Trial Innovation Centers, a

Recruitment Innovation Center and the CTSA Program hubs. NCATS' vision for the Trial Innovation Network is to address critical roadblocks in clinical trials and to accelerate the translation of novel interventions into life-saving therapies. The CTSA Program Recruitment Innovation Center (RIC) leverages expertise in clinical informatics and patient and community engagement to increase the number of disenfranchised persons, including women of color, enrolled in clinical research studies. The RIC pairs informatics expertise with engagement expertise to make customized engagement and recruitment materials. The RIC researchers and their collaborators have published several peer reviewed manuscripts, videos, and provided other resources that promote evidence-based strategies that may enhance engagement, recruitment, and retention of disenfranchised persons in clinical trials. To date, the RIC has provided more than 60 consultations to investigators seeking assistance with their clinical trial. RIC investigators collaborate with other investigators to establish the best methods to incorporate underserved communities in research.

- Training & Career Development

The CTSA Program supports two types of formal clinical research training awards at CTSA Program hubs. Both programs combine formal course work with direct research experience, and many institutions' programs offer opportunities to pursue additional advanced degrees. The KL2 awards support mentored research career development for clinical investigators who have recently completed professional training and who are commencing basic, translational and/or clinical research. The CTSA Program hub selects KL2 candidates, providing them with a rich career development experience in a multidisciplinary setting. KL2 appointees—referred to as Clinical Research KL2 Scholars—come from a variety of fields (e.g., medicine, dentistry, nursing, the behavioral sciences, biostatistics and epidemiology) and can receive up to five years of career development support.

Many CTSA Program hubs also include programs that provide predoctoral trainees with an introduction to clinical and translational research through the TL1 program. The TL1 awards support students seeking a practical introduction to clinical and translational research. The CTSA Program hub selects TL1 candidates, providing full-time research training support for predoctoral candidates and combined health-professional doctorate-master's candidates as well as postdoctoral fellows seeking additional training in clinical research.

An analysis of the CTSA KL2 program from 2006 to 2013 (Sweeney et al, 2017) found this program is successful in supporting women seeking research careers. Information was collected from 48 institutions that provided information about 914 KL2 scholars. Of those, 620 (68%) were medical doctors, 114 (12%) had other clinical training, and 177 (19%) were non-clinician PhDs. Fifty-three percent (487) were female; 12% (108/865) were members of racial or ethnic groups underrepresented in medicine (URM). After completing KL2 training, 96% (558/582) remained engaged in research. Among scholars who completed KL2 training two or more years earlier, 39% (149/374) had received independent funding. Independent funding was from non-National Institutes of Health (NIH) sources (120 scholars) more often than from NIH (101 scholars). The odds of a non-clinician attaining independent funding were twice those of a clinician (odds ratio 2.05, 95% confidence interval 1.11–3.78). Female and URM scholars were equally as likely as male and non-URM scholars to attain independent funding.

III. Additional information

NIH Strategic Plan for Women's Health Research

1. NIH Strategic Plan Mapping to NCATS Research

   a. Tissue Chips for Drug Screening maps to Goal 1: INCREASE SEX DIFFERENCES RESEARCH IN BASIC SCIENCE STUDIES, specifically:

      1.2 Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

      1.3 Study sex differences using a systems biology-based approach. This will include research based on new technology platforms

   b. Recruitment Innovation Center maps to GOAL 2: INCORPORATE FINDINGS OF SEX/GENDER DIFFERENCES IN THE DESIGN AND APPLICATION OF NEW TECHNOLOGIES, MEDICAL DEVICES, AND THERAPEUTIC DRUGS, specifically:

      2.3 Develop the information systems needed for collecting, sharing, and comparing clinical data for diseases and conditions of women and girls.

Inclusion activities 2017-2018

1. CTSA Program Collaboration & Engagement Domain Task Force

2. Recruitment Innovation Center

IC STEM Efforts 2017-2018

1. Clinical Research KL2 Scholars Program of the CTSA Program

2. CTSA Program hub TL1 programs.

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National Center for Complementary and Integrative Health

I. Executive Summary

The National Center for Complementary and Integrative Health (NCCIH) is the lead Federal agency for scientific research on the usefulness and safety of complementary and integrative health practices. Complementary and integrative health approaches include modalities and products with a history of use or origins outside of conventional medicine. Examples include mind-body interventions, such as massage, acupuncture, yoga, and meditation; and natural products, such as dietary supplements and probiotics. To address the need for objective evidence regarding the safety and efficacy of many of these approaches, NCCIH supports rigorous scientific investigation to better understand how these interventions work, for whom, and the optimal method of practice and delivery.

Many individuals seek complementary and integrative health approaches to improve their health and well-being or to manage symptoms associated with pain, chronic diseases, or other conditions. Results from the 2017 National Health Interview Survey, conducted by the Centers for Disease Control and Prevention with support from NCCIH, indicate that more than one-third of the population uses complementary and integrative health approaches (1). Yoga was the most commonly used complementary health approach among U.S. adults in both 2012 and 2017, with women more than twice as likely to use yoga compared with men. Women are also more likely to meditate – the second most used approach – and to see a chiropractor.

NCCIH is supporting basic, mechanistic, clinical, and translational research to determine if complementary and integrative health approaches are effective in treating a variety of conditions, including pain and depression. The Center is looking at the effect of the microbiome on a variety of psychological conditions. Investigators have shown that a ketogenic diet may improve some of the behaviors associated with autism spectrum disorder in a mouse model of the disease.

Pain is an important factor in many conditions affecting women of all ages and is a common reason for individuals to turn to complementary and integrative health approaches. NCCIH is supporting high-resolution imaging techniques to explore the gut-brain axis and the effect of the microbiome on behavior. Fibromyalgia is a common, painful disorder that mostly affects women. Using functional magnetic resonance imaging, investigators showed that there were increased signals in areas of the brain responsible for pain processing. Multidisciplinary treatment is an important component to manage fibromyalgia. Investigators have recently demonstrated that tai chi is as effective as aerobic exercise for the management of fibromyalgia and individuals are more likely to do it.

NCCIH has a robust research portfolio in natural products, including botanicals. Investigators are developing ways to separate the components of these plant products and to determine their therapeutic effects in pre- and post-menopausal women.

NCCIH is increasing its focus on wellbeing and the effects of stress on the body. Researchers have demonstrated that exposure to stress may worsen endometriosis in women of child-bearing age.

II. Accomplishments and Activities

Women's Health Research

Goal 1: Increase sex differences research in basic science studies

1.5: Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders.

1.8: Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and wellbeing.

Ketogenic Diet in Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a development disorder that affects communication and behavior. Although autism can be diagnosed at any age, it is said to be a "developmental disorder" because symptoms generally appears in the first two years of life. Autism is known as a "spectrum" disorder because there is wide variation in the type and severity of symptoms. Although ASD can be a lifelong disorder, treatments and services can improve a person's symptoms and ability to function. Medication may help to treat some of the symptoms that are common in ASD and behavioral, psychological, and educational programs can be helpful as well. Research is ongoing to determine if there is any correlation between certain diets and improvement in the behaviors associated with ASD.

A ketogenic diet is made up of high-fat, moderate protein, and low carbohydrates. The goal of a ketogenic diet is to reach a state of ketosis where the body is burning fats rather than carbohydrates. Normally, the carbohydrates contained in food are converted into glucose, which is particularly important for brain function. However, if there is a lack of carbohydrates in the diet, the liver converts fat into fatty acids and ketone bodies. The ketone bodies pass into the brain and replace glucose as an energy source.

Symptoms of ASD are frequently paired with a diagnosis of epilepsy. Medically-supervised ketogenic diets are remarkably effective nonpharmacological treatments for epilepsy, even in cases that do not respond well to conventional medications. There is accumulating evidence that supports the efficacy of ketogenic diets in treating the core symptoms of ASD in animal models as well as limited reports of benefits in patients. Investigators tested the behavioral effects of a ketogenic diet in a mouse model with behavioral characteristics of ASD and comorbid epilepsy. Both male and female mice were fed a control diet or one of two ketogenic diet protocols beginning at 5 weeks of age. Beginning at 8 weeks of age, sociability and repetitive behavior of the mice was tested. A ketogenic diet improved behavioral characteristics of ASD in a sex- and test-specific manner and never worsened behaviors. Ketogenic diet feeding improved multiple measures of sociability and reduced repetitive behavior in female mice, with limited effects in males. Additional experiments in female mice showed that a less strict, more clinically-relevant diet formula was equally effective in improving sociability and reducing repetitive behavior. Taken together these results add to the growing number of studies suggesting that ketogenic and related diets may provide significant relief from the core symptoms of ASD and suggest that in some cases there may be increased efficacy in females.

Goal 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs

2.6: Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas, such as pain, brain activity, metabolism infectious diseases, inflammation, and drug delivery.

Gut-Brain Interactions in Healthy Women

Comprising trillions of organisms and responsible for numerous biologically important processes, the human microbiota has a role in health and disease. One area of interest is the role of the gut microbiota within the gut-brain axis and their relationship to emotional processing. While spatially separated from the brain by both the intestinal epithelial barrier and the blood brain barrier, there is bidirectional communication between the gut microbiota and the central nervous system (CNS) via the vagus nerve, the immune system, and neuroactive metabolites released into systemic circulation. Evidence for the influence of the microbiota on the CNS has been plentiful in the preclinical literature and suggests that beyond brain development, the microbiota can influence behavior and affect. Animals raised in germ-free environments exhibit altered brain chemistry as well as changes in behavior, with increased risk taking, reduced anxiety, and decreased sociability. Some of the biochemical changes resulting from germ-free status are irreversible, even after colonization of the animals with normal gut microbiota later in life. Other abnormalities, such as anxiety behavior, can be reversed after reconstitution of the gut microbiota. While rodent models have demonstrated effects of the gut microbiota on emotional, nociceptive and social behaviors, there is little translational human evidence to date. Investigators sought to identify brain and behavioral characteristics of healthy women clustered by gut microbiota profiles. Two bacterial genus-based clusters were identified, one with greater Bacteroides abundance, one with greater Prevotella abundance. The Prevotella group showed less hippocampal activity viewing negative images. White and gray matter imaging discriminated the two clusters, with accuracy of 66.7 percent and 87.2 percent respectively. The Prevotella cluster was associated with differences in emotional, attentional, and sensory processing regions. For gray matter, the Bacteroides cluster showed greater prominence in the cerebellum, frontal regions, and the hippocampus. These results support the concept of brain-gut-microbiota interactions in healthy humans. Further examination of the interaction between gut microbes, brain and affect in humans is needed to inform preclinical reports that microbial modulation may affect mood and behavior.
Objective

Brain-gut-microbiota interactions may play an important role in human health and behavior. However, while rodent models have demonstrated effects of the gut microbiota on emotional, nociceptive and social behaviors, there is little translational human evidence to date. In this study we identify brain and behavioral characteristics of healthy women clustered by gut microbiota profiles.

Methods

Forty women supplied fecal samples for 16s rRNA profiling. Microbial clusters were identified using Partitioning Around Medoids. Functional magnetic resonance imaging was acquired. Microbiota-based group differences were analyzed in response to affective images. Structural and diffusion tensor imaging provided gray matter metrics (volume, cortical thickness, mean curvature, surface area) as well as fiber density between regions. A sparse Partial Least Square-Discrimination Analysis was applied to discriminate microbiota-clusters using white and gray matter metrics.

Results

Two bacterial genus-based clusters were identified, one with greater *Bacteroides* abundance (n=33), one with greater *Prevotella* abundance (n=7). The *Prevotella* group showed less hippocampal activity viewing negative valences images. White and gray matter imaging discriminated the two clusters, with accuracy of 66.7% and 87.2% respectively. The *Prevotella* cluster was associated with differences in emotional, attentional, and sensory processing

regions. For gray matter, the *Bacteroides* cluster showed greater prominence in the cerebellum, frontal regions, and the hippocampus.

Conclusions

These results support the concept of brain-gut-microbiota interactions in healthy humans. Further examination of the interaction between gut microbes, brain and affect in humans is needed to inform preclinical reports that microbial modulation may affect mood and behavior.

Tai Chi and Fibromyalgia

Fibromyalgia is a common disorder that involves widespread pain, tenderness, fatigue, and other symptoms and can interfere with a person's ability to perform everyday activities. An estimated 5 million American adults have fibromyalgia, and 80 to 90 percent of them are women. Though fibromyalgia is often considered challenging to treat, some pharmacologic and nonpharmacologic interventions have shown promise in reducing its symptoms and impact.

Tai chi is a traditional Chinese mind and body practice that combines meditation with deep breathing, relaxation, and gentle movements. Past research found that tai chi lessened pain and improved physical and mental health in patients with fibromyalgia. However, larger and more rigorous studies were needed to confirm the benefits. Investigators compared the effectiveness of tai chi with that of aerobic exercise, a core part of standard fibromyalgia treatment, and determined whether tai chi's effects were related to its frequency and duration. This study assessed improvements in intensity of pain, physical function, fatigue, morning tiredness, depression, anxiety, job difficulty, and overall well-being in individuals randomly assigned to supervised aerobic exercise or tai chi. Tai chi resulted in greater improvement in symptoms when compared to aerobic exercise, and great improvement was seen with 24 weeks than 12 weeks of tai chi. As aerobic exercise may sometimes be difficult in individuals with fibromyalgia and tai chi appears to be at least as effective, if not better, to manage fibromyalgia, this may be an important therapeutic option for individuals with fibromyalgia.

Brain Circuitry in Pain Catastrophizing

Pain catastrophizing (CAT) is a common feature of chronic pain, including fibromyalgia, and is strongly associated with amplified pain severity and disability. CAT is an irrational thought in believing that something is far worse than it is. Individuals with pain often catastrophize feeling helpless, pessimistic, ruminate about pain-related symptoms, and magnify pain complaints. While previous neuroimaging studies have focused on evoked pain response modulation by CAT, the brain mechanisms supporting pain CAT itself are unknown. Investigators designed a functional magnetic resonance imaging (fMRI)-based pain CAT task where individuals with fibromyalgia reflected on how CAT statements impact their typical pain experience. When compared with their responses to neutral statements, fMRI scans showed a higher signal in brain areas that show altered function in chronic pain. Understanding the brain circuitry encoding pain CAT in fibromyalgia may be important in identifying and evaluating the success of interventions target negative affect in chronic pain management.

Goal 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices and therapeutic drugs

2.1: Encourage the development of technologies that will address sex-based differences at all scales of detail, from the nanometer to the whole person.

2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women

Modulating Concentrations of Bioactive Compounds

Many adults in the United States take one or more dietary supplements either every day or occasionally. Today's dietary supplements include vitamins, minerals, herbals and botanicals, amino acids, enzymes, and many other products. Botanicals are plants, or a plant part valued for its medicinal or therapeutic properties, flavor, and/or scent. Botanical supplements contain multiple bioactive compounds that target numerous biological pathways, which may produce a variety of clinical effects. The development of a given botanical preparation for eventual clinical application requires extensive, detailed characterizations of the chemical composition, as well as the biological availability, biological activity, and safety profiles of the botanical. Interdisciplinary evaluation and standardization of botanical dietary supplements widely used for women's health is the overarching goal of the University of Illinois at Chicago/NIH Center for Botanical Dietary Supplements Research. A portion of the hops plant (*Humulus lupulus)* has a long tradition of use as a botanical remedy for mood and sleep disturbances and more recently for the relief of menopausal symptoms. The major bioactive compounds in hops include 8-prenylnaringenin (8-PN), which is estrogenic, and xanthohumol (XH), which has chemopreventive properties. Investigators generated DESIGNER extracts of the hops plant through a process that depletes select ingredients and enriches others to study the biological activity of several active compounds in hops. Hops extracts were designed for pre- and post-menopausal women containing various amounts of 8-PN and XH. For post-menopausal women, the levels of 8-PN and XH were balanced for both estrogenic and chemopreventive properties, while the extract designed for pre-menopausal women contained reduced 8-PN levels and high XH concentrations to minimize estrogenic while retaining chemopreventive properties. This study demonstrates the feasibility of modulating the concentrations of bioactive compounds in botanical extracts that may lead to the development of safer products that are more effective.

Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women

3.1: Conduct developmental and developmentally-framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan.

Stress and Endometriosis

Endometriosis is a common gynecological disease associated with pelvic pain and infertility. The symptoms may be so severe and chronic that they may be considered stressful events that negatively impact the quality of life of patients. Women with endometriosis report more stress, pain, depression, and anxiety, as well as poorer quality of life than women with other pain syndromes. Although the relationship between stress and endometriosis is not completely clear, current understanding in reproductive biology suggests that stress may impact the mechanisms responsible for endometriosis. Investigators have used an animal model to show that stress prior to the surgical induction of endometriosis resulted in more severe disease than in those animals that were not exposed to stress. They have also showed that stress management could prevent the outgrowth of lesions and inflammation. This study provides further evidence for the important role of stress in enhancing inflammatory and pain mechanisms that may results in a higher morbidity of patients with endometriosis who are exposed to chronic stress.

Funding Initiatives

NCCIH has funded several major projects in FY2017-2018 with a focus on women's health.

- Self-Administered Hypnosis Treatment for the Management of Hot Flashes in

Women: A Randomized Clinical Trial - The health of breast cancer survivors and post-menopausal women is negatively impacted by hot flashes (vasomotor symptoms). This study will determine the efficacy of a fully self-administered hypnosis intervention for hot flashes and the effect on mood, sleep, and quality of life. This study is innovative because it seeks to deliver a provider-intensive therapy in a fully self-administered way, and to explore mechanisms by which it reduces hot flashes.

- Mindful Moms in Recovery: Yoga-based Mindfulness Relapse for Pregnant Women with Opioid Disorder - Building capacity for providing medication-assisted therapy and collaborative care to pregnant and parenting women with opioid-use disorder (OUD) in obstetric settings is a priority of the New Hampshire State Targeted Response (STR) to the Opioid Crisis. This project represents a partnership with NH leadership to augment this STR initiative through development and pilot evaluation of a trauma-informed yoga and mindfulness relapse prevention intervention (Mindful Moms in Recovery: MMORE) to support recovery and treatment retention for pregnant women. If successful, MMORE will offer a non- pharmacological alternative to support recovery and improve the lives of pregnant and parenting women with OUD and their infant children.
- Optimizing a Mindfulness-based Intervention for Poor Sleep Quality during Pregnancy - Sleep is a key aspect of health that often worsens during pregnancy, but there is a lack of interventions to address this problem. This project will optimize and conduct preliminary testing of a mechanism-focused, mindfulness-based intervention to improve poor sleep quality during pregnancy.
- Inositol Supplementation to Treat Reproductive and Metabolic Dysfunction in Polycystic Ovarian Syndrome: A Double-Blind Randomized Controlled Trial - Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in women in the U.S. and is characterized by both reproductive (anovulation and androgen excess) and metabolic dysfunction (insulin resistance). PCOS lacks a simple, safe and effective treatment for women of all ages and all weights. Recently a dietary supplement, inositol, has been used widely to treat women with PCOS. However, there are no well-designed trials to address the risk/benefit ratio, identify the mechanism of action and select the proper dose. This study will test three doses of inositol to determine effects on clinical outcomes.
- Flaxseed Effects on Gut Microbial Metabolism and Circulating Inflammation-related Metabolic Profiles in African American and Non-Hispanic White Women – An imbalance in the gut microbial environment has been associated with alterations in production of immune and inflammatory cytokines and other circulating metabolites contributing to inflammation. Gut microbial composition and function are amenable to modification by diet. Flaxseed (FS), a whole food commonly consumed as a dietary adjuvant for several purported health effects, is a rich source of the polyphenolic lignans. The proposed study offers a unique opportunity to characterize changes in microbial function and subsequent modification of circulating metabolic profiles related to chronic low-grade inflammation in a large sample of AA and NHW white women. Given the higher incidence of inflammation related chronic disease in AA, this study will contribute significantly to our understanding of the role of the microbiome in inflammatory metabolic processes.

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National Human Genome Research Institute

The origin of the National Human Genome Research Institute (NHGRI) dates back to 1989, when its preceding organizational entity (the National Center for Human Genome Research) was created to lead NIH's efforts in the Human Genome Project (HGP). Since the HGP's completion in 2003, NHGRI has funded and pursued genomics research to advance basic knowledge about how genomes function, discover the genomic underpinnings of health and disease, and facilitate the application of genomics to clinical care.

NHGRI is a pioneer in the development and dissemination of new genomic technologies, which has consistently catapulted the field forward and dramatically increased the accessibility of genomic approaches in biomedical research. NHGRI's focus on technology development has had a positive impact on the immediate field of genomics, but also the many disease-specific research efforts inside and outside of NIH, including those specific to women.

NHGRI also funds research that positively affects women in a more targeted manner, and NHGRI-funded research in FY17 and FY18 has led to advances in disease areas specific to women's health (such as endometrial cancers) and issues affecting maternal and child health (such as prenatal genetic testing). Women represent over half of the participants in NHGRI-funded human subjects research, and NHGRI ensures that male and female tissue, cell lines and model organisms are included equally in all studies.

Women are often at the center of health-related decision-making in families, and bear disproportionate psychosocial burdens associated with genetic testing and participation in genomics research. NHGRI has funded research and conducted outreach activities on the ethical and psychosocial aspects of participating in genomics research through activities in the NHGRI Ethical, Legal, and Social Implications (ELSI) research program and the intramural Social and Behavioral Research Branch.

Finally, NHGRI is committed to supporting the most qualified trainees, and ensuring that our training programs are accessible to all. Approximately half of the NHGRI intramural and extramural trainees are women.

Intramural Research

Intramural researchers at NHGRI carry out research relevant to several areas of women's health including reproductive cancers, maternal nutrition and reproductive health, perceptions and behaviors of women who are overweight, and prenatal genetic screening. The nature of these studies and some of their accomplishments are highlighted here.

One group of NHGRI intramural researchers has focused its research on understanding the genomic basis of endometrial (uterine) cancers. In one study, the researchers aimed to find genetic mutations associated with clear cell endometrial cancer (CCEC), which has a relatively poor prognosis, and found a new candidate driver gene—TAF1 (Le Gallo, et al., 2017). In another study, the researchers found that the FOXA2 gene is likely a driver gene for uterine carcinosarcomas (Le Gallo, et al., 2018). Lastly, the researchers explored the effects of FBXW7 mutations in aggressive endometrial cancers. They found several associated proteins in druggable pathways and uncovered evidence that endometrial cancer cells with FBXW7 mutations are more sensitive to certain cancer drugs in

lab-based experiments, providing a rationale for future research into their possible relevance to treatment (Urick & Bell, 2018).

NHGRI researchers have also participated in social and behavioral research with women. One study found that women's history with their own weight (whether they have always been overweight, have recently become overweight or have steadily become obese) influenced their concerns for their child's weight, their feelings of shame or guilt, and how they perceived their restriction of their children's diets (Bouhlal et al. 2018). In another study with women who are overweight, the researchers found that women who perceived themselves as having a family history of overweight had higher body acceptance than those who didn't (Eisenberg et al., 2017). This is important because low body weight acceptance is a strong predictor of disordered eating and unhealthy behaviors. The knowledge gained from these studies can help formulate effective interventions for women who are overweight, as well as their children, to ensure better emotional and physical health.

Maternal nutrition can have a large impact on reproductive health. For this reason, NHGRI researchers have also examined the influence of maternal vitamin B12 deficiency on pregnancy in a mouse model of lacking the transcobalamin-vitamin B12 receptor, CD320. When vitamin B12 was limited, fetal development was arrested. Supplementing mothers with vitamin B12 allowed for full fetal development, but the offspring still died soon after birth. This experimental model will continue to allow researchers to study vitamin B12 deficiency during pregnancy in mammals (Bernard, et al. 2018).

As non-invasive prenatal testing becomes more prevalent in the clinic, NHGRI intramural researchers are studying why results are sometimes inconsistent between non-invasive prenatal testing (through maternal cell-free DNA [cfDNA] testing) and diagnostic fetal karyotype testing. They are also working on how to resolve these inconsistencies. A pilot study showed that it was possible to resolve inconsistencies in 7 of 12 cases using a systemic approach. Among the reasons for inconsistency were cancer in the mother and abnormalities that were in the placenta but not the fetus (Wilkins-Haugh et al., 2018). A review paper from this group also showed that many types of maternal factors and abnormalities can be responsible for inconsistencies, including maternal copy-number variants, maternal tumors, and disorders that affect DNA size and metabolism (Bianchi, 2018). Such findings can help inform clinical recommendations for how to handle prenatal screening results that point to maternal abnormalities. These NHGRI researchers are also conducting research providing pregnant women who are carrying fetuses with trisomy 21 (Down syndrome) with safe medication that can improve brain function after birth; they have recently published an ethical exploration of this kind of therapy (de Wert et al. 2017). In addition, they have performed a comprehensive comparison of the three most utilized mouse models of Down syndrome, with a particular focus on different phenotypes at different stages of the lifespan. The purpose of this work is to find the model that best mimics changes in the developing brains of humans with trisomy 21 (Aziz et al. 2018).

Ethical, Legal, and Social Implications (ELSI) Research Program

NHGRI's Ethical, Legal and Social Implications (ELSI) Research Program was established in 1990 as an integral part of the Human Genome Project (HGP). The Program's primary mission is to foster basic and applied research on the ethical, legal and social implications of genomic research and medicine for individuals, families and communities. NHGRI dedicates at least 5% of its annual extramural research budget to support research focused on these issues, including ELSI issues related to the health of women. NHGRI is currently funding a number of projects that focus

on ELSI issues related to noninvasive prenatal testing (NIPT) (in which a maternal blood sample is used to screen DNA from the mother and fetus for chromosomal abnormalities) and women's health.

Preparing for Emerging Applications of Noninvasive Prenatal Testing

This study (R21 HG008511) anticipated the widespread adoption of noninvasive prenatal genetic testing and aimed to ensure that informed consent practices and counseling are structured to meet the needs of expectant parents for the decision-making process. The study, through focus groups with pregnant women, found that access to prenatal genetic screening (specifically, cell-free fetal DNA screening) will increase the complexity of decision-making for women and that the patient-provider relationship and shared decision-making processes will be of key importance as prenatal genetic screening becomes more prevalent (Agatisa et al., 2018). The project also highlighted the importance of collaborations between genetic counselors and obstetric providers to better equip obstetric providers to educate their patients about prenatal screening (Agatisa et al., 2018).

Ensuring Patients' Informed Access to Noninvasive Prenatal Testing

Obstetric providers will increasingly need to be equipped to have conversations with their patients about NIPT to help them make informed decisions. This project (R01 HG010092) aims to test whether an evidence-based communication tool will equip patients and their partners to make informed decisions about NIPT while decreasing their decisional conflict.

Factors Influencing Access and Utilization of Genetic Prenatal Care Services Among Women from Underserved Populations

There is a lower uptake of prenatal screening services among underserved populations, which has resulted in disparities in outcomes. Researchers carrying out this study (K01 HG009542) will conduct community based participatory research with African American and Latina women to learn about their understanding of prenatal genetic services as well as their desire for these services. The researchers will then communicate their results to the communities to facilitate discussions about prenatal testing. In the long term, this could increase uptake of these services in underrepresented communities and improve outcomes.

Utah Center of Excellence in ELSI Research: UCEER

The University of Utah Center for Excellence in ELSI Research (UCEER) (RM1 HG009037) began in spring of 2016 and has a focus on population screening for genetic conditions in the health care of women and children, specifically prenatal genetic screening and newborn screening. Among its goals are to identify how aneuploidy screening information and choices are communicated to couples by providers and to use the Utah Population Database to describe rates of prenatal screening in the population of pregnant women in Utah. Research from this center has already shown that prenatal screening results are often confusing for women and highlighted the need for educational interventions (Rothwell, et al. 2017); that video education tools about newborn screening and dried blood spots improved knowledge, support, and satisfaction among fathers for the use of dried blood spots for research (Rothwell, et al. 2017); and that many factors affect women's decisions about in vitro fertilization, including cost as well as their beliefs and values about conception and disability (Lamb et al., 2018); among others results.

Health care system-led familial risk notification: design and ethical assessment

Genetic testing that reveals an individual's susceptibility to a disease also has implications for the individual's family. This study (R01 HG010144) aims to assess the feasibility of notifying the family members of an individual

(when they receive care in the same healthcare system) about their potential risk for actionable genetic findings based on the results of the individual. The study will test this approach with breast cancer/ovarian cancer and Lynch syndrome susceptibility genes. This type of familial testing, if successful, could help identify more individuals with high risk for certain diseases, including breast and ovarian cancer, and help provide them with appropriate follow-up care.

CSER

NHGRI, with co-funding from NCI, began the Clinical Sequencing Exploratory Research (CSER) initiative to: 1) leverage the Institute's long-standing experience in genomic sequencing and analysis to ease the adoption of these methods into clinical care, 2) guide the development and dissemination of best practices for the integration of clinical sequencing into clinical care, and 3) research the ethical, legal, and psychosocial implications of bringing broad genomic data into clinical decision-making including, for example, evaluation of the risks and potential benefits associated with the return of incidental findings or information on variants of uncertain effect. The CSER program was continued for a second phase as the Clinical Sequencing Evidence-generating Research program, with an expanded focus of assessing the clinical utility of genome sequencing in diverse participants. In line with these goals, CSER funded the following projects:

Clinical Implementation of Carrier Testing using NGS

This project (UM1 HG007292), which ended in 2017, investigates the clinical implementation of carrier testing using whole genome sequencing to aid reproductive decision-making in adults. The study population includes women and their partners requesting pre-conception testing for cystic fibrosis carrier status, as well as other conditions. The group is working on a variety of projects that address the outcomes associated with carrier testing using WGS, which variants should be reported to doctors and patients, and the ethical and psychosocial implications of expanded carrier screening. So far, the research team has created a taxonomy for patients to help women and their partners make decisions about what categories of disease they would like to learn about for reproductive decision-making. They validated this taxonomy tool by surveying 1500 adult females who were Kaiser Permanente Northwest members and had received preconception genetic testing in the three years prior to this study (Leo et al., 2016). The study also observed that compared with targeted mutation screening, genome sequencing improves the sensitivity of detecting clinically relevant variants (Punj, et al., 2018).

Genomic sequencing to aid diagnosis in pediatric and prenatal practice: Examining clinical utility, ethical implications, payer coverage, and data integration in a diverse population.

This project (U01 HG009599), funded beginning in 2017, examines the clinical utility of whole exome sequencing in relation to a variety of health and reproductive outcomes. The study population includes pediatric and prenatal patients from diverse backgrounds who are affected by structural anomalies and developmental disorders. In addition to studying measures of clinical utility, the project will also address ethical, social and economic issues in the delivery of sequencing results and pilot a user-friendly application integrating clinical and genomic data for use by patients and providers. Recruitment for this project is underway.

Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT)

Newborn screening programs currently screen more than 4 million U.S. infants per year making them the most common form of genetic testing performed in the United States. Traditionally,

DNA-based testing has not been a primary newborn screening methodology but has been used for second-tier confirmation of the diagnosis for many newborn screening disorders for which molecular testing is available (e.g., cystic fibrosis). Genomic technologies have advanced dramatically over the past decade, however, to the point where the prospect of incorporating individuals' whole genome sequence information into their medical care is under serious discussion and careful study. The Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT) program, which began in 2013 and concluded in 2018 and was jointly funded by NHGRI and NICHD, featured pilot research projects investigating the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period. The intent of funding such projects is to further the understanding of disorders that appear during the newborn period and to improve treatments for these diseases.

NSIGHT funded 4 U19 cooperative agreement awards: 1) Genome Sequence-Based Screening for Childhood Risk and Newborn Illness (U19 HD077671, known as BabySeq), 2) Clinical and Social Implications of 2-day Genome Results in Acutely Ill Newborns (U19 HD077693, known as Stat-seq), 3) Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening (U19 HD077627, known as NBSeq), and 4) NC NEXUS, North Carolina Newborn Exome Sequencing for Universal Screening (U19 HD07763).

Two 2018 papers out of the consortium showed how genome sequencing newborns in neonatal intensive care units (NICUs) can accelerate diagnosis of genetic disease and result in better outcomes (Petrikin et al., 2018; Farnaes et al., 2018). These studies showed that genome sequencing allowed doctors to intervene more quickly than would otherwise be possible, and the resulting interventions lead to decreases in infant morbidity as well as cost savings due to avoidance of inappropriate treatment and rehospitalization.

In 2018, the NSIGHT studies were highlighted in a *Hastings Center Special Report* titled *"The Ethics of Sequencing Newborns: Recommendations and Reflections."*. In the lead article, *"Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies,"* the UCSF NSIGHT Ethics and Policy Advisory Board recommends the diagnostic use of targeted or genomic sequencing to inform medical management of symptomatic newborns while arguing that genomic sequencing is not yet ready for implementation in universal screening programs, such as newborn screening (Johnston et al., 2018).

Population Architecture using Genomics and Epidemiology (PAGE) Consortium

Genome-wide association studies, mostly in European populations, have identified many genetic variants related to disease, highlighting the need to further explore initial findings in non-European populations. PAGE is a consortium of U.S. studies that focuses on analyzing the relationship between genetic variants and a range of common diseases and traits. Beginning in 2011, PAGE focused on studying findings in non-European (African American, Hispanic/Latino, Asian, and Native Hawaiian) populations. Investigators collaborated with other consortia in developing a new genotyping method that is tailored to non-European populations and in conducting new analyses spanning a broad range of diseases and characteristics. A flagship paper summarizing the results of 26 genome-wide association studies in non-European participants and outlining best practices for studying genomic associations in diverse populations is under review.

Exonic variants and their relation to complex traits in minorities of the WHI

This PAGE study (U01 HG007376) is using over 40,000 samples from African Americans,

Hispanics, and Native Americans in the Women's Health Initiative (WHI) to investigate the genetic basis of common complex traits such as cardiovascular disease, cancer, body composition, blood lipids, glucose, and insulin. They will use the newly developed MEGA genotyping platform tailored to non-European populations. These studies will begin to address the under-representation of traditionally underserved populations, and therefore women in these populations, in genomic studies and provide mechanisms for these populations to benefit from genomic medicine.

Trans-NIH Initiatives

Because of the foundational and cross-cutting nature of genomics, NHGRI is also involved in several trans-NIH initiatives that have implications for women's health.

The Cancer Genome Atlas (TCGA)

The Cancer Genome Atlas (TCGA) was initiated in 2006 as a collaborative program directed and funded jointly by NCI and NHGRI. TCGA investigators are generating the atlas of genomic and molecular changes present in the genomes of numerous cancers, including reproductive cancers, breast ductal and lobular carcinoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma, endometrial carcinoma and uterine carcinoma. Importantly, TCGA data are made rapidly and publicly accessible to enable researchers anywhere around the world to make important discoveries (http://cancergenome.nih.gov). Findings from TCGA have been important in understanding and treating female reproductive cancers. Similar recent publications characterizing uterine carcinosarcomas, cervical cancer and pan-gynecological cancers provide important insights into their biology and potential treatments.

Molecular Characterization of Gynocological Cancers

Recent publications by the TCGA network have comprehensively analyzed gynocological cancers. This work demonstrates the importance of molecular characterization of gynecological cancers and provides important insights into their biology and potential treatments. For example, a comprehensive study of 57 uterine carcinosarcoma (USC) patients found that copy-number variation and recurrent TP53 somatic mutations are identified in 91% of cases. UCS are rare and aggressive tumors that account for less than 5% of all uterine malignancies. USC tumors show low levels of some hormone receptors, leading to a theory of USC being unlikely to benefit from hormone therapy. Instead, PARP, EZH2, PI3K/AKT pathway and cell-cycle inhibitors may be better therapeutic options for patients with USC (Cherniack et al., 2017). A novel approach to characterize and classify 228 primary cervical cancers identified several clusters including HPV-negative endometrial-like, keratin-low squamous, keratin-high squamous, and adenocarcinoma-rich subgroups. For the first time, several genes (ERBB3, CASP8, HLA-A, SHKBP1 and TGFBR2) were implicated in cervical cancer (The Cancer Genome Atlas Research Network, 2017). Finally, as part of the capstone Pan-Cancer Atlas project, TCGA investigators performed an integrated molecular analysis of 2,579 gynecological and breast cancer cases. This analysis highlighted shared characteristics across tumor types, and identified significant subtypes, suggesting potential therapeutic targets. The investigators were also able to develop a decision tree to classify patient samples using six laboratory-assessable molecular features (Berger et al., 2018).

Knockout Mouse Phenotyping Program (KOMP)

The Trans-NIH/Common Fund Knockout Mouse Phenotyping Program (KOMP2) provides broad, standardized phenotyping of a genome-wide collection of mouse knockouts. KOMP2 has led the way in ensuring reproducibility and transparency, as well as in considering sex as a biological variable, in research. Each knockout

is assessed for phenotype(s) in cohorts of mice, composed of 7 females and 7 males, and all data is analyzed and reported by sex. A report, entitled "Prevalence of sexual dimorphism in mammalian phenotypic traits", was published in 2017 (Karp et al., 2017). As with other projects supported by NHGRI, KOMP2 provides a foundational resource that delivers important data for a vast array of projects concerning women's health.

Genomics research in Africa: Human Hereditary and Health in Africa (H3Africa)

As part of the Common Fund Global Health Initiative, in partnership with the Wellcome Trust and the African Academy of Sciences (AAS), Human Heredity and Health in Africa (H3Africa) aims to facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases with the goal of improving the health of African populations. To accomplish this, the H3Africa Initiative is contributing to the development of the necessary expertise among African scientists and establishing networks of African investigators. Integrating research and training, the program funds several large research collaborations and smaller research projects investigating the genomic and environmental contributors to both communicable and non-communicable diseases in Africa. NIH-funded projects cover a large range of diseases including kidney disease, cervical cancer, TB, stroke, cardiometabolic diseases, neurological disorders, respiratory diseases, fevers of unknown origin, trypanosomiasis, and schizophrenia. In addition, several projects look at ethical, legal, and social implications of genomics research in Africa including cultural concepts and understanding, ethics of biobanking, public health interventions, and stigma. Finally, H3Africa encompasses infrastructure necessary for genomics research including Biorepositories to enable future use of samples and a pan-African informatics network to enable analysis of genomic-scale data. Several projects within H3Africa are focused on women's health issues.

The Role of the Microbiome in Cervical Cancer in Nigeria: The African Collaborative Center for Microbiome and Genomics Research

As part of the Human Heredity and Health in Africa Consortium (H3Africa), NHGRI supports the African Collaborative Center for Microbiome and Genomics Research (ACCME) (U54 HG006947). ACCME was established to study the associations between vaginal microenvironment, Human Papilloma Virus (HPV) genomics, and germline and somatic mutations in cervical cancer. The group has investigated the challenges and potential strategies to reduce cancer caused by coinfection of HPV in women who are HIV positive. Cervical cancer caused by HPV is a major contributor to women's preventable morbidity and mortality in Africa. In addition to contributing to knowledge about the complex vaginal microbiome, HPV persistence, and cervical carcinogenesis (Adebamowo et al., 2017), ACCME also develops capacity by training postdoctoral students to become the new generation of African scientific leaders while empowering hundreds of African scientists to conduct research in microbiome and genomics. Several papers have been published regarding Nigerian women's risk- and health-care-related behavior (Dareng et al., 2017; Dareng et al., 2018), methods for and attitudes towards screening (Daring et al.,2018; Filade et al. 2017; Modibbo et al., 2017), and incidence and prevalence of persistent HPV infection (Adebamowo et al., 2017) and vaginal microbiome composition (Adebamowo et al. 2017).

African Female Breast Cancer Epidemiology (AFBRECANE) Study

NHGRI also supports the African Female Breast Cancer Epidemiology (AFBRECANE) Study (U01 HG009784). Breast cancer is the commonest cancer in women globally and it is increasingly

overtaking cervical cancer as the commonest female cancer in low- and middle-income countries (LMIC). It is now a major cancer burden in Nigerian women. There are controversies about the epidemiology and molecular subtypes of breast cancer in African women including limited knowledge about the incidence of breast cancer and determinants of this incidence such as the role of different risk factors; incidence and prevalence of molecular subtypes of breast cancer and the contributions of indigenous African diets to breast cancer incidence. This study will focus on genomic and nutritional risk factors in Nigerian women.

Exploring Sex Differences in Genomic and Environmental Risk Factors for Cardiometabolic Disease in Africans

This Wits-INDEPTH H3Africa Collaborative Centre (CC) (U54 HG006938) aims to study the genetic and environmental risk factors for obesity and related cardiometabolic diseases (CMD) across four African countries, Ghana, Burkina Faso, Kenya and South Africa, as well as an urban study site in Soweto. The study has examined the genetic architecture of these African populations and is investigating genomic contributions to body fat distribution, considering the relevant environmental and social contexts, in order to contribute to an understanding of cardiometabolic disease susceptibility. This project received supplemental funding to increase the power to examine sex as a biological variable in their cohort given the clear sexual dimorphisms in several phenotypic variables including age of onset. Several recent publications in a supplemental issue of Global Health Action describe these gender differences (https://www.tandfonline.com/toc/zgha20/11/sup2?nav=tocList; Asiki et al., 2018; Boua et al., 2018; Micklesfield et al., 2018; Nonterah et al., 2018). Finally, this project now includes a study of the menopausal transition focused on examining changes over the menopausal transition in body composition and CMD risk factors, and evaluating the resulting risk from physiological, genetic and epigenetic perspectives.

Elucidating the differential gender impact of hereditary neurological disorders in the Malian population

Hereditary neurological disorders are very disabling diseases that are under-studied in Africa. This project (U01 HG007044) aims to clinically characterize these disorders in the Malian population, identify gene mutations related to neurological diseases, and to explore their effects in cell culture models to further our understanding of their function and interactions and our knowledge of common disease mechanisms. This project is addressing and mitigating the social stigma of women who give birth to children with disabilities through community education.

Stigma in African genomics research

Another way that women are disproportionately impacted by hereditary disorders and genomic studies in many African populations, including the study in Mali, is that mothers are often held responsible for hereditary diseases of their children. In a cultural environment where women are often valued for their ability to produce healthy offspring, stigma associated with genetic disorders can often result in severe societal and economic consequences for a woman who may or may not actually be a carrier, as well as for her family.

The H3Africa Ethics and Regulatory Working Group, the H3Africa Community Engagement Working Group, and a funded research project studying the Stigma in African Genomics Research on Schizophrenia and Rheumatic Heart Disease (U01 HG008226) are all working on aspects of this issue to provide support to women, families, and communities to understand and manage hereditary risk factors and disorders in a way that reduces the burden of blame and stigma that often falls disproportionately to women.

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National Library of Medicine

I. Executive Summary

The National Library of Medicine (NLM) is a leader in biomedical informatics and data science research and is the world's largest biomedical library. NLM conducts and supports research in methods for recording, storing, retrieving, preserving, and communicating health information; it also develops computational tools for molecular biology and biotechnology. By providing electronic access to reliable health sciences, toxicology, environmental health, and health services information issued by the National Institutes of Health (NIH) and other trusted sources, NLM serves as a national information resource for the public, patients, and families, as well as for medical education, research, and service activities of Federal agencies, industry, and other organizations. NLM also provides grant support to medical libraries for training biomedical librarians and other health information specialists.

The NLM Strategic Plan 2017-2027 positions NLM as a platform for biomedical discovery and data-powered health. It will accomplish this through the provision of tools for data-driven research, through enhanced dissemination and engagement pathways to reach more people in more ways, and by building a workforce for data-driven research and health. While NLM is disease-agnostic in its support of research and information services, many of its new directions support aims highlighted in the Office of Women's Health (ORWH) Strategic Plan.

In Fiscal Year (FY) 2017-2018, NLM's intramural research efforts and support for extramural research helped to advance computation approaches and information science in support of Women's Health Research. For example, NLM partnered with the National Cancer Institute to develop deep learning models to aid in interpreting cervical images to detect the presence of human papillomavirus infection, improve classification of the disease, and assist in early treatment in low-resource areas. NLM researchers also conducted investigations on the effects of hormone replacement therapy on Alzheimer's Disease using longitudinal databases available through the Centers for Medicare & Medicaid Services. Through its extramural portfolio, NLM provided funding for a wide range of research projects, including the development of computational personalized medicine approaches to detect biomarkers of breast cancer resistance, and the development of a clinical decision support system for making personalized assessments and recommendations concerning breast cancer patients. The goals and outputs of these research efforts align to the objectives set forth in Goal 2 of the ORWH Strategic Plan.

NLM is continuing to facilitate research on sex/gender influences on health through its publicly accessible information resources, which allow the reporting and querying of results by sex. For example, the Database of Genotypes and Phenotypes (dbGaP) archives and distributes data from studies that investigate the interaction of genotype and phenotype in humans. The database provides researchers with a wealth of data for such studies, including gender-related investigations, since sex is a phenotype measure in virtually all studies. The ability of researchers to query this database by sex of study participant is an important way that NLM is helping enable research that addresses investigations that account for sex/gender differences.

NLM's development of and support for health information resources are relevant to furthering Goal 5 of the ORWH Strategic Plan related to communication and social networking technologies. Examples of NLM information portals that contain information directly related to women's health issues include Medline Plus,

HealthReach, and the National Information Center for Health Services Research and Health Care Technology (NICHSR) ONESearch. In addition to these information registries, NLM has active outreach projects in communities around the country that address women's health issues, such as domestic violence and childbirth. Many of the programs are offered in multiple languages. NLM's outreach strives to meet communities where they are, providing information in tailored ways to reach diverse populations.

NLM's has actively sought to enhance training in data science and biomedical informatics for a wide range of populations and professional constituents. In FY 2017-2018, NLM funded 11 university-based training programs, as well as short-term training positions to undergraduate and graduate students to enhance recruitment of women and other groups underrepresented in biomedical informatics and data science. During this time, NLM also recruited women and minorities into its on-campus training programs as part of its intramural research efforts. In FY 2018, approximately one quarter of NLM's trainees were women. NLM's training efforts have helped to advance Goal 6 of the ORWH Strategic Plans objectives around enhancing the recruitment, retention, and advancement of women in science.

II. Accomplishments and Activities

Highlighted on the following pages are significant NLM accomplishments related to:

- Funding for computational approaches and information science in support of women's health research
- Data resources that facilitate research on sex/gender influences
- Data resources to support inclusion in clinical trials
- Efforts to enhance career development for women in biomedical sciences information resources to support women's health research and care delivery, and
- Outreach to reduce health disparities

Computational Approaches and Information Science in Support of Women's and Girls' Health

NLM oversees a broad portfolio of intramural and extramural research that utilizes computational approaches and information science to address public health and biomedical issues affecting women's and girls' health. Below is a selection of research advances funded by NLM during FY 2017-2018:

Deep Learning for Uterine Cervix Cancer Screening (Goal 2, Objective 2.5): A major data science effort is underway to screen uterine cervix images for pre-cancer. This work, in collaboration with the National Cancer Institute (NCI), is to assess the effectiveness of machine learning and artificial intelligence (ML/AI) techniques using deep learning neural networks for this purpose. This effort has led to the development of an automated visual evaluation (AVE) algorithm based on a deep-learning model to improve heretofore subjective and less reliable human visual inspection of aceto-whitened (VIA) regions of the uterine cervix (Hu et al, 2019). These whitened regions are indicative of human papillomavirus (HPV) infection, select types of which cause uterine cervical cancer. The AVE algorithm is trained and validated using a large archive of digitized cervical images collected by the NCI in a population-based longitudinal study of 9,406 women and substantially outperforms human interpretation (VIA). The digitized cervical images were taken with a fixed-focus camera ("cervicography") and are also called cervigrams. Automated visual evaluation of enrollment cervigrams identified cumulative precancer/cancer cases with greater accuracy (area under the curve [AUC] = 0.91, 95% confidence interval

[CI] = 0.89 to 0.93) than original cervigram interpretation (AUC = 0.69, 95% CI = 0.63 to 0.74; P < .001) or conventional cytology (AUC = 0.71, 95% CI = 0.65 to 0.77; P < .001). It can provide very sensitive screening (albeit with reduced specificity) with minimal clinical training or cost. Alternatively, it could be combined with HPV testing for greater risk stratification. The research partnership is also exploring the installation of automated visual evaluation on high quality smart phones or similar devices to realistically provide high-quality, point-of-care cervical screening.

Assessing the Effect of Hormone Replacement Therapy on Alzheimer's Disease (Goal 2, Objective 2.3): Large database collections of clinical data—from longitudinal research projects, electronic health records, and health information exchanges— provide opportunities to further examine findings from smaller scale clinical studies and to conduct retrospective epidemiological studies in areas that lack clinical trials. Given the importance of such databases to future research strategies, NLM has obtained access to and continues to gain research experience with deidentified longitudinal intensive care databases and the Centers for Medicare & Medicaid Services Virtual Research Data Center. One current research project is investigating the effect of hormone replacement therapy on Alzheimer's Disease and dementia among postmenopausal Medicare beneficiaries. The prevalence of Alzheimer's Disease and dementia is typically higher in women than in men, possibly due to their longer life expectancy or a decline in sex steroid hormone levels around menopause. For this study, about 700,000 female Medicare beneficiaries were identified and traced from the entry to the Medicare outpatient prescription drug program (Part D) to the onset of Alzheimer's Disease (Baik et al., 2017; Kury et al., 2017; Zhang et al., 2018; Rodriguez et al., 2018; Edinger et al., 2017).

Computational Personalized Medicine Approach to Detect Biomarkers of Breast Cancer Resistance (Goal 2, Objectives 2.5 and 2.7): The objective of this study, titled "Novel integrative method to detect biomarkers of breast cancer resistance," is to develop a computational framework, based on signal processing and machine learning techniques, to more accurately and efficiently identify novel cisplatin response candidate biomarkers in triple-negative breast cancer (TNBC) from next-generation sequencing data. NLM-funded researchers observed that TNBC and ovarian cancer tumors from non-carriers of germline mutation in BRCA1/2 (BReast CAncer genes 1 and 2) have upregulated immune functions, were aggressive and drug resistant, and progressed to metastasis. The researchers have developed a preliminary method to integrate genomic data when only a few samples are available. They also developed a method for differential expression analysis of single cell RNAseq data and a method for clustering cells using RNAseq data. (Wang et al., 2018; Zare et al., 2017; de Oliveira Taveira et al., 2017). [Grant Number: 5R00LM011595, University of Connecticut].

A Clinical Decision Support System for Making Personalized Assessments and Recommendations Concerning Breast Cancer Patients (Goal 2, Objectives 2.3 and 2.7): Even a modest improvement in the efficacy of clinical decision making has the potential to significantly improve patient outcomes and reduce health care costs. This research project, funded in FY 2017, aims to develop a novel decision support system that utilizes both the clinical features and the genomic profile of a breast cancer patient to assist the physician in integrating information about a specific patient (e.g., diagnostic subtype, tumor stage and grade, age, comorbidities) to make therapeutic plans for the patient. As a result of this grant, the project team developed a new method for identifying local recurrences of breast cancer that performed substantially better than other methods. They also developed an algorithm, called Integrative Causal Discovery (ICD), that has the capability to identify direct

causal influences of breast cancer. (Lee et al., 2017; Morris et al., 2017; Rathnam et al., 2017; Cai et al., 2016). [Grant Number: 5R01LM011663, University of Pittsburgh].

Elucidating the Role of the Genetic and Environmental Determinants of Preterm Birth Using Integrative Computational Approaches (Goal 2, Objectives 2.3, 2.4, and 2.7): Given the wealth and availability of genomic and environmental exposure data, computational methods provide a powerful opportunity to identify population-specific determinants of disease. The goal of this research project, funded in FY 2018, is to develop computational approaches to integrate diverse genetic and environmental exposure data sets to elucidate factors that affect disease in diverse populations and apply them to the study of preterm birth. These NLM-funded researchers leveraged existing genetics data to identify a large lineage-matched cohort. They used integrative computational methods to carry out population-specific case-control analyses, and discovered several variants significantly associated with preterm birth. In the context of elucidating environmental determinants of preterm birth, the researchers are working on a study to investigate relationships between singleton preterm birth, environmental exposures, and socioeconomic factors across California. (Padula et al., 2018; Wang et al., 2018; Kosti et al., 2018). [Grant Number: 5K01LM012381, University of California at San Francisco].

Enhancing Intimate Partner Violence Identification through Automated Electronic Health Record Summarization (Goal 2, Objective 2.3): Computer-based approaches for intimate partner violence (IPV) universal screening have led to significantly higher screening rates and detection rates, as well as receipt of IPV services in the emergency department. However, these approaches rely on information collected from the patient and do not utilize the longitudinal IPV data existing in electronic health records, which have high predictive power of IPV risk. In order to enhance the effectiveness of IPV screening, NLM-funded researchers were awarded funds in FY 2018 to develop and assess an automatic clinical data summary tool that extracts, abstracts, and synthesizes patient historical IPV information from the electronic health record and then delivers that critical information to emergency department providers at the point of care. As this grant was recently issued, no findings have yet been submitted. [Grant Number: 1R21LM012945; Medical University of South Carolina].

Decision-Making Modeling for Treating Intimate Partner Violence (Goal 2, Objective 2.4): Reports on the effectiveness of standard treatments for intimate partner violence (IPV), as well as research findings, suggest that different treatments may be more effective in reducing violence recidivism in certain situations. Many factors influence how participants respond to treatment. These factors include demographics, types of violence, and treatment delivery. Standard IPV treatment does not reflect this variability and does not provide equal opportunity for recovery to all who are struggling with IPV. The goal of this project, awarded in FY 2018, is to reveal which treatment is most effective in reducing violence recidivism for each subgroup. The researchers are utilizing a data-driven approach to systematically investigate patterns of violence to identify subgroups of individuals who respond similarly to treatment. The research aims to reduce the inequality faced by many individuals who are currently only offered generic treatment for the complex problem of IPV despite their circumstances calling for tailored solutions. [Grant Number: 1R01LM012518; Case Western Reserve University].

Leveraging EHR to Collect and Analyze Social, Behavioral & Familial Factors (Goal 2, Objective 2.3) The importance of understanding interactions among social, behavioral, environmental, and genetic factors and their relationship to health has led to greater

interest in studying these determinants of disease in the biomedical research community. While some knowledge exists regarding contributions of specific determinants such as socioeconomic status, educational background, tobacco and alcohol use, and genetic susceptibility to particular diseases or conditions, enhanced methods are needed to analyze and ascertain interrelationships among multiple determinants and to discover potentially unexpected relationships that may ultimately contribute to improving patient care and population health.

The goal of this project was to use data from electronic health record (EHR) systems and computational approaches for collecting information related to social, behavioral, and familial (SBF) factors for subsequent analyses in order to enhance the understanding of how these factors interact in patients with specific health conditions.

The main findings and contributions included: 1) There is variation in where and how SBF factors are documented in the EHR. Insights and guidance have been provided for standardizing and improving future EHR documentation of these factors; 2) Details associated with different SBF factors can be extracted, encoded, and structured from clinical text in the EHR using automated natural language processing (NLP) techniques for subsequent use (open-source NLP modules have been developed, evaluated, and disseminated for family health history and substance use information); 3) relationships among SBF factors and comorbidities can be generated, visualized, and validated by clinical experts and established medical knowledge sources (open-source data mining pipelines have been developed, disseminated, and applied for pediatric asthma and adult epilepsy); and 4) a number of challenges with data quality and integration associated with SBF factors were revealed and are to be addressed as part of future work. (Winden et al., 2018; Lindemann et al., 2018; Haddad et al., 2017). [Grant Number: R01LM011364].

Computational Methods and Tools that Support Research on Sex/Gender Influences on Health and Disease

NLM directly and indirectly supports research on sex and gender influences on health. Intramural researchers at NLM are working on models for the construction of sex-specific regulatory networks. Through its publicly accessible databases, NLM is also enabling researchers and members of the public to analyze results of studies by sex/gender. The inclusion of these fields is allowing users to more rapidly and effectively sort study results by sex/gender, which enhances study analysis and the design of follow-on studies.

Network Reprogramming using EXpression (NetREX): NLM researchers developed a new method, called Network Reprogramming using EXpression (NetREX), that provides for the construction of sex-specific gene regulatory networks (GRNs), as well as other context-specific GRNs. A GRN is a collection of regulatory relationships between transcription factors and the genes to which they bind. GRNs control maintenance of cell type-specific states, the response to stress, sexual dimorphism (differences between the sexes beyond the differences in sexual organs), and other cell functions. Previous methods to infer GRNs were not specific for context. Since many human diseases are sex and tissue specific, such context-specific regulatory networks will be very helpful for disease studies. NetREX was validated first on simulated data, then on E. coli GRN. The research team, which also included researchers from NIDDK, then applied NetREX to construct sex-specific GRNs for the model organism Drosophila melanogaster (fruit flies) (Wang, et al. 2018). As more sex- and tissue-

specific data for mammalian organism (including humans) continues to emerge, the groups plans to apply their method to construct such networks for higher organisms. Methods like NetREX will empower future studies of sex/gender influences on health and disease.

The Database of Genotypes and Phenotypes (dbGaP) Supporting Sex-Based Research (Goal 5, Objective 5.6): The Database of Genotypes and Phenotypes **(**dbGaP) archives and distributes data from studies that investigate the interaction of genotype and phenotype in humans. The database contains more than 1,000 studies with de-identified genomic and phenotypic (clinical observation) data on more than 2 million subjects. Researchers are able to request datasets in dbGaP to conduct their own analyses, for instance looking across multiple studies for a common genetic feature associated with a certain condition. Because sex is a phenotype measure in virtually all studies, researchers are able to conduct analyses that examine hypotheses related to biological and medical differences that might exist between the sexes. For example, researchers could request large datasets from studies that included cholesterol measurements and then analyze whether certain genotypes thought to be related to elevated LDL differed between males and females. The ability of researchers to analyze genotype and phenotype data in dbGaP by sex of study participant is an important way that NLM is helping to enable research that addresses sex/gender differences. The dbGaP archives also include data from numerous studies that specifically relate to women's health, such as the Women's Health Initiative and the Women's Interagency HIV Study.

Data Resources and Efforts to Advance Inclusion of Women in Clinical Trials

NLM supports the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research through its information resources that include the eligibility of women in clinical research studies, health standard vocabularies that are inclusive of women's health phenomena, and outreach activities in collaboration with key partners.

ClinicalTrials.gov Enhances Capabilities Related to Women's Health Data (Goal 2, Objective 2.3): ClinicalTrials.gov, a resource provided by the NLM, is a public database of privately and publicly funded clinical studies conducted around the world. In January 2017, NLM implemented requirements related to the HHS Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11). These regulations require submitted registration information to include the sex/gender of participants who may enroll in the clinical trial and, after the trial is completed, results information must include the number of participants enrolled in each arm of the clinical trial by sex/gender. The associated NIH Policy on the Dissemination of NIH-funded Clinical Trial Information also expects the same reporting by sex/gender for all NIH-funded clinical trials. These new reporting requirements, which help ensure that information about the sex/gender of trial participants is publicly accessible and transparent, represent an important step in facilitating the monitoring of the participation of women in clinical trials. Additionally, Section 2053 of the 21st Century Cures Act, enacted on December 13, 2016, required the submission of summary results with valid analyses by sex/gender and race/ethnicity for NIH-defined Phase III applicable clinical trials to ClinicalTrials.gov. Since December 13, 2017, NIH has required that the plans for conducting such valid analyses for each primary outcome measure be indicated as part of registration information on ClinicalTrials.gov. These pre-specified analyses by sex/gender and race/ethnicity must then be submitted to ClinicalTrials.gov as part of summary results information. In May 2018, NLM collaborated with the NIH Office of Extramural Research to develop guidance for NIH grantees to comply

with this policy for reporting valid analyses to ClinicalTrials.gov, which will allow for better tracking and understanding of trial outcomes for women and men enrolled in trials. Finally, as part of ongoing efforts and in the context of the NLM Strategic Plan, NLM will enhance the manner in which information on ClinicalTrials.gov (including sex/gender information) is searched, displayed, accessed, and analyzed to enable increased monitoring of the participation of women in trials and their results.

Responsive Additions to Health Data Standard Vocabularies for Women's Health Topics (Goal 2, Objective 2.3): Electronic data captured using electronic health records (EHRs) for clinical research, as well as clinical care and administrative purposes, requires clear vocabulary and definitions. NLM serves as the U.S. Department of Health and Human Services coordinating body for clinical terminology standards, responsible for collaborating or working directly with clinical terminology standards organizations for conditions (SNOMED CT), laboratory tests and assessments (LOINC), and medications (RxNorm). In FY 2017-2018, NLM and its partner standard development organizations assessed and, where needed, added or refined terms and codes to support more accurate data capture for a number of topics related to women's health, including pregnant women and newborns. These included new or revised clinical terminology to support the routine clinical reporting by EHRs of key social and behavioral health indicators, programs to efficiently collect interoperable long-term follow-up data, and regional and national registries to improve screening and treatment protocols, all with the ultimate goal of improving patient outcomes.

NLM also increased the topics and vocabulary related to women's health in Medical Subject Headings (MeSH), which is the controlled vocabulary thesaurus used for indexing articles for PubMed. Women's Health-related MeSH terms added in FY 2017-2018 included:

- Women's nutrition terms: Special Supplemental Nutrition Program for Women, Infants, and Children (U.S.); and Women, Infants, and Children Program (WIC)
- Pregnancy-related terms: Recurrent Early Pregnancy Loss; Sepsis in Pregnancy; Sepsis during Pregnancy; Early Pregnancy Loss; Pregnancy Weight Gain; and Obesity in Pregnancy; Reproductive system (Female)
- Violence against Women; Gender-Based Violence; and Intimate Partner Violence

Newborn Screening (Goal 2, Objective 2.3): Of particular relevance to the health of women and families is newborn screening —a complex public health program working to identify seemingly healthy infants who have serious conditions, begin treatment before they suffer significant disability or death, and in doing so, decrease the burden of disease on society. NLM is working with multiple agencies to create new codes for NBS, as well as national guidance for standardization and electronic reporting of newborn screening results using HL7 messages that contain a prescribed set of LOINC and SNOMED CT codes, report quantitative test results, and use standardized units of measure. The standard terms and codes will allow newborn screening programs to efficiently collect interoperable long-term follow-up data, and regional and national registries to improve screening and treatment protocols. In FY 2018, NLM led and/or facilitated the development of two new chapters in HL7's Version 2.5.1: Laboratory Results Interface implementation guide). The new chapters included specific guidance for laboratories on the delivery of structured newborn screening and genetic diagnostic test reports (Goodwin et al., 2018).

Women's Health Technologies Coordinated Registries Network Project (Goal 2, Objective 2.3): Funded by the Patient-Centered Outcomes Research Trust Fund, the overall goal of this project is to address the need for

a comprehensive approach to women's health by creating a new strategically coordinated registry network for women's health technologies. The project is building data capacity through registries to study the real-world safety and effectiveness of procedures and devices that are common to women. This includes studies of uterine fibroids, which is the most common reason that hysterectomy is performed in women. NLM provided technical expertise and resources used in this project including the NIH Common Data Elements (CDE) Repository, the Value Set Authority Center (VSAC), and the Unified Medical Language System (UMLS), which were leveraged to assist with the harmonization of a shared set of common data elements across the clinical domains of sterilization/long acting reversible contraceptives, pelvic floor disorders, and uterine fibroids. An extension for this project has been proposed in 12 clinical areas that will build gender/sex analyses work streams into each participating coordinated registry network (Baird et al., 2018).

The National Network of Libraries of Medicine (NNLM) All of Us National Program: The NLM partnership with NIH All of Us Research Program, which began in FY18, aims to reach library audiences to raise awareness and educate the public about its ability to participate in a national research data collection effort. As community centers, libraries are poised to target populations underrepresented in biomedical research (UBR) for All of Us outreach. Two of those UBR populations include women and children under the age of 18. The goal for All of Us is that 50% of participants belong to at least one UBR population. The NLM partnership includes activities that engage women and girls in health literacy activities, as well as programs aimed to increase awareness of the All of Us research program. One example project is Women's Health Wednesdays at the Steger-South Chicago Public Library in the Greater Midwest Region (GMR). This health literacy project has focused on helping women in the community to understand and value their own health and wellness. Topics include heart disease, reproductive safety and health, depression and mental health, eating healthy, working out, cancer, yearly screenings, autoimmune disease, caring for a loved one, and self-defense.

STEM Efforts to Enhance Career Development of Women in Informatics

NLM is committed to building a workforce for data-driven research and health. NLM continues to promote and fund doctoral-level research training in biomedical informatics and data science in its quest to devise scalable, extensible, and reusable methods to draw knowledge from data. Such efforts will help to ensure data science and open science proficiency, expand research methods that support rigor and reproducibility, promote and increase workforce diversity, and engage the next generation of researchers.

NLM efforts undertaken to address career development of Women in Informatics (Goal 6, Objective 6.1): NLM scientists regularly participate in the Grace Hopper Celebration of Women in Computing event. In addition to keynote speakers and a career fair expo, the meeting includes career panels and workshops organized to inspire, inform, and encourage women to pursue careers in computing, science, and technology. The meeting provides NLM staff the opportunity to meet with undergraduate and graduate students in computer science and encourage the students to consider the programs of NLM in their future careers.

NLM scientists have made specific efforts to advertise their educational, training, and mentoring programs to a broad audience that invites participation of women. NLM also continues to encourage staff to participate in training and career development programs for women. For example, NCBI's Acting Chief of the Information Engineering Branch participated in the NIH Women in Leadership training in 2017,

and each year an NLM scientist participates in the NIH Women Scientist Advisors Committee. Among other activities, NLM hosted a visit to NLM for a group of middle and high school girls who won a raffle from Women in Technology to visit NIH. The visit provided the Girls in Technology group with the opportunity to learn about NLM and talk with 12 NLM scientists.

In FY 2018, approximately one quarter of NLM's trainees were women. Of the 65 trainees placed at the National Center for Biotechnology Information and the Lister Hill Center for Biomedical Communications, 16 of them were women.

Through 11 university-based training programs, NLM offers short-term training positions to undergraduate and graduate students to enhance recruitment of women and other groups underrepresented in biomedical informatics and data science. Also, NLM scientists are active in the Women in American Medical Informatics Association (AMIA) Initiative, a mentoring program for women scientists. Women in AMIA is committed to informing and inspiring the informatics community toward action around opportunities for women in AMIA to improve health and healthcare.

In FY 2018, NLM offered supplemental funds to support partnerships with minority-serving institutions. Three such supplements were awarded to help facilitate recruitment of high school and undergraduate students into biomedical informatics training programs. To enhance outreach, these supplements emphasized the presentation of student work in order to increase awareness of biomedical informatics and data science literacy among diverse young scholars.

NLM is also participating in NIH-wide efforts to foster a culture which not only advances science, but also ensures the development and retention of a diverse, safe, and respectful workforce for the future.

Information Resources to Support Women's Health Research and Care Delivery

NLM funds a large number of health information resources that contain important information in support of women's health research and care delivery. Examples of these information resources include:

HSRProj Database Captures Ongoing Health Research on Women and Families (Goal 5, Objective 5.1): The HSRProj database (https://www.nlm.nih.gov/databases/download/hsrproj.html) contains detailed information on health services research (HSR) projects in progress but not yet published; the database can be searched by researcher, funder, and topic and contains more than 36,000 project descriptions from the mid-1990s to the present, representing more than 375 funders of HSR. Health disparities and women's issues figure frequently in these research projects. Examples of studies included in the database in 2018 are: 1) Disability-related disparities in sex education, contraceptive use, and unintended pregnancy; and 2) Mapping perceptions of pre-exposure prophylaxis use in trans women and barriers to care in providers to inform intervention development.

HSR Information Central and Partners in Information Access for the Public Health Workforce (Goal 5, Objective 5.1): The HSRIC Information Central database (hsric.nlm.nih.gov/hsric_public/topic/domestic_violence/) is a web portal for the health services research community. Partners in Information Access for the Public Health Workforce (https://phpartners.org/ph_public/) similarly advises the public health workforce. These resources contain topic pages that allow focused tracking and identification of high-quality grey literature, data sets, tools, and other resources in a particular domain, plus structured search strategies for PubMed and other resources. Their communities are informed via RSS feed, as well as GovDelivery alerts. During FY 2017 and 2018, the websites informed

their communities of new information relevant to their research in these areas, including: National Women's Health Week; U.S. Department of Veterans Affairs (VA) Women's Health Research Network Webinar: Accelerating Research Impacts and Advancing Learning Healthcare System Principles; and a publication on Racial, Ethnic and Gender Disparities in Health Care in Medicare Advantage.

Medical Genetics Databases (Goal 5, Objective 5.6): NLM's Genetic Testing Registry (GTR, https://www.ncbi.nlm.nih.gov/gtr/) includes information on tests for numerous conditions that relate to women's health. Over the last two years, information was added to GTR on more than 200 tests for conditions such as ovarian cancer, premature ovarian failure, breast cancer and uterine growth restriction. NLM's ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) – which aggregates information about genomic variations and their relationship to human health – also extensively expanded its offerings related to women's health. For example, ClinVar added more than 7,000 new variants related to the BRCA1 and BRCA2 genes and more than 27,000 submitter reports about the clinical significance of those variations.

Systematic Reviews and Clinical Guidelines (Goal 5, Objective 5.6): NLM's Bookshelf provides free online access to books and documents in the life sciences, including systematic reviews and clinical guidelines. In FY 2017-2018, the Bookshelf added 37 new systematic reviews as well as guidelines related to women's health. Among the many topics were screening for syphilis in pregnant women; sexual harassment of women in academic sciences, engineering and medicine; and strategies for improving the lives of women aged 40 and above living with HIV/AIDS.

MedlinePlus (Goal 5, Objective 5.1 and Objective 5.6): Produced by the NLM, MedlinePlus (https://medlineplus.gov) is a portal for patients and their families and friends containing information that is authoritative and up-to-date, including extensive information from the NIH and other trusted sources on over 1,000 disease and conditions. The portal contains a page devoted to Women's Health issues that includes links explaining conditions specific to women, prevention and risk factors, and topical issues such as body image and menopause. It also has numerous health topic pages specific to other women's health matters, including HIV/AIDS in Women, Heart Disease in Women, Sexual Problems in Women, and Women's Health Checkup. On each page, the site provides links to relevant journal articles and key statistics and research relevant to women's health. Research indicates that the majority of online health information seekers are women,[50] and this is also true for the MedlinePlus audience, which is estimated to be two-thirds women. Many of the articles are available in languages other than English through the HealthReach initiative, described below.

HealthReach: Multilingual Women's Health Resources (Goal 5, Objective 5.1 and Objective 5.6): HealthReach (https://healthreach.nlm.nih.gov) is a resource of multilingual and multicultural health information for those working with or providing care to people with limited English proficiency. HealthReach has materials in more than 60 languages and in multiple formats, including audio, video, and print. It contains 170 titles for women's health topics (see https://healthreach.nlm.nih.gov/searchindex/Women's+Health). In response to the current opioid crisis, the National Library of Medicine partnered with Healthy Roads Media (https://www.store.healthyroadsmedia.org/) to produce a collection of materials that teach people about opioids and opioid misuse in English and Spanish and in print and video formats (https://healthreach.nlm.nih.gov/searchindex/Opioid+Abuse+and+Addiction). NLM developed

50 Pew Research Center. Profiles of Health Information Seekers, 2011. http://www.pewinternet.org/2011/02/01/profiles-of-health-information-seekers

a topic specifically to address Pregnancy and Opioids (https://healthreach.nlm.nih.gov/document/940/Pregnancy-and-opioids-Opioid-addiction-part-10).

AIDSinfo and AIDSource Feature Women's Health Topics (Goal 5, Objective 5.1): AIDSinfo (https://aidsinfo.nih.gov) is an HHS resource providing information on HIV/AIDS clinical trials and federally approved HIV treatment and prevention guidelines, information on HIV/AIDS treatment, clinical trials, and other HIV/AIDS-related research information for health care providers, researchers, people affected by HIV/AIDS, and the general public. AIDSinfo also provides guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents and a health topic on women that includes treatment resources, related conditions, prevention, clinical research, and more. (https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/25/69/hiv-and-women). AIDSource is a portal that provides current content that addresses the specific needs of women related to prevention, treatment, and living with HIV/AIDS, regardless of age (https://aids.nlm.nih.gov/resources-for/1675/general-public#women).

LactMed® for Breastfeeding Women (Goal 5, Objective 5.1): The LactMed® database (https://www.toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to ensure scientific validity and accuracy. LactMed® also is available as an app.

Partnering with Women with Disabilities to Develop a Health Information Website (Goal 5, Objective 5.6): The goal of this project is to improve the reproductive and pelvic health of women with disabilities through the development of a health information website that is fully interactive and searchable. The purpose of this website is to employ common information technology to empower women with disabilities to become self-informed about decisions related to health. An award was issued in FY 2018 to allow researchers at Texas Medical Center to conduct focus groups and a national survey of 500 women with physical disabilities to identify their information needs and use of digital technologies. Comprehensive literature reviews of relevant topics will be undertaken, and downloadable topical summaries with links to other information resources will be produced. There will also be training for women with physical disabilities on how to use this website. During the first project year, the project team interviewed their community advisory board, carried out a focus group study, and completed a literature review. The results of these activities include a list of topics for developing consumer-oriented information guides, using a template based on MedlinePlus. [Grant Number: 1G08LM012702; Memorial Hermann Hospital – Texas Medical Center].

Outreach Initiatives to Reduce Health Disparities and Improve Women's Health

A number of NLM's outreach activities address women's health issues and seek to mitigate health disparities. Many of the outreach initiatives and resources are developed with community partners or grantees in a culturally-sensitive manner and delivered in customized ways to reach the diverse communities they are targeting.

National Network of Libraries of Medicine Outreach Projects targeting Women's Health (Goal 5, Objectives 5.1, 5.2 and 5.6): The 7,100-member institutions of the NNLM are valued partners in ensuring that health information, including from NLM services, is available to

scientists, health professionals, and the public. NNLM is comprised of eight Regional Medical Libraries (RMLs), each anchoring a regional consortium of academic health sciences libraries, hospital libraries, public libraries, and community-based organizations. The RMLs provide funding for projects that improve access to health information, increase engagement with research and data, expand professional knowledge, and support outreach that promotes awareness and use of NLM resources in local communities. Funded projects in FY 2017-2018 targeting issues related to women's health included:

- The New England Region of NNLM funded a project to empower new mothers with education and support throughout the prenatal and postpartum period and to help achieve healthy newborn outcomes through healthier and prolonged pregnancies. The project provided a three-phase, evidence-based training curriculum in which doulas educate and enlighten mothers about the birthing experience. The curriculum also assisted in enhancing the continuum of complete service delivery between the Doula and members by helping expectant mothers' partners and family. In addition, to ensure improved maternal and birth outcomes, the project provided in-home practical and emotional support with childbirth education, parenting skills, meal preparation, household organization, and breastfeeding.

- The Middle Atlantic Region of NNLM funded the Clinton-Essex-Franklin Library System (CEFLS) to conduct the "Seeds of Hope" project to raise awareness of domestic violence among residents in Clinton, Essex, and Franklin counties. CEFLS collaborated with STOP Domestic Violence to coordinate a series of events in our shared service area. This included hosting the NLM traveling exhibit *Confronting Violence, Improving Women's Lives* (described below), providing viewings of the feature documentary, Home Truth, followed by a training session on resources; offering book club and resource discussions addressing domestic violence; and coordinating an awareness event for youth.

- The Greater Midwest Region of NNLM funded a project that focused on several different topics of women's health, including heart disease, reproductive safety and health, depression and mental health, healthy eating, exercise, cancer, yearly screenings, autoimmune disease, caring for a loved one, and self-defense. Many women who have no insurance (or are under insured) come into the library asking for materials on different health topics, such as breast cancer, ways to de-stress, and stay healthy. The project offered nine training sessions, each one hour long, once per month over the course of a year. An outcome of the project was to help women in their communities understand and value their own health and wellness.

- The Pacific Southwestern Region of NNLM funded the NEC-Zero project. The goal of NEC-Zero was to eliminate necrotizing enterocolitis (NEC) to "zero cases" by increasing access to evidence-based information to promote risk awareness and prevention. NEC, a devastating intestinal complication that involves death of tissue that can spread to the entire body, affects mostly pre-term infants. Gaps in implementation of prevention evidence and parent engagement strategies may explain variation in NEC occurrence across Neonatal Intensive Care Units (NICUs). Working with an interdisciplinary team of academic experts and parent support group agencies, NEC-Zero's primary objective is to disseminate health information related to NEC broadly. The project aims to create short video novellas about NEC in both English and Spanish, and also to refine the Spanish translation of parent-focused materials

already developed for NEC-Zero and add a brochure targeting women who may deliver a pre-term infant.

- The Southeastern/Atlantic region of NNLM funded the "Continuing on PATHS Leading to Excellent Patient Care" technology improvement project. It supports patients and families of the University of South Alabama (USA) Medical Center and the High-Risk OB/GYN and Well Baby units of the USA Children's & Women's Hospital to access quality health information through the use of Android tablets. For example, rolling bedside stands equipped with Android tablets provide patients with access to resources such as MedlinePlus, Drug Information Portal, and LactMed. Patients can locate information free of medical jargon, in their native language, and at a time when they can absorb the material. By providing access to health information using multiple educational interventions, more patients in this health disparate community can take an active role in the understanding of their condition and become engaged in an interdisciplinary team approach to their medical care.

NLM Exhibition *Confronting Violence* Engages the Public in Conversations About Domestic Violence (Goal 5, Objective 5.1): NLM launched the special display, online exhibition, and traveling exhibition, titled, *Confronting Violence: Improving Women's Lives* (https://www.nlm.nih.gov/exhibition/confrontingviolence/index.html) with a public symposium and reception co-sponsored by ORWH in September 2015. The traveling exhibition was immediately booked through the end of 2019, with 50 venues across the country reserving the exhibition for six-week showings and more than a dozen more placed on a waiting list. Two copies of the exhibition continue to travel today. During FY 2017-2018, 22 host venues in 14 states and Canada reported a total of 37,446 visitors to the exhibition.

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Office of AIDS Research

I. Executive Summary

The Office of AIDS Research (OAR), located within the National Institutes of Health (NIH), Office of the Director, Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), coordinates the scientific, budgetary, legislative, and policy elements of NIH HIV/AIDS research. The OAR has the responsibility of overseeing NIH's vision for HIV/AIDS research to end the HIV pandemic and to improve the health outcomes of people with HIV (PWH). To accomplish this goal, the OAR coordinates, collaborates, and advances HIV research activities across almost every NIH Institute and Center (IC). In August 2015, NIH released a notice outlining *NIH HIV/AIDS Research Priorities and Guidelines for Determining AIDS Funding* (NOT-OD-15-137). The Guidelines provide a framework for HIV research for 3 to 5 years [2016 to 2020] and include four overarching priorities (Reduce the Incidence of HIV; Develop Next-Generation Therapies; Research Toward a Cure; HIV-Associated Comorbidities, Coinfections, and Complications) and Cross-cutting Research areas. Implications for research concerning women and girls intersect all priority and crosscutting areas.

II. Background

Globally

In 2017, women (15 years and older) accounted for 49% of 36.9 million people living with HIV worldwide and 42% of 1.8 million new HIV infections. The burden of disease is even higher among young women and adolescent girls. Globally, adolescent girls and young women constituted 62% of all young people aged 15-24 living with HIV and 59% of new HIV infections in young people. Young women in Sub-Saharan Africa are particularly affected. UNAIDS estimated that 75% of new infections in 2016 were among 15-19 years old young women and adolescent girls.

The risk of infection and prevalence is disproportionally higher among specific groups of women worldwide. For example, the risk of infection is 14 times higher for female sex workers compared to other women of reproductive age (15-49 years old). Data reported by 30 countries indicates that 13% of women that inject drugs are infected with HIV compared to 9% men who inject drugs. In addition, regional studies indicate that women who experience partner violence are 1.5 times more likely to acquire HIV than women who do not.

United States

In the United States, women accounted for 19% of total new HIV diagnoses (7,312 of 38,281) in 2017 and 20% of the total AIDS diagnoses (~255,000 of 1.25 million) since the beginning of the epidemic. The burden of disease is disproportionally higher among African American women compared to other races/ethnicities. Among all women diagnosed with HIV in 2017, an estimated 15% (1,117) were Hispanic/Latino, 20% (1,474) were White and 60% (4,395) were African American. Women from 25-39 years old comprised the largest portion of women newly diagnosed with HIV at 40% (2931). Heterosexual contact is the major route of transmission in women accounting for 86% of HIV diagnoses. Injection drug use accounts for 14% of new diagnoses in women overall; however, 32% of HIV diagnoses among White women are attributed to injection drug use. HIV prevalence in transgender women in the United States is estimated at 22-28%. African-American transgender women are the most affected with an estimated 56% living with HIV.

III. NIH HIV/AIDS Research Priorities

Reduce the Incidence of HIV/AIDS

Preventing new infections is crucial to ending the HIV pandemic. Approaches to preventing transmission are especially important for women and girls as interpersonal and societal-level factors may limit their agency to control their HIV risk. The NIH's efforts to reduce the incidence of HIV/AIDS include research on the development of an effective HIV vaccine, as well as treatments and strategies to prevent the acquisition and transmission of HIV.

Significant progress continues in the development of non-vaccine interventions to reduce the incidence of HIV/AIDS. NIH-sponsored studies have demonstrated that oral pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) can prevent infection. In addition, the NIH has supported the development of multipurpose prevention technologies (MPTs), including microbicides and intravaginal rings, to protect women from acquiring HIV through sex. Such methods will offer particular advantages for women who may not have other options for protection. Ongoing efforts in HIV prevention research include a clinical trial to assess if broadly neutralizing antibodies are safe, tolerable and effective at preventing HIV infection.

NIH-sponsored studies on prevention of the transmission of HIV have demonstrated that antiretroviral therapy (ART) can significantly reduce transmission of HIV during pregnancy and breast-feeding. Furthermore, combination ART regimens reduce the risk of sexual transmission of HIV to effectively zero for patients that achieve undetectable viral loads.

Despite the significant advances in non-vaccine biomedical preventions approaches, infection rates in the U.S. have been constant over the past several years. As such, the development of an effected vaccine continues to be a high priority area for the NIH. Efforts in this area included exploring immunologic correlates of protection against HIV and novel approaches to modulate immune responses, including vaccine adjuvants.

Funded Initiatives and research in HIV related to women for FY 17 and FY 18:

- Funded, coordinated, and developed specific approaches to HIV prevention in women such as research on vaccines, microbicides and pre-exposure prophylaxis (PrEP).
- Provided support for promising clinical trials to test the effectiveness of a variety of multipurpose prevention technologies, including microbicides and intravaginal rings.
- Provided support for large-scale HIV vaccine studies in men and women ages 18 to 35 (HVTN 702) and women ages 18 to 35 (HVTN 705).
- Provided support for a Phase 2b/3 Study of Injectable Cabotegravir LA Compared to Daily Oral TDF/FTC for PrEP in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men (HPTN 083).
- Funding to support the 2018 HIV Research for Prevention Conference (HIV R4P), a major biennial conference for researchers, advocates, program developers, funders, policy makers, and communities impacted by the epidemic.

Next Generation HIV Therapies

NIH-sponsored research has led to the development of combination antiretroviral therapy (cART), which has significantly improved the health outcomes of PWH. However, even with simplified daily one-pill treatment regimens capable of suppressing HIV, only 22 million of the approximately 37 million PWH worldwide currently receive treatment. Barriers to receiving and adhering to cART include treatment availability, the high cost, the need for daily treatment, interactions with other drugs, and drug resistance

and/or adverse events. In addition, stigma and disparities in access to cART adversely impact health outcomes in PWH across race, ethnicity, sex and gender, age, and socioeconomic status. Therefore, the NIH has allocated funding for the development of new long-acting medications with fewer side effects and complications, including monthly injections of continuously released cART, anti-HIV antibody infusions, and a 6-month cART implant. Simpler treatment schedules compared to current daily medication regimens are expected to improve adherence. Parallel research focused on development of novel delivery and testing technologies including sensitive, rapid point-of-care or self-administered viral load testing. Technologies that make it easier to monitor viral loads will improve treatment adherence leading to viral suppression and prevention of HIV transmission.

The World Health Organization recently reported that an increasing number of people receiving cART worldwide are resistant to at least one of its drugs. Therefore, the NIH has funded the early stage development of new immune-based treatment regimens capable of suppressing the replication of virus that is resistant to antiretroviral drugs. Immune-based treatments may provide an additional advantage in that they may reverse the weakening of the immune system that occurs even when the virus is suppressed by ART.

Funded Initiatives and research in HIV related to women for FY 17 and FY 18:

- Through the OAR Research Advisory Council (OARAC), OAR provided support for the annual convening of the U.S. Department of Health and Human Services (HHS) HIV Treatment Guidelines Working Groups. These working groups update federally approved guidelines for HIV/AIDS care providers with the most current information on: combination antiretroviral therapy regimens; treatment and prevention of opportunistic infections for people living with HIV; the prevention of HIV transmission from an infected mother to her infant; and the safety and efficacy of HIV/AIDS therapies.
- Provided supplemental funding to NICHD for key ongoing research awards addressing potential mechanisms for the effects of the impact of Dolutegravir, an HIV integrase inhibitor, on neural tube defects in human fetal development.

Research Toward a Cure

The mechanisms by which HIV persists in reservoirs within the body and intermittently becomes activated are poorly understood and represent the major barrier to sustained viral remission (also called a functional cure) without ART and to the longer-term goal of viral eradication (also called a sterilizing, or classic, cure). The NIH has supported basic, preclinical, and clinical studies on innovative and sustainable cure strategies. In addition, the NIH has funded studies to assess the ability of a range of techniques, such as single-cell and imaging technologies, to identify and describe the HIV reservoir and discover mechanisms of viral reactivation from latently infected cells. Recent studies indicate that there are sex-based differences in susceptibility and pathogenesis of HIV that will need to be further explored in the context of Cure research.

HIV-Associated Comorbidities, Coinfections, and Complications

HIV/AIDS is a disease often associated with coinfections and comorbid conditions, including end-organ dysfunction. HIV infection can be preceded by and co-occur with other health issues, such as substance use, mental disorders, and malnutrition. Examples of coinfections and comorbidities are numerous and include, but are not limited to, tuberculosis; hepatitis B and C; human papillomavirus (HPV); other sexually transmitted infections (STIs); metabolic and bone abnormalities; cardiovascular disease; certain cancers; and neurologic and cognitive disorders. Although the widespread use of ART has resulted

in significant improvements in mortality and morbidity due to HIV and its many associated comorbidities, the global challenges of clinical management of these concurrent conditions continue. These coinfections and comorbid conditions differ by sex and gender. Some comorbidities are more prevalent in women with HIV; for example, there is a higher incidence of HPV-associated cervical and anal cancer among these women. NIH research efforts have focused on differentiating between complications related to underlying immune dysfunction, ART use, co-occurring chronic illnesses such as diabetes and hypertension, aging, and other conditions more common in women, such as osteoporosis.

Funded Initiatives and research in HIV related to women for FY 17 and FY 18:

- Guided the merging and integration of the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) into a single MACS-WIHS Combined Cohort Study (launched in early 2019) conducted by 13 sites and a data center involving more than 4,500 participants. The study will support basic, clinical, and contextual research on HIV across the lifespan, with an emphasis on HIV-related comorbidities and health disparities.
- Provided supplemental funding to REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study, which will evaluate the safety of statin therapy; the effects of statins on cholesterol levels, immunologic parameters, and serious non-cardiovascular disease events, such as new-onset diabetes; and gender differences in the effects of statins on people with HIV.

The Crosscutting Areas

Basic Research

Basic research provides the underlying foundation for all HIV/AIDS studies, and includes studies to examine HIV virology, transmission, acquisition, susceptibility, and host-viral interactions. Furthermore, studies that elucidate the genetic and immune mechanisms involved in HIV disease progression are important as are studies to determine how sex, gender, age, race/ethnicity, culture, pregnancy, nutritional status, and behavioral and socio-cultural factors influence disease and treatment.

Funded Initiatives and research in HIV related to women for FY 17 and FY 18:

- OAR has funded programs to study mucosal immunology and the female genital tract microbiome.

Behavioral and Social Sciences Research

Various sociodemographic, behavioral, social, and related clinical variables contribute to women's HIV risk, engagement with testing and care services, and disparities found in viral suppression. NIH-supported research focuses on efforts to develop effective interventions to better prevent HIV in women at risk and to treat women who are living with HIV. This research has significant implications for HIV prevention and treatment as these measures will only be effective if they are widely used. NIH research efforts have focused on identifying the social factors that influence treatment uptake and adherence, as well as the development of innovative strategies that will increase the uptake of treatment and engage PWH in their own care to prevent transmission, achieve viral suppression, and improve health.

Funded Initiatives and research in HIV related to women for FY 17 and FY 18:

- Support for the 2017 National Conference on Alcohol and Opioid Use in Women and Girls: Advances in Prevention, Treatment and Recovery Research
- Funded a program to use next-generation, real-time monitoring for PrEP adherence in young Kenyan women (NCT02915367)

Research to Reduce Health Disparities

Disparities in HIV infection persist worldwide despite significant advances in HIV prevention and treatment. The reasons for these disparities are many and can be linked to the conditions in which individuals and communities live, work, and make their social connections. Social determinants of health include socioeconomic status and community/cultural norms that influence a woman's position in society, her community, and her family. Determinants of risk include factors such as stigma, mental health, and substance use. NIH research focused on defining the intersection of social determinants of health and women's risk for HIV and subsequent poor health outcomes to inform the development of interventions to prevent infection and improve health.

Initiatives and research that was funded in HIV related to women for FY 17 and FY 18:

- Support for HIV Research in Women in Latin America Conference, which was held as a pre-conference workshop at the 2017 STI & HIV World Congress.

Training and Information Dissemination

The NIH supports the training of a diverse, global research workforce to build the critical capacity and infrastructure to conduct HIV/AIDS research. Multidisciplinary teams and approaches, training, mentoring, capacity building, developing collaborations, and maintaining the highest ethical standards for HIV research are all critical to address the many challenges and scientific opportunities in HIV/AIDS research and its related disciplines.

Funded Initiatives and research in HIV related to women for FY 17 and FY 18:

- Funded programs to improve information dissemination of reproductive and sexual health resources.
- Support for the Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA), led by the NIH Fogarty International Center (FIC) to catalyze collaboration and communication among implementation scientists, program implementers, and policymakers to enhance the effective use of evidence-based approaches and overcome challenges related to HIV prevention, treatment, and care among adolescents in Sub-Saharan Africa.

Implementation Science

As part of its comprehensive program, NIH continues to support research to advance the methodologies of implementation science as well as specific implementation science studies designed to identify approaches that maximize the effectiveness of health programs. These studies aim to address organizational and system-level barriers at multiple levels. Specific barriers that require rigorous implementation science studies include hurdles to access, uptake of, retention in, and scale-up and sustainability of effective HIV prevention, care, and treatment interventions. Implementation science research also includes the assessment of applicability of particular interventions to diverse settings, as well as among underrepresented and hard-to-reach populations.

Funded Initiatives and research in HIV related to women for FY 17 and FY 18:

- Support for the Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA), led by the NIH Fogarty International Center (FIC).

IV. Other Activities Related to Women's Health

- Annual evaluation of the NIH HIV/AIDS research portfolio to ensure that current

scientific priorities related to women and girls with or at risk for HIV/AIDS are addressed.

- NIH OAR coordinates monthly meetings of the NIH AIDS Executive Committee (NAEC) composed of representatives from all ICOs, including NIH ORWH, to address research issues and foster communication and collaboration among ICOs on HIV research including research relevant to women and girls.
- Development of the NIH Strategic Plan for HIV and HIV-Related Research that addresses issues relevant to women and girls. Input to the Plan is provided by NAEC members and other public and community stakeholders through the published Request for Information (RFI).
- OAR staff were represented on workgroups related to women and HIV, including:
  - The HIV Prevention Trials Network Women's Research Working Group
  - Center for AIDS Research HIV and Women's Working Group and Workshop Planning Committee
  - AIDS Clinical Trials Group Women's Research Working Group
  - Women's Research Institute Working Group
  - The United States Agency for International Development Cooperating Agencies Working Group
  - National HIV/AIDS Strategy
  - NIH Sexual and Gender Minority Research Coordinating Committee

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Office of Behavioral and Social Sciences Research

I. Executive Summary

Situated within the Office of the Director's Division of Program Coordinating, Planning, and Strategic Initiatives, the National Institutes of Health (NIH) Office of Behavioral and Social Sciences Research (OBSSR) furthers the mission of the NIH by emphasizing the critical role that behavioral and social factors play in health, health care, and well-being. As a coordinating office, OBSSR serves as the focal point for coordination and development of policies, goals, and objectives in the behavioral and social sciences at the NIH. Although OBSSR does not hold or administer any research grant awards, the Office does offer co-funding support to the 27 NIH Institutes and Centers. In Fiscal Years (FY) 2017 and 2018, OBSSR co-funded many grants and initiatives with a focus on the health of women, particularly related to the behavioral and social sciences aspects of sex and health and disease, health disparities, inclusion of women in clinical research, and women in biomedical science careers.

II. Communications and Education Efforts

- In FY 17–18, OBSSR promoted research on the health of women, recent research results and training initiatives through communication channels, such as blog posts, social media, webinars and newsletters:
  - » OBSSR hosted several blogs on research developments regarding behavioral and social health and the role gender and sex as a biological factor plays in research and health outcomes. For example, in FY17, OBSSR featured a blog post titled "Women's work pathways: Results from longitudinal survey research" by Sarah Damaske, PhD that described analyses on how women work within and outside of the formal workforce over their lifetime.
  - » OBSSR also hosted webinars featuring presenters whose research focuses on behavioral interventions and women's health. In FY18, OBSSR hosted a director's webinar with Tamara Somers, Ph.D., whose research utilizes a Sequential, Multiple Assignment, Randomized Trial (SMART) to examine doses of a behavioral pain intervention in women with breast cancer and is expected to provide novel information on scaling and personalization of behavioral pain interventions.
- OBSSR partners in NICHD's PregSource; a tool intended to crowdsource pregnancy experiences and provide current research findings to pregnant and lactating women. OBSSR has been communicating the tool's rollout and disseminating information both to advertise the tool and assist in enrollment.

III. Funding Initiatives, Workshops and Conferences

- Health Disparities: In May 2018, OBSSR hosted a meeting on "Screening and Referral for Social Determinants of Health, Innovative Health Care Applications and Future Directions." The meeting aimed to follow up on the 2014 National Academy of

Medicine recommendations on electronic health records (EHR). Social and behavioral measures are now routinely collected in many EHR systems and are increasingly being used in clinical care and population health assessment. Routine screening for a patient's unmet social needs and adverse health behaviors, combined with referral to precision interventions to reduce the patient's health risks associated with these "social determinants," is an emerging trend in healthcare. This one-day meeting highlighted recent innovative applications and ongoing research and facilitate dialogue between scientific researchers in the field and staff from NIH and other federal agencies regarding future research directions and the application of these techniques to diverse populations.

- OBSSR also hosts an annual NIH Behavioral and Social Sciences Research Festival. This festival features presentations of recent research results from behavioral and social scientists funded by the NIH (this includes researchers from both the NIH Intramural Programs and researchers funded by the Institutes' and Centers' extramural research programs). The 2018 Festival included highlighted research on the health of women: for example, Jennifer Buher-Kane, PhD's research on "Intergenerational pathways Linking Maternal Early-Life Adversity to Offspring Birthweight" and Sheri Weiser, MD PhD's work that heavily focuses on the health of women, "Food for Thought: Examining the Vicious Cycle of Food Insecurity and Poor Health."

- Because data suggest that women report higher rates of chronic pain, NIH efforts related to addressing the opioid crisis and challenge of chronic pain are particularly relevant to the health of women. In support of the NIH efforts, the Office of Behavioral and Social Sciences Research (OBSSR), in collaboration with the National Institute on Drug Abuse (NIDA), the National Institute of Neurological Disorders and Stroke (NINDS), the National Center for Complementary and Integrative Health (NCCIH) and the National Institute on Minority Health and Health Disparities (NIMHD), hosted a meeting highlighting behavioral and social science strategies and interventions for the prevention and treatment of opioid use disorder and for pain management. The meeting, Contributions of Social and Behavioral Research in Addressing the Opioid Crisis (CSBR-AOC), was held on March 5-6, 2018. A diverse panel of researchers, academics, clinicians, patients and advocacy groups presented and discussed the most recent and relevant behavioral and social scientific data, identified the greatest needs and areas of opportunity related to the current crises and recommended what research findings in pain management can be disseminated and implemented quickly. A panel was devoted to specifically present research findings related to challenges and barriers to implementation for prevention, treatment and recovery from opioid use disorders.

IV. Co-Funding Support

OBSSR supported and continues to support research related to the health of women in the area of behavioral and social sciences by signing onto and providing co-funding support for Funding Announcement Opportunities that meet OBSSR's mission of advancing behavioral or social sciences research.

Examples of such research include projects focused on prevention of serious conditions and risk factors such as the prevention of lower urinary tract symptoms (5U01DK106786-03) and prevention of postpartum smoking relapse using social media (5R21CA198036-02). OBSSR also helps support research that further investigates recent epidemiologic studies that suggest that women with adverse pregnancy outcomes (APOs) are at increased risk for subsequent health

problems such as cardiovascular diseases. This project 3U10HL119991-04S2) focuses on whether women with APOs, such as preeclampsia, are at increased risk for subsequent cardiovascular diseases.

Trauma Research

Through its co-funding program, OBSSR continues to support research related to sexual victimization and sexual assault. These projects include research focused on risk factors for college aged women for sexual assault and potential strategies to mitigate such factors. For example, OBSSR supports the development of a brief intervention to reduce college sexual victimization risk by reduced drinking (1R34AA024854-01A1). Another OBSSR supported research project (1R34AA026055-01A1) focuses on analyses of the relationship between sexual assault, alcohol use and risky sex behavior among college women using Ecological Momentary Assessment (EMA). EMA data are collected in near real- time and are considered to have greater validity than retrospective accounts and may result in providing college campuses a cost-effective approach to preventing assault. Following assaults, many women seek emergency care but rarely forms of longer term follow up to prevent or address potential health outcomes post sexual assault (SA). OBSSR is also helping to support the work of investigators that are evaluating the relationships among SA, post-traumatic stress disorder (PTSD) and the development of chronic musculoskeletal pain (MSP) with a goal to development preventive interventions (5R01AR064700-05).

Health Disparities Research

Knowledge of demographic differences among women helps to better understand sociological and biological factors of health. In 2017-2018, OBSSR has contributed to research that focuses on topics such as breast cancer, pregnancy outcome disparities, race and obesity and HIV prevention.

For example, OBSSR provides support for research related to breast cancer by supporting work that tests for the feasibility and reliability of using assays on older breast tumor specimens, dating back to the 1950s, that will allow for research on trends in both tumor characteristics and social disparities in these characteristics (5R03CA193078-02).

OBSSR also helps provide funding support for evaluating social factors that may influence pregnancy outcomes through a community-based participatory research project focusing on Latina health during pregnancy and reducing poor birth outcomes (5R21HD087734-02).

There is evidence that disparities also appear among women of different racial backgrounds. The growing racial disparity in obesity has increased and obesity is also perpetuated across generations. OBSSR contributes to support research that focuses on the relationships and influences of income and race as associated with higher levels of both objective and perceived stress, which the investigators suggest are in turn are associated with higher rates of dysregulated eating. This dysregulated eating then may lead to increased rates of obesity in these populations (3R01HD073568-04S1).

OBSSR also supports global research that targets the health of girls and women. For example, South Africa has the world's largest HIV epidemic and South African girls and young women acquire HIV at twice the rate of their male peers. OBSSR contributes to research that applies behavior change within these populations: research that adapts and evaluates the effectiveness and cost-effectiveness of a family-based HIV prevention package for adolescent girls and young women as well as female caregivers. The goals of this research include establishing the cost-effectiveness of comprehensive HIV prevention packages. This research addresses a compelling need to reduce incident HIV and STI infections among South African girls and women.

Office of Disease Prevention

Activities

- Pathways to Prevention (P2P) Workshop on Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention

  Among U.S. adults age >50, 8 million women and 2 million men 21 have osteoporosis, and 27 million women and 16 million men have low bone mass.[51] It is estimated that by 2025, five fractures will occur for every 100 people age >65, and total U.S. health care costs attributable to fractures will reach $25 billion annually. Getting adequate nutrition and regular exercise, quitting tobacco use, limiting alcohol use, and preventing falls help reduce a person's risk of osteoporotic fractures. Further, pharmacologic treatments may be prescribed to prevent fractures for people who have very low bone mineral density or a prior fragility fracture, and the U.S. Food and Drug Administration has approved medications that inhibit bone loss and stimulate bone formation. Nevertheless, many people at high fracture risk are untreated. Less than 20% of women received osteoporosis treatment in the year following diagnosis of an initial fragility fracture, and compliance rates are low.[52] On October 30 and 31, 2018, the NIH convened this workshop to assess the available scientific evidence to better understand the appropriate use of drugs for osteoporotic fracture prevention. A final report from this workshop will be available by mid-summer 2019.

- The ODP developed a prevention research taxonomy to characterize the NIH prevention research grant portfolio. The taxonomy consists of six categories: rationales, exposures, outcomes, populations, study designs and types of prevention research. The populations category represents the population groups being studied with 11 topics, including pregnant and/or post-partum women and youth, which is inclusive of infants, children and adolescents. As a means of supplementing our existing data, ODP collected information from grants with completed targeted enrollment tables, including gender, ethnic and racial categories, and the gender, minority, and child (GMC) codes that were assigned during their review. By incorporating these population data into our existing prevention research taxonomy dataset, we expect to gain more insight into the targeted enrollment of women and minority populations among NIH research projects, including research topics where these populations are being studied.

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Office of Disease Prevention—Office of Dietary Supplements

I. Executive Summary

The Office of Dietary Supplements (ODS) was created in 1995 in the Office of Disease Prevention, Office of the Director, National Institutes of Health (NIH), to meet the requirements of the Dietary Supplement Health and Education Act (DSHEA) of 1994. DSHEA defined the purposes and responsibilities of ODS as follows:

Purposes

- To explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care.
- To promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions.

Responsibilities

- To conduct and coordinate scientific research within NIH relating to dietary supplements and the extent to which the use of dietary supplements can increase resilience or limit or reduce the risk of diseases.
- To collect and compile the results of scientific research relating to dietary supplements, including scientific data from foreign sources.
- To serve as the principal advisor to the Secretary and to the Assistant Secretary for Health and provide advice to the Director of NIH, the Director of the Centers for Disease Control and Prevention (CDC), and the Commissioner of the Food and Drug Administration (FDA) on issues relating to dietary supplements. These issues include dietary intake regulations, the safety of dietary supplements, the claims characterizing the relationship between the use of dietary supplements and the prevention of disease or other health conditions and the maintenance of health, and scientific issues arising in connection with the labeling and composition of dietary supplements.
- To compile a database of scientific research on dietary supplements and individual nutrients.
- To coordinate funding relating to dietary supplements for NIH.

Subsequent congressional mandates directed ODS to develop a botanical research center initiative (1999), conduct evidence-based reviews of the efficacy and safety of dietary supplements (2001), accelerate the validation of analytic methods and reference materials for dietary supplements (2001) and support the development of a dietary supplement label database (2004).

ODS developed its mission statement as part of its first strategic planning process in 1998. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

II. Initiatives

ODS Extramural Investments

ODS's guidelines and criteria for initiating, expanding, or otherwise modifying its extramural

investments have reflected DSHEA and congressional mandates. These guidelines are a response to gaps in scientific knowledge, opportunities for research relevant to dietary supplements, requests for research support from investigators, requests for information, and available resources. ODS extramural investments are categorized into four broad areas: (1) research support, (2) research tools, (3) communications, and (4) science-policy interactions.

The Office's key activities are grouped into 15 programs under these 4 areas (see below); these 15 programs capture most of ODS's activities. In FY 2018 the ODS budget was $25.2 million with $16.8 million of that amount awarded to research projects including grants, contracts, and interagency agreements.

Communication and science policy efforts rely heavily on investments of ODS staff time and expertise rather than direct funding. An ODS staff member is responsible for overseeing each of the 15 ODS programs that support extramural research, and most ODS staff members are active in more than one program. Each program interacts with one or more stakeholder communities, including researchers; educators and teachers; health practitioners; research and educational institutions; Agencies of the Federal Government; dietary supplement, food, and related industries; media; consumer, and public interest groups; and members of the public. The 4 areas and 15 programs are described briefly below.

III. Area 1: Research Support

Research Grant Portfolio. This portfolio consists of grants administered by NIH Institutes and Centers that receive funding from ODS for research components related to dietary supplements. This investment supports the development of new knowledge on the health effects of dietary supplements.

Botanical Dietary Supplement Research Centers (BDSRCs). ODS currently co-funds three BDSRC and two Centers for Advancing Natural Products Innovation and Technology (CANPIT) in response to a congressional mandate. The Office administers these Centers (which together make up the NIH Centers for Advancing Research on Botanicals and Other Natural Products, or CARBON Program) in partnership with the National Center for Complementary and Integrative Health (formerly the National Center for Complementary and Alternative Medicine). These Centers expand the scientific knowledge base for botanical dietary supplements with a strong focus on those used by post-menopausal women; BDSRC have participated in the ODS Analytical Methods and Research Materials Program. All of the CARBON Centers also train new transdisciplinary dietary supplement researchers and the BDSRC support pilot project programs to foster innovation in botanical dietary supplement research. The CANPIT are mandated to actively work to disseminate both the innovative methods they're charged with developing and discipline-specific "good practices" critical to research reproducibility. FOAs for competitive renewal of the CARBON Program were recently published.

Training and Career Development. These extramural investments consist primarily of co-funding for selected NIH research training and career grants. The grants enable junior scientists to develop research programs related to dietary supplements. In addition, ODS each year organizes the Mary Frances Picciano Dietary Supplements Research Practicum. The Practicum offers a multiday opportunity for faculty, students and practitioners to acquire a broad, fundamental understanding of dietary supplements. The 2017 Practicum will be videotaped and made broadly available.

Conferences and Workshops. ODS funds research conferences and workshops primarily through NIH grant mechanisms, although it also

supports conferences and workshops initiated by NIH. These conferences and workshops bring together key scientists to discuss and define the research needs for various dietary supplements. In 2018, with input and support from ORWH, NCI, NCCIH, NIA, NIAAA, FDA and USDA, ODS organized a workshop titled “Enhancing Natural Product Clinical Trials”, focused on approaches to improve rigor, transparency, and translational relevance (including consideration of sex differences), in the full range of clinical trial-relevant research on natural products, from foundation data, including source and chemistry authentication, through clinical trial design and interpretation.

IV. Area 2: Research Tools

Analytical Methods and Reference Materials. ODS established this program in response to a congressional mandate and administers it primarily through contracts originated by ODS. Supporting the development of analytic methods and reference materials for dietary supplements has been key to making informative studies of dietary supplements possible.

Surveys of Dietary Supplement Use. ODS provides intellectual and financial support to Federal agencies conducting national nutritional surveys that include use of dietary supplements. As part of this effort, the Population Studies Program focuses on the evaluation of dietary supplement use, including the assessment of biological measures of supplement exposure and associated health effects in nationally representative populations, in order to evaluate nutrients of concern for inadequacy or excess. In collaboration with other Government agencies and academia, the efforts of this program are building our capacity to analyze population data (including economic cost), such as those from the National Health and Nutrition Examination Survey, and will serve as a training environment for postdoctoral fellows.

Dietary Supplement Databases. ODS provides intellectual and financial support and leadership to Federal agencies that are establishing databases to enable the interpretation of survey data on public nutrition habits and use of dietary supplements. ODS and its Federal partners at the United States Department of Agriculture, CDC, National Library of Medicine, and FDA have created a dataset of dietary supplement ingredients (the Dietary Supplement Ingredient Database [DSID]) and and a comprehensive database of information on supplement labels (the Dietary Supplement Label Database [DSLD]).

Evidence-Based Reviews. In response to encouragement from Congress, ODS provides intellectual and financial support, primarily to the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, to conduct reviews that are critical to determining the research needs for selected dietary supplements. These reviews are published on the AHRQ Web site and in peer-reviewed journals. Evidence-based reviews are key to identifying the status of scientifically validated knowledge about dietary supplements and the important gaps in research.

V. Area 3: Communications

Communications. ODS’s communication activities include a broad spectrum of outreach activities, such as the ODS Web site, Twitter feed, and public information pieces in three versions, one for health care professionals, and two for consumers, one in English and one in Spanish related to dietary supplements.

Computer Access to Research on Dietary Supplements (CARDS). ODS developed this consumer-friendly, Internet-based database in response to the DSHEA mandate to compile a database of scientific research on dietary supplements. CARDS contains information on

federally funded research projects pertaining to dietary supplements.

PubMed Dietary Supplement Subset. ODS and the National Library of Medicine (NLM) partnered to create this Dietary Supplement Subset of NLM's PubMed. The subset is designed to limit search results to citations from a broad spectrum of dietary supplement literature including vitamin, mineral, phytochemical, ergogenic, botanical, and herbal supplements in human nutrition and animal models.

Federal Dietary Supplement Working Group. ODS established the Federal Dietary Supplement Working Group in 2005 to share information and discuss issues related to dietary supplements among Federal agencies.

VI. Area 4: Science-Policy Interactions

These programs reflect the philosophy that good policy is founded on good science. ODS furnishes expertise in nutritional sciences to address public health issues related to dietary supplements.

Nutrient Initiatives. The Office of Dietary Supplements (ODS) leads and sponsors several efforts to advance scientific understanding that may enhance the reproducibility and interpretation of clinical assays for some nutrients. These initiatives include efforts to advance scientific understanding of the validity of various biomarkers of exposure, status, and overload within different subpopulations and at different life stages. Examples of these efforts include: 1) a 2016 ODS supported conference on "Iron Screening and Supplementation of Iron-replete Pregnant Women and Young Children;" 2) a 2017 ODS supported conference entitled, "Vitamin D Standardization Program: The Road Ahead;" and 3) a 2017 ODS supported forum entitled, "The Vitamin D Paradox: A Systems-based Approach to Investigating Clinical Practice, Research, and Public Health."

Dietary Supplement Use in the Military. This partnership with the Department of Defense is evaluating the impact of dietary supplement use by military personnel and is closely aligned with the new Resilience & Health Studies Program at ODS. An example of efforts stemming from this partnership include a research project (interagency agreement) entitled, "Dietary ingredients to minimize environmental heat injury." Relevant to women's health, one of the goals of the project is to assess the impact of extreme heat conditions on reproductive organs of male and female mice.

Dietary Reference Intakes. ODS supports Federal programs to evaluate the reference standards for intakes of nutrients, including vitamins and minerals.

ODS Strategic Plan

Goal 1: Expand the scientific knowledge base on dietary supplements by stimulating and supporting a full range of biomedical research and by developing and contributing to collaborative initiatives, workshops, meetings, and conferences.

Goal 2: Enhance the dietary supplement research workforce through training and career development

Goal 3: Foster development and dissemination of research resources and tools to enhance the quality of dietary supplement research.

Goal 4: Translate dietary supplement research findings into useful information for consumers, health professionals, researchers, and policymakers.

ODS Grant Funding and alignment with Office of Research on Women's Health Strategic Goals and Objectives

Fiscal Year 2017: $2,348,618

Project Title	ORWH Strategic Goals and Objectives	ORWH Congressional Topics
Botanical Dietary Supplements for Women's Health 5P50AT000155-18 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5P50AT000155-18)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. **3.8.** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.	
Cardiovascular protection by phytosterols in dyslipidemic mothers and progeny 5K01AT007826-05 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5K01AT007826-05)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women.	Cardiovascular disease
Trial of vitamin D supplementation and neuromuscular function in older adults 5R01AG042411-05 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01AG042411-05)	**3.8.** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.	Inclusion of women in clinical research
Mechanistic basis of probiotic prevention of osteoporosis 5R01AT007695-05 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01AT007695-05)	**3.8.** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.	Microbiome
Enhancing recruitment and retention of underrepresented pregnant Hispanic Women in a phase III randomized clinical trial	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women. **3.9.** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening therapeutic interventions.	Inclusion of women in clinical research Health disparities
The global network and preconception maternal nutrition 5U10HD076474-05 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5U10HD076474-05)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women. **4.6.** Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries.	
The VITamin D and OmegA-3 Trial (VITAL) 5R01CA138962-09 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01CA138962-09)	**3.7.** Explore differences in response to therapeutic interventions among samples of elderly women, including those with comorbid conditions. **3.8.** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and halth-related quality of life. **3.9.** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status..as they influence health…	Cardiovascular diseaseInclusion of women in clinical research Sex differences in …clinical research

Vitamin D and HA Signaling in TNBC 5R01CA194500-03 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01CA194500-03)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.	
Maternal and infant immunization to eliminate breast milk transmission of HIV-1 5P01AI117915-03 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5P01AI117915-03)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women.	
BMI-based prenatal vitamins to ameliorate oxidative stress in obese pregnancy 5K23HD074648-05 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5K23HD074648-05)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women.	Precision medicine

Fiscal Year 2018: $3,582,535

Project Title	ORWH Strategic Goals and Objectives	Congressional Topics
Role of PUFA-Gene Interactions in Health Disparities 5R01AT008621-03 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01AT008621-03)	**3.9.** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.	Health disparities
Activation of probiotic bifidobacteria by milk glycans 5R01AT008759-05 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01AT008759-05)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women	
Mechanisms of Carotenoid Transport and Interactions with Nutrient Absorption 5R01AT008099-05 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R00AT008576-04)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. **6.1.** Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH	
Botanical Dietary Supplements for Women's Health 5P50AT000155-19 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5P50AT008661-04)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. **3.8.** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.	
The VITamin D and OmegA-3 TriaL (VITAL) 5R01CA138962-10 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01CA138962-10)	**3.7.** Explore differences in response to therapeutic interventions among samples of elderly women, including those with comorbid conditions. **3.8.** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and halth-related quality of life. **3.9.** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status..as they influence health…	Cardiovascular disease Inclusion of women in clinical research Sex differences in …clinical research

Exercise Effects in Men & Women on Colon DNA Methylation 5R21CA209203-02 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R21CA209203-02)	**1.1.** Encourage genetic and epigenetic studies to identify sex differences in gene expression **1.8.** Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and wellbeing.	Precision medicine Inclusion of women in clinical research Sex differences in basic, applied and clinical research
Role of Glycine Metabolism in Cardiovascular Disease 5R01HL133169-02 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01HL133169-02)	**2.1.** Encourage the development of technologies that will address sex-based differences at all scales of detail… **2.4.** Develop computational models that will utilize multiple levels of analyses to address both qualitative and quantitative outcomes of clinical research related to women.	Cardiovascular disease
Gut Flora Metabolism of Dietary Phosphatidylcholine and CVD 5R01HL103866-09 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01HL103866-09)		Microbiome Cardiovascular disease
Microbial Trimethylamine Lyases and Atherosclerosis 5R01HL130819-03 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01HL130819-03)	**3.9.** Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors…	Microbiome Cardiovascular disease
Vitamin D Supplements to Prevent Falls in Older Adults: A Dose-Response Trial 5U01AG047837-05 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5U01AG047837-05)	**3.8.** Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.	Inclusion of women in clinical research Sex differences in basic, applied and clinical research
Docosahexaenoic Acid (DHA) Supplementation in Pregnancy to Reduce Early Preterm Birth 5R01HD083292-03 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01HD083292-03)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women	Health disparities
Mechanism of Selenoprotein Synthesis 5R01DK047320-22 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01DK047320-22)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.	Sex differences in basic, applied and clinical research
Nutrigenomics of Intestinal Vitamin D Action 5R01DK112365-02 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01DK112365-02)	**1.3.** Study sex differences using a systems biology-based approach. This will include research based on new technology platforms such as microbiomics, genomics, phenomics, proteomics, and metabolomics.	Precision medicine
Molecular Mechanisms of Intestinal Metal Ion Transport During Iron Deficiency 2R01DK074867-11 (https://ods.od.nih.gov/Funding/abstract.aspx?g=2R01DK074867-11)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women	Health disparities
The Transport of Nutritional Heme in Animal Development 5R01DK085035-08 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01DK085035-08)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women	

Vitamin D and type 2 diabetes (D2d) 2U01DK098245-06 (https://ods.od.nih.gov/Funding/abstract.aspx?g=2U01DK098245-06)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.	Inclusion of women in clinical research
Intestinal Biotin Absorption: Physiological and Pathophysiological Aspects 5R01DK058057-19 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01DK058057-19)	Study sex differences using a systems biology-based approach. This will include research based on new technology platforms such as microbiomics, genomics, phenomics, proteomics, and metabolomics	Microbiome
Redefining Vitamin D Deficiency: The Role of Bioavailable Vitamin D 5R01DK094486-07 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01DK094486-07)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.	Health disparities Precision medicine
Copper Homeostasis in Mammals 5R01DK074192-16 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01DK074192-16)	**3.3.** Encourage research on safe and effective interventions for conditions affecting pregnant women	
Selenium in gastrointestinal inflammatory diseases 5R01DK099204-06 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01DK099204-06)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.	
Folic Acid Prevention Pathways for ASD in High Risk Families 5R01ES025574-04 (https://ods.od.nih.gov/Funding/abstract.aspx?g=5R01ES025574-04)	**2.7.** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. **3.4.** Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.	

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Office of Research Infrastructure Programs

Executive Summary

Established in December 2011, the Office of Research Infrastructure Programs (ORIP) is located within the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), NIH Office of the Director. ORIP brings together research activities managed by the Division of Comparative Medicine and the Division of Construction and Instruments. ORIP's mission is to provide research infrastructure and research-related resource programs. ORIP's infrastructure programs are trans-NIH in nature and align with DPCPSI's mission to ensure that NIH effectively and efficiently addresses and coordinates important areas of emerging scientific opportunities to improve human health.

ORIP stimulates innovation and leverages shared resources to:

- develop and provide access to critical animal models, including those relevant to women's health;
- provide access to state-of-the art technologies and instruments that enable biomedical research and clinical investigations of a multitude of health issues, including those of consequence to women and girls;
- explore strategies for consideration of sex differences in animals and cell lines used in NIH-funded studies as a means of enhancing experimental design and increasing reproducibility in preclinical research in women's health and other research disciplines; and
- train veterinarian-scientists and support underrepresented minorities to become valuable partners in an integrated, multidisciplinary approach to biomedical/translational research.

Research on women's health utilizes many of the animal models supported by ORIP, from invertebrates such as worms and fruit flies to vertebrates such as fish and mammals, including rodents, swine, and nonhuman primates (NHPs). This report highlights one featured program from ORIP, the National Primate Research Centers, which supports the implementation of the first 3 goals of the NIH Strategic Plan for Women's Health Research. This report also provides an overview of ORIP's accomplishments and activities within its broad-based research portfolio on women's health, including research on the impact of other diseases such as Alzheimer's disease, cardiovascular disease, and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) on women's health; the neurosciences; sex differences; and reproductive health. Included with this report are highlights of ORIP's initiatives to enhance education and diversity of the future biomedical workforce through training and mentoring programs that focus on veterinary students and veterinarians and educational programs targeting underrepresented minorities. In addition, this report describes several ORIP-sponsored initiatives, including program announcements, conferences, and workshops with a focus on women's health and related trans-NIH research and training programs.

NIH Strategic Plan for Women's Health Research

This section highlights one featured program from ORIP which supports the implementation of the NIH Strategic Plan for Women's Health Research.

The National Primate Research Centers (NPRCs)

NHPs provide critical models for understanding human health, including areas specific to women and girls and areas where it is critical to study the difference between males and females. Of all widely available animal models, NHPs are closest to humans in physiology, behavior, and genetics. Furthermore, the environment and diet of NHPs can be controlled rigorously, thus eliminating variables that often confound preclinical research in humans.

The NPRCs were established over 55 years ago as it is not cost effective or feasible to duplicate NHP facilities at every institution. As national resources, each year the seven NPRCs facilitate more than 1,000 projects funded by all NIH Institutes and Centers, scientific foundations and other research entities and accommodate the needs of researchers throughout the U.S. The NPRC Research and Capabilities website (http://nprcresearch.org/primate/) provides comprehensive information for researchers and the public regarding the range of available programs, resources, and achievements of the NPRCs.

ORIP's Division of Comparative Medicine manages the NPRCs' activities aligned with three of the ORWH/NIH Strategic Plan Goals and Objectives described below.

Goal 1: Increase sex differences research in basic sciences studies.

Studies using systems biology-based approaches, such as DNA and RNA sequencing and proteomic analysis, are done at the NPRCs to enable a better understanding of sex differences at the genetic and molecular levels (Objectives 1.1, 1.3, 1.8). For example, monkeys exhibit many of the same behaviors as humans, including those related specifically to the well-being of women and girls. Female monkeys living in large groups experience varying levels of social stress, depending on the dominance status of a particular female. The effects of stress on female physiology and gene expression are studied at the NPRCs as well as the impact of controlled diet and caloric intake. This permits analysis of the differential effects of maternal nutrition on female versus male fetuses, which can also lead to differences in newborn and neonatal health.

Goal 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices and therapeutic drugs.

Female monkeys can serve as an animal model of many diseases and conditions that women experience, including diabetes, endometriosis, polycystic ovary syndrome, HIV/AIDS, and Zika virus (ZIKV) infection. For example, a priority in HIV/AIDS prevention is the development of new devices or therapies that give women personal control (Objective 2.7). The NPRCs have pioneered many studies using a monkey model of human AIDS, which involves analysis of animals infected with simian immunodeficiency virus (SIV), the monkey analog of HIV. In addition to testing strategies for AIDS vaccines, the NPRCs have supported the development and testing of potential microbicides, compounds that women can use as a vaginal preparation to decrease acquisition of HIV. Other research avenues include prevention of maternal transmission of AIDS to infants and examination of the pathobiology of ZIKV infection on the developing fetus.

Goal 3: Actualize personalized prevention, diagnostics and therapeutics for girls and women.

The NPRCs conduct studies on all aspects of the female reproductive cycle, as most aspects

are the same in NHPs and humans, including fertility, conception, pregnancy, and menopause. NPRC investigators are developing novel non-surgical contraceptives, exploring epigenetic control of puberty, and studying the effects of various hormones on menopausal transition, with the aim of describing and ultimately finding new treatments for weight gain, loss of libido, metabolic syndrome, and cardiovascular disease that some women experience as a result of menopause (Objective 3.1). Studies in pregnant monkeys evaluate disease impact on the developing fetus and provide the groundwork for developing safe and effective interventions in pregnant women (Objective 3.3).

The projects described above are just a few examples of the many studies related to women's health that are performed at the NPRCs.

Accomplishments and Activities

Alzheimer's Disease and Other Dementias

Alzheimer's Disease (AD): The role of the gut microbiota in sex differences

AD has a higher occurrence in women, as well as sex differences in disease progression and treatment efficacy. The Rat Resource and Research Center at the University of Missouri maintains a leading rat model of AD, which carries important human AD mutations in the Presenilin 1 and amyloid beta (A4) precursor protein genes. Before the onset of overt signs of AD, sex-related differences in the microbiota, which were not related to genetic modification, were observed. After AD signs were apparent, no differences in microbiota were present in females, but males did show differences between the strains. These results and small human studies that show improvement in cognitive function in AD patients who use probiotics suggest that interventions targeting the microbiome may have a beneficial effect on disease onset, progression and/or severity. Supported by ORIP and ORWH.

Cardiovascular Disease

Cardiovascular Disease: Prenatal factors affecting heart disease

Preterm birth, low birth weight, or abnormal fetal growth can cause problems with the fetal heart and have been linked to heart disease later in life. Understanding the fetal origins of adult heart disease may lead to therapies to protect the fetal heart during development. Researchers at the Washington NPRC studied how infection-associated preterm birth can impair cardiac development (Mitchell et al., 2018). Critical gene networks for development of the fetal heart and blood vessels were disrupted in fetuses born preterm with severe bacterial infection. This study may allow for development of therapeutics to protect fetal organs from inflammatory injury and preserve the potential for normal cardiac functioning as an adult. Supported by ORIP, NIAID, NICHD and the March of Dimes.

Other Diseases

Breast Cancer: Lung fibroblasts alter sensitivity of breast cancer cells to anticancer therapy

Most breast cancer deaths are due to metastasis and anti-cancer drug resistance. Researchers at Colorado State University developed an experimental model to evaluate the role of lung fibroblasts on anti-cancer drug responses and found a putative mechanism by which fibroblasts negatively impacted breast cancer sensitivity to commonly used anti-cancer therapies. Targeting this extrinsic mechanism of drug resistance may hold promise for re-sensitizing breast tumor cells to standard of care therapies. Supported by ORIP and ORWH.

HIV/AIDS: Characterization and modulation of mucosal immunity for HIV prevention in women

Women often lack control over behavioral, barrier, and pharmacological HIV prevention measures. Pre-exposure prophylaxis (PrEP) with antiretrovirals has recently shown efficacy, but results in women have been mixed, and for this reason it is important to determine how the female genital tract could be modified to improve PrEP. One possibility is to administer a drug that exerts both anti-inflammatory and antiviral effects. This project is focused on the effects of Maraviroc, an antiretroviral drug that blocks the human CCR5 receptor, on changes in HIV target cells (Iyer et al., 2017), T-cell activation, and inflammatory cytokines in genital mucosa. The results of this study could influence use of pharmacological interventions to improve PrEP efficacy in women. Supported by ORIP and NIAID.

HIV/AIDS: Epithelium-innate immune cell axis in mucosal responses to SIV

Researchers at the Yerkes NPRC are exploring the early immunological events in the cervicovaginal epithelia in macaques vaccinated with SIVΔnef variants. Unvaccinated animals have a chemokine gradient that is spatially correlated with the recruitment of CD4 T-cells, which is absent in animals vaccinated with SIVmac239Δnef (Shang et al., 2017a, 2017b). Further, SIV exposure in vaccinated animals produces an immunologically quiescent state in the mucosa and protection against vaginal challenge. In vaccinated animals, early stress responses were suppressed, and the maintenance of epithelial barrier integrity correlated with prevention of virus entry (Shang et al., 2018). These effects were associated with locally producing and concentrating trimeric gp41 antibodies at the mucosal interface and with formation of SIV-specific immune complexes. Macaques vaccinated with SIVΔnef also demonstrated a tissue-resident memory population of SIV-specific CD8 T cells in vaginal mucosa. Repeated immunizations with SIV envelope trimeric gp41 elicited antibodies in the cervicovaginal epithelium. Passive immunization experiments suggest that sufficiently high antibody levels can be concentrated at mucosal frontlines. Collectively these studies illuminate the mechanisms of vaccine protection and support development of HIV vaccines that can interrupt viral transmission at mucosal portals of entry and sites of viral dissemination. Supported by ORIP, ORWH, and NIAID.

HIV/AIDS: Impact of progestin contraception on risk of HIV acquisition and transmission

This project investigates the hypothesis that certain hormonal contraceptives, particularly depot medroxyprogesterone acetate (DMPA), increase HIV infection risk due to alterations in HIV target immune cells and function within the female genital mucosa. This project is assessing the relative impact of three progestin-only contraceptives (DMPA, Etonogestrel implant [Eng-Implant] and Levonorgestrel intrauterine device [Lng-IUD]) on markers of T-cell activation and trafficking as well as secreted cytokines and chemokines within the female genital mucosa (Iyer et al., 2017). Because mucosal immune changes with progestin-only contraceptives are largely mediated via estrogen suppression, the impact of contraceptives with milder anti-estrogen effects (e.g., Eng-Implant and Lng- IUD) is expected to be significantly less pronounced. The outcomes of this study have significant clinical implications for family planning services for women worldwide. Supported by ORIP and NICHD.

HIV/AIDS: Mechanisms of vaccine protection against intravaginal HIV infection

The Emory Consortium for Innovative AIDS Research and the Yerkes NPRC are working towards an HIV vaccine that is long-lived and maintains high levels of protection in genital and rectal mucosal tissue and on effective immunotherapy to control HIV infection in infected individuals. Adjuvants such as R848 and 3M052 (toll-like receptor 7/8 agonists)

delivered in nanoparticles with protein-based HIV vaccines induce robust and long-lived antibody responses against diverse HIV strains in serum and mucosa, albeit at low levels (Kasturi et al., 2017). These results have important implications for the development of vaccines against HIV with particular effectiveness in women. Supported by ORIP, ORWH, and NIAID.

HIV/AIDS: Preventing mother-to-child transmission (MTCT)

In the developing world, HIV infection in newborns and children is almost exclusively due to MTCT. The Oregon NPRC is studying the potential treatment of newborns and infants with potent human neutralizing antibodies delivered shortly after birth using an NHP model of rhesus macaque newborns orally infected with simian-human immunodeficiency virus (SHIV; Hessell et al., 2018b). A cocktail of purified human neutralizing monoclonal antibodies given to newborn macaques one day after oral SHIV exposure cleared the infection in 100% of animals. Treatment initiated 48 hours after viral exposure cleared the virus in half of the infants and attenuated the disease in most infants. An HIV human monoclonal antibody with limited neutralizing activity used for pre-exposure prophylaxis could limit tissue seeding of the virus (Hessell et al., 2018a; Jaworski et al., 2017). These studies suggest that a combination of antibodies and antiviral drugs may be more effective than drugs alone in limiting HIV transmission. The California NPRC is also using NHPs to optimize HIV vaccine strategies aimed at reducing MTCT through breastfeeding, by testing various vaccine constructs and adjuvants to induce better immune responses in infants (Curtis et al., 2018; Phillips et al., 2018). Supported by ORIP, NICHD and NIAID.

Infectious Disease: Listeria may be a serious miscarriage threat early in pregnancy

Listeria, a common food-borne bacterium, may pose a greater risk of miscarriage in early pregnancy than appreciated. Listeria infection in pregnancy may go unnoticed as symptoms are nearly indistinguishable from the discomfort most newly pregnant women feel. Investigators at the Wisconsin NPRC performed ultrasounds on rhesus macaque fetuses during infection. None of the monkeys showed obvious signs of infection before their pregnancies came to abrupt ends. Tissue samples taken after each monkey experienced intrauterine fetal death showed listeria had invaded the placenta and endometrium (Wolfe et al., 2017). Supported by ORIP, NIAID, NCATS, and NICHD.

Neurosciences

Behavior: Social effects on immune gene regulation and emotional feeding

The Yerkes NPRC is studying the effect of chronic social stress on immune gene regulation, infection risk and emotional feeding, which is more common in women and is likely a key factor in higher rates of obesity. Social subornation in adult female rhesus monkeys produces several stress-related characteristics similar to those observed in women (Roman et al., 2018), including a compromised dopamine reward circuitry (Godfrey et al., 2018) that may result in excessive consumption of diets high in fat and sugar, decreased immune cell sensitivity to glucocorticoids, and downregulation of genes involved in immune cell adhesion. Short-term administration of a stress hormone antagonist attenuates emotional feeding. A behavioral intervention to alleviate chronic stress, improve dopamine function, and diminish emotional feeding is being explored. The immune study is being extended to examine social stress effects on gene expression levels and antibody response across 30 physiologically relevant environmental conditions (e.g., pathogen exposure, steroid hormone signaling, influenza vaccination). These studies address health risks associated with social stress in women. Supported by ORIP, ORWH, NIGMS, and NIDDK.

Neurobiology: Estrogen and the aging brain

Researchers at the California NPRC and the Icahn School of Medicine at Mount Sinai have discovered molecular and structural effects of estrogen treatment in the prefrontal cortex that are linked to cognitive enhancement as well as the importance of timing and duration of estrogen treatment in an NHP model (Baxter et al., 2018; Crimins et al., 2018; Hara et al., 2018). These results have significance with respect to potential molecular targets related to both aging and estrogen treatment and help inform the nature of hormone treatments that might facilitate cognitive performance in women. Supported by ORIP and NIA.

Neurodevelopment: Environmental exposures, reproduction and infant development

The Washington NPRC has a long-standing program on the maternal and fetal effects of neurotoxicant (e.g., methylmercury, methanol and thimerosal) exposure during pregnancy. Current research using an NHP model is focused on maternal and infant effects of exposure during pregnancy to domoic acid (DA), a naturally occurring biotoxin found in ocean waters that is consumed with contaminated finfish and shellfish. Slow absorption results in a longer than anticipated half-life for DA (Jing et al., 2018), and exposure to DA at environmentally relevant levels does not impact maternal reproductive outcomes but does induce subtle neurological signs in pregnant dams. Examination of prenatally exposed infants during the first months of life demonstrates that DA does not negatively impact neonatal survival reflexes or responsivity to the environment but is associated with disruptions in early memory. Further, chronic, low-level exposure to DA is associated with injury to the adult and developing central nervous system (CNS) but regulatory guidelines may not be adequate for high-frequency shellfish consumers. Results are being shared with regulatory authorities (e.g. FDA, EPA, NOAA) to help ensure that current thresholds are adequate to protect human health. Supported by ORIP, NIEHS, and NCATS.

Neurodevelopment: Maternal obesity and infant behavior

Maternal adiposity is a risk factor for adverse neurodevelopment. A retrospective cohort analysis examined whether maternal pre-pregnancy adiposity and gestational weight gain were associated with behavioral outcomes in 173 rhesus macaque infants at the California NPRC. Offspring of mothers with greater baseline adiposity or gestational weight gain exhibited poorer adaptability characterized by greater emotionality, blunted affective response to an intruder challenge, and reduced interest in novel stimuli, outcomes associated with poorer social functioning later in life (Walker et al., 2018). They exhibited lower cortisol levels following dexamethasone suppression, perhaps a response to cortisol excess during gestation. These results amplify growing public health concerns implicating maternal adiposity in impaired fetal neurobehavioral programming. Supported by ORIP and NICHD.

Neurodevelopment: Non-invasive magnetic resonance imaging (MRI) methodology for assessing fetal brain sensitivity to ethanol exposure

Alcohol consumption prior to awareness of pregnancy contributes to fetal alcohol spectrum disorder in the US. Methods for early detection of adverse effects on brain development of prenatal alcohol exposure would facilitate new therapeutic interventions that could be initiated early in life (Coleman et al., 2017). Research at the Oregon NPRC is underway to characterize fetal brain development with recently-developed *in utero* MRI methods which allow non-invasive monitoring of cellular and macroscopic brain development throughout pregnancy (Lo et al., 2017b; Wang et al., 2017). Supported by ORIP, NICHD, NIBIB, NINDS, NIAAA, and NIDDK.

Neurodevelopment: Prenatal risk factors for neurodevelopmental disorders

The California NPRC uses NHPs as model systems to evaluate prenatal risk factors for autism, schizophrenia and other neurodevelopmental disorders. They have documented long-standing immune dysregulation in animals born to dams that experienced maternal immune activation during pregnancy (Rose et al., 2017) and have highlighted contributions of NHPs to our understanding of prenatal risk factors for neurodevelopmental disorders (Bauman & Schumann, 2018; Careaga, Murai, & Bauman, 2017; Kentner et al., 2018). The NHP model plays a critical role in bridging the gap between rodent models and translation to human patients. Supported by ORIP and NIMH.

Sex Differences in Basic, Applied and Clinical Research

Sex Differences: Neuroteratogenesis and congenital Zika syndrome

Congenital Zika Syndrome has devastating consequences on the newborn. The California NPRC is addressing the relationship between infection during pregnancy and at birth and includes a focus on the interactions between early neural precursor cells and microglia, the immune cells of the brain (Barger et al., 2018). *In vivo* imaging methods to monitor the virus and track outcomes and to identify any sex differences associated are key. Understanding critical cell populations during development and the role of the immune system will aid in determining future intervention strategies to protect the fetus and infant of both sexes. Supported by ORIP, ORWH, NIAID, and NINDS.

Sex Differences: Potential for decreased ZIKV pathogenesis in female non-human primates

Understanding ZIKV pathogenesis and host immune responses elicited by the infection is important for safely implementing vaccines and therapeutic interventions. The Washington NPRC found that female pigtail macaques had unique immune signatures and less ZIKV viral persistence when compared to their male counterparts (O'Connor et al., 2018). These results highlight that sex disparate ZIKV pathogenesis may occur during human infection. Supported by ORIP and NIAID.

Sex Differences: Sex- and pregnancy-specific responses for fluorescent light exposure

Researchers at the University of Virginia are using the southern platyfish (*Xiphophorus maculatus*) to study sex-specific effects of fluorescent lighting. Females appear to require a lower dose of lighting to alter their global genetic profiles. Additionally, males and females exhibit opposite ultraviolet B induced changes in gene expression of several important genetic pathways, such as synaptic development, wound healing, glucose metabolism, free radical scavenging, and cell differentiation, apoptosis, and proliferation (Boswell et al., 2018). Ongoing work is focused on the effect(s) of pregnancy in these live-bearing fish on the ability of the skin and other organs to genetically respond to various light wavelengths (Walter et al., 2018). Supported by ORIP and ORWH.

Sex Differences: Tissue and organ repository illuminating diseases impacting women's health

The Human Tissue and Organ Research Resource (HTORR) is a critical link between organs and tissues donated for research and investigators working on treatments or cures. Lymphangioleiomyomatosis (LAM) is a rare lung disease that occurs primarily in women and results in decline in pulmonary function and respiratory failure. In fiscal years 2017-2018 HTORR distributed 260 tissues from 20 LAM donors to investigators (Dongre et al., 2017; Li et al., 2017; Miller et al., 2018; Murphy et al., 2017). To prevent and effectively treat breast cancer, it is essential to identify the genes and cellular protein interactions that contribute to breast

tumorigenesis (Gil et al., 2017; Markiewski et al., 2017). HTORR provides breast cancer tumor samples recovered following surgery. To develop improved microbicides that can prevent vaginal transmission of HIV, normal cervical tissue removed following surgical procedures serves as a model system. HTORR provided over 200 cervical samples to investigators working in this field (Ñahui Palomino et al., 2017; Vanpouille et al., 2017). Supported by ORIP, ORWH, and NHLBI.

Reproductive Health

Fertility and Contraception: Drying, storing, and reanimating egg germinal vesicles to preserve fertility

This project focuses on preservation of the oocyte's nucleus or germinal vesicle in a domestic cat model to detect candidate nuclear proteins involved in oocyte competence acquisition. Results have led to optimized microwave-assisted drying and storage with trehalose buffer solutions. Dried samples were stored in glass vials at ambient temperature with non-significant changes of moisture content and no increase in DNA damage over an 8-week period (Lee et al., 2018; Morselli et al., 2017; Songsasen et al., 2017). New findings have widespread, practical application to more effective, economical preservation, propagation and management of germplasm from women as well as from animal models used to study woman's fertility. Supported by ORIP and ORWH.

Fertility and Contraception: Epigenetic regulation of female puberty

Early or delayed puberty is associated with increased risks for several disorders including cardiometabolic, gynecological, gastrointestinal, musculoskeletal, and neurocognitive disorders. Because this cannot be explained by DNA sequence variation, Oregon NPRC investigators propose that puberty is regulated by an epigenetic process that relays environmental signals to modulate reproductive development. The Polycomb group (PcG) of gene silencers was shown to be a major contributor in a mechanism responsible for repressing Kiss1 expression in the hypothalamus during infancy, ultimately controlling gonadotropin releasing hormone release. Recent results suggest that activation of key puberty-inducing genes, such as Kiss1, depends on the balance between two fundamental forces of epigenetic regulation: The PcG family of gene silencers and the Trithorax group of gene activators (Toro et al., 2018a; 2018b; Horikoshi et al., 2018; Vazquez et al., 2018). Supported by ORIP and NICHD.

Fertility and Contraception: Estrogen source impacts ovulation

Discoveries related to estrogen sources and their role in ovulation may reveal the cause of previously undiagnosed infertility or point to new contraceptive methods. When the researchers at the Wisconsin NPRC blocked the production of hypothalamic estrogen in NHPs, the ovarian hormonal surge was drastically reduced, falling short of that required for ovulation, demonstrating that the brain's estrogen release is necessary for ovulation (Kenealy et al., 2017). Supported by ORIP and NICHD.

Fertility and Contraception: Nonsurgical permanent contraception for women

The Oregon Permanent Contraception Research Center was established at the Oregon NPRC to develop simple, low-cost, safe, and highly effective methods of nonsurgical permanent contraception (NSPC) for women (Jensen et al, 2017; Aengst et al; 2017). A lead approach involving polidocanol/doxycycline foam (PDF) was identified as well as several promising alternative methodologies. Preclinical studies evaluating alternative NSPC approaches are explored in guinea pig and baboon models concurrent with the PDF program (Jensen at al., 2018). Supported by ORIP and the Bill & Melinda Gates Foundation.

Fertility and Contraception: Polycystic ovary syndrome (PCOS)

PCOS is a major cause of infertility in women and is thought to originate from genetic and environmental influences. The Oregon NPRC has used NHPs to demonstrate that chronic androgen exposure during puberty combined with a high-fat diet can lead to many features of PCOS, particularly impaired fertility (Varlamov et al 2017; True et al, 2017; Bishop et al., 2018a, 2018b). Reduction or antagonism of excess androgen, combined with diet/lifestyle changes, may prevent or cure PCOS in adolescent or young women and restore fertility. A parallel clinical project suggests PCOS impacts endocrine function resulting in opposing effects of stimulatory reproductive versus inhibitory metabolic factors. This study is being extended to examine the continued effect of androgen exposure and a Western-style diet in NHPs on subsequent pregnancies, as well as the reversibility of these changes upon treatment removal. Clinical studies will assess whether hyperandrogenemia in normal-weight women with PCOS results in an altered programing of adipose progenitor cells, which may lead to subsequent metabolic dysfunction. Supported by ORIP and NICHD.

Fertility and Contraception: Preserving fertility for female cancer survivors

Cancer therapies can produce infertility due to ovarian failure leading to cryopreservation of ovarian tissue in hopes of its future use; however, techniques to restore ovarian function and fertility remain experimental. At the Oregon NPRC, vitrification was successfully used for cryopreserving rhesus monkey ovarian tissue and individual ovarian follicles in a closed system. Successful transplantation of thawed ovarian tissue produced early preimplantation stage embryos *in vitro* (Lee et al., 2018; Laronda et al, 2017). A mathematical model of the secondary follicle was developed and is being used to inform optimal cryoprotectants for vitrification of individual follicles (Bulgarelli et al, 2018; Jones et al., 2018). Supported by ORIP and NICHD.

Menopause: Does menopause increase the risk for diabetes?

Researchers at the Wisconsin NPRC explored the effects of ovarian estradiol depletion combined with diets higher in fat and sucrose in female marmosets (Kraynak et al., 2018). This treatment did not increase body weight and decrease glucose tolerance as hypothesized, opening up the intriguing possibility that estrogens produced elsewhere in the body may function in in regulating metabolism. Supported by ORIP, ORWH and NICHD.

Menopause: Hormone replacement therapy and the CNS

The influence of daily steroid supplements on the CNS of aged female rhesus macaques at the Oregon NPRC showed that supplementation with dehydroepiandrosterone, instead of estrogen, had no obvious beneficial effect on cognitive performance and did not enhance estrogen concentrations within brain cognitive centers (Urbanski et al., 2017; Sorwell et al., 2017). Hormone replacement to old ovariectomized animals consuming a high-fat, high-sugar Western-style diet showed an increase in body weight and a decrease in overall activity levels. This obesogenic diet also blunted or increased variability in estrogen-induced gene expression in brain areas (Bethea et al., 2017; Urbanski et al., 2017). These results suggest that diet may impact hormonal replacement therapies, which may not be as beneficial for obese women as normal-weight women. Supported by ORIP and NIA.

Pregnancy: Congenital Zika syndrome in guinea pigs

Investigators at the University of Hawaii developed a guinea pig model of fetal Zika virus infection during early pregnancy that results in a syndrome resembling the intrauterine growth restriction and spontaneous miscarriage observed in ZIKV-infected pregnant women (Krause et al., 2017 and Kim et al., 2018). Zika viral RNA was detected in the brain of fetuses from infected dams. This model may be used for the evaluation

of vaccines and therapeutics. Supported by ORIP, ORWH, NIGMS and NINDS.

Pregnancy: Congenital Zika syndrome in NHPs

Researchers at the Washington NPRC demonstrated that a maternal ZIKV infection leads to loss of neural stem cells and subtle injuries in the hippocampus of the fetal brain (Adams Waldorf, 2018). Viral injury to these cells may result in cognitive or emotional processing disorders in children exposed to ZIKV *in utero*. Researchers at the California NPRC have developed an NHP model to study fetal ZIKV infection by intra-amniotic inoculation and have demonstrated the development of neurological lesions (Coffey et al., 2018; Keeffe et al., 2018). Supported by ORIP, NIAID, NICHD, NINDS and FDA.

Pregnancy: Effects of maternal protein restriction in fetal and neonatal development

Oregon NPRC investigators are pursuing a translational NHP model to systematically dissect complex physiological and behavioral outcomes in offspring associated with maternal malnutrition. Study outcomes include effects of protein restriction during pregnancy on placental function (Roberts et al., 2018), fetal brain development, metabolic status and growth, response to infectious disease, and cognitive and neurodevelopmental outcomes. The goal is to have a well-characterized model to test specific intervention strategies that effectively prevent developmental abnormalities caused by maternal malnutrition. Supported by ORIP and the Bill & Melinda Gates Foundation.

Pregnancy: Health risks of being born to an obese mother

Mechanisms linking maternal obesity to pregnancy complications and offspring disease are being explored by researchers at the University of Colorado. Using a mouse model of maternal obesity, low levels of the maternal hormone adiponectin may be the underlying cause of the health risks to the offspring. Normalizing adiponectin levels prevented pregnancy complications and the development of obesity, insulin resistance and cardiac dysfunction in the offspring of obese mice. Interventions to stimulate maternal adiponectin signaling may represent a novel approach to prevent pregnancy complications and poor health in children of obese mothers. Supported by ORIP, ORWH, and NICHD.

Pregnancy: Infectious diseases and preterm birth

Oregon NPRC investigators have shown that maternal treatment with antibiotics can protect newborns from adverse outcomes due to the bacteria *Ureaplasma parvum.* The early stages of intrauterine infection with *Ureaplasma* as well as the safety of azithromycin treatment to improve long-term neurological and cardiovascular outcomes for premature infants are being studied. These projects explore how early intrauterine infection begins and how these processes may cause premature labor (Kelleher et al., 2017; Ellery et al., 2018). This early stage of infection also produces inflammation that may cause injury in the developing brain. Supported by ORIP and NICHD.

Pregnancy: *In utero* measurement of placental blood flow by MRI

Abnormalities in placental function contribute to most pregnancy complications including preterm labor, preeclampsia, fetal growth restriction, stillbirth, and a higher risk of long-term disease such as heart disease, obesity and diabetes. The Oregon NPRC developed placenta-specific MRI protocols to measure maternal blood flow to the placenta in the absence of a contrast agent (Lo et al., 2017a; Prola Netto et al., 2018; Salati et al., 2018). Once validated, the non-contrast MRI method can be safely used in pregnant women. These *in vivo* tools to assess placental function are crucial to advance the ability to detect

pregnancies at-risk for placental insufficiency. Supported by ORIP and NICHD.

Pregnancy: Maternal diet and developmental programming

Studies with baboons at the Southwest NPRC show that maternal obesity and exposure to a high-fat, high-simple-carbohydrate diet during pregnancy predisposes offspring to obesity, metabolic and cardiovascular disorders in later life (Gandhi et al., 2018; Huber et al., 2018; Mata-Greenwood et al., 2018; Puppala et al., 2018). Also, intrauterine growth restriction leads to cardiovascular dysfunction in offspring and an accelerated aging phenotype (Kuo et al., 2017, 2018a and 2018b; Light et al., 2018; Salmon et al, 2018). The marmoset is also being explored as a useful model for developmental programming of pediatric obesity. Initial studies indicate the placenta is a strong candidate as an agent of developmental programming effects (Riesche et al., 2018). Supported by ORIP, NICHD, and NIA.

Pregnancy: Pediatric immunology and prevention of viral diseases in infants

Studies to reduce MTCT of viral diseases and improve vaccine responses in newborn infants continue to be explored in NHP models at the Tulane NPRC. The persistence of maternal antibodies in newborn macaques, infant immune responses to vaccination at different stages of development, routes of immunization, and different adjuvants are actively under investigation (Veazey et al., 2018). Supported by ORIP and NIAID.

Pregnancy: Prevention and treatment of congenital cytomegalovirus (CMV) infection

CMV is the most common congenital infection worldwide and most infected infants will have subtle to severe lifelong neurologic deficits. The California NPRC uses an NHP model to study natural disease progression and to develop a vaccine to protect pregnant women. Mother to child CMV infection in rhesus macaques is associated with CD4+ T lymphocyte dysfunction that is partially reversed by the programmed death 1 molecule. While intact CD4+ T cells are required to prevent placental transmission, the presence of pre-existing neutralizing antibodies at the time of primary infection can protect the fetus from clinical infection. This research informs clinical practices to improve vaccine design and therapeutic options (Fan et al., 2017; Nelson et al., 2017; Chiuppesi et al, 2017; Wussow et al., 2018; Itell et al., 2017). Supported by ORIP and NIAID.

Pregnancy: ZIKV vertical transmission and risk of miscarriage

A large collaborative group from the Tulane NPRC and the University of Miami established a fetal transmission model of ZIKV infection in pregnant rhesus macaques. Inoculation with a Brazilian isolate resulted in acute viremia, virus in amniotic fluid, loss of two fetuses *in utero*, and one unresponsive newborn (Magnani et al., 2018). At the Southwest NPRC, additional results suggest that marmosets may be at particular risk of fetal loss due to fetal ZIKV infection (Chiu et al., 2017; Seferovic et al., 2018). A trans-NPRC collaboration demonstrated that 26% of rhesus and pigtail macaques and marmosets infected with ZIKV in early pregnancy experienced a miscarriage despite few clinical signs of infection (Dudley et al., 2018). Pregnancy loss due to an asymptomatic ZIKV infection may be underrecognized in humans. Supported by ORIP, NCATS, NIAID, and NICHD.

Sexually Transmitted Infections (STIs): Herpes simplex virus-2 (HSV-2) and HIV acquisition in women

HSV-2 is associated with increased HIV-1 acquisition in women but anti-herpes drugs do not decrease this risk. At the California NPRC, HSV-2 establishes latency in the nervous system after vaginal inoculation in rhesus monkeys and spontaneously reactivates, mimicking key features of HSV-2 infection in women (Lo et al., 2018). This model can be used to develop prevention

strategies for HSV-2 infection and reactivation. Supported by ORIP and NIAID.

STIs: Models and multipurpose prevention technologies (MPTs)

MPTs simultaneously address multiple reproductive health needs, including prevention of STIs, HIV infection and unintended pregnancy. At the Washington NPRC, pigtail macaques have been used to establish safety profiles for multiple extended release intravaginal films, which were evaluated for product retention, distribution, and active ingredient pharmacokinetics, in the presence and absence of coitus. The pigtailed macaque model for *Chlamydia trachomatis* (CT) infection actively supports MPT, vaccine and therapeutic product development by determining a product's efficacy in preventing/treating CT infection (Patton et al., 2018). Efforts are also underway to expand this model to include *Neisseria gonorrhoeae* (GC) infection, a model that would be invaluable in developing novel therapies for antibiotic resistant strains of GC that are arising worldwide. Supported by ORIP and NIAID.

IC STEM Efforts

Career Development Activities and Programs Advancing Women in Biomedical Science Careers

Development awards (K01) assist veterinarians to become independent investigators in research related to comparative medicine. Individual fellowships (F30) provide research training opportunities for veterinary dual degree students. T32 and T35 training grants offer opportunities for career development, providing long- and short-term support for training veterinarians and veterinary students for research careers in biomedical areas related to comparative medicine, comparative pathology, or other disciplines to improve and extend healthy lives and prevent illness. The Loan Repayment Program (LRP) recruits and retains health professionals, including veterinarians, into biomedical or biobehavioral research careers through educational debt assistance. Women represent approximately 70% of K01 grantees, 85% of F30 fellows, 80% of trainees in the T32 and T35 mentoring/training program, and all LRP awardees supported by ORIP. Lastly, ORIP supports research supplements to promote diversity in health-related research (PA-16-288). Underrepresented minority (Hispanic/Latino-origin and individuals with disabilities) women represent just over 60% of trainees supported by ORIP through research supplements.

Funding Initiatives, Workshops and Conferences

Program Announcements

PAR: Animal and Biological Material Resource Centers (P40) (PAR-17-006): Animal and Biological Material Resource Centers provide support for special colonies of laboratory animals, as well as other resources such as informatics tools, reagents, cultures (cells, tissues, and organs) and genetic stocks that serve the biomedical research community in a variety of research areas (including women's health research) on a local, regional, national and international basis.

PAR: Shared Instrumentation Grant (SIG) Program (S10) (PAR-17-074/PAR-18-600) and PAR: High-End Instrumentation (HEI) Grant Program (S10) (PAR-17-076/PAR-18-598): These programs encourage applications from groups of NIH-supported investigators (including women's health researchers) to purchase or upgrade a single item of expensive, specialized, commercially available instrument or integrated system.

PAR: Limited Competition: National Primate Research Centers (P51) (PAR-17-144): Proper husbandry and management of NHPs require

specialized physical and intellectual resources, which are most effectively and economically provided in centralized primate centers. The National Primate Research Centers (NPRCs) provide these resources to investigators who utilize NHPs in biomedical research (including women's health research). In particular, the NPRCs undertake studies addressing women's fertility (contraception or infertility disorders), maternal-fetal disorders and infections, sexually transmitted infections, and research on neural sex differences.

PA: Development of Novel and Emerging Technologies for Cryogenic or Long-term Preservation and Revival of Drosophila and Zebrafish Genetic Stocks (R41/R42 and R43/R44 Clinical Trial Not Allowed) (PA-18-609, PA-18-610**):** ORIP encourages applications from small business concerns proposing research and development of technology for cryogenic or other long-term preservation and revival of *Drosophila* and zebrafish genetic stocks, including female germplasm cryopreservation.

Conferences and Workshops (in chronological order)

34th Annual Symposium on Nonhuman Primate Models for AIDS, October 11-14, 2016

35th Annual Symposium on Nonhuman Primate Models for AIDS, August 22-25, 2017

Meeting goals are to disseminate knowledge about ongoing projects that use NHPs to study HIV/SIV pathogenesis, host immune responses to HIV/SIV, and vaccines for HIV/SIV in both sexes. Supported by ORIP and OAR.

Cryopreservation of Aquatic Biomedical Models, January 7, 2017

To address gaps in reliable and cost-effective approaches for long-term preservation of critical aquatic species used to study biological mechanisms that underline human health and disease (including diseases that impact women's health), ORIP sponsored a workshop to assess the status of male and female germplasm cryopreservation in various aquatic models; identify obstacles, opportunities, and priorities that may address the need for improved methods; and evaluate novel and emerging research and technologies that might lead to successful preservation of other germplasm formats.

HIV Vaccine Trials Network Translational HIV Vaccine Early Stage Investigator Conference, May 22-23, 2017

HIV Vaccine Trials Network Translational HIV Vaccine Early Stage Investigator Conference, May 17-18, 2018

This conference enables greater translation of HIV vaccine research in both sexes between preclinical NHP studies and clinical trials and is oriented to meet the needs of early stage investigators conducting translational HIV vaccine research under the mentorship of basic science and translational researchers. Supported by ORIP, OAR, and NIAID.

The 2017 National Veterinary Scholars Symposium, August 3-5, 2017

This symposium is the premier annual scientific colloquium which showcases research accomplishments by veterinary students completing summer research internships as well as D.V.M./Ph.D. students and postdoctoral veterinarians in research training programs. The symposium, hosted and co-organized by the Center for Cancer Research/NCI/NIH and the Association of American Veterinary Medical Colleges, highlighted the ways veterinary scientists advance basic and applied biomedical and environmental research. The major themes of the meeting were neuroscience, global health, conservation medicine, and comparative oncology. The meeting also provided a forum for emerging women biomedical researchers to learn about research resources and opportunities.

Strengthening Research Resources - Integration, Innovation, and Standardization: Twelfth Comparative Medicine Resource Directors Meeting, August 7-8, 2018

Meeting goals were to provide a forum for exchange of new information, advances and ideas; to facilitate development and continuation of synergistic working groups, interactions and collaborations among resources and between resources and various NIH ICOs; and to offer opportunities for sharing experiences, strategies and best practices for optimizing access, use, and administration of valuable resources. Reproducibility and studying both sexes in animal disease models were discussed during a session addressing good resource practices.

Challenges in Assessing NHP Needs and Resources for Biomedical Research, August 23-24, 2018

Meeting objectives were to forecast future NHP use in biomedical research, including women's health research; discuss and determine scientific advances driving future research; define relevant and emerging NHP models needed for future biomedical advances; assess capabilities of existing resources and their ability to adapt to future needs; and address challenges in resource planning, especially NHPs with limited availability (i.e. pregnant animals). ORWH staff reviewed the goal of the NIH's Sex as a Biological Variable (SABV) policies and how ORWH has supported SABV in NHP research during a session on future NIH research priorities.

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Sexual & Gender Minority Research Office

Executive Summary

In fiscal years 2017 and 2018 the Sexual & Gender Minority Research Office (SGMRO) supported a number of projects specific to women, including transgender and cisgender women, bisexual and lesbian women. The topical health areas addressed with these populations included health disparities, cancer, HIV/AIDS, and hormone therapy.

VII. Accomplishments and Activities

During the biennial period, the SGMRO funded, in part, five projects that specifically addressed the health concerns of women. These projects were funded as part of the SGMRO's annual administrative supplement for research on sexual and gender minority populations. The projects were as follows:

Validation of Stigma Metric for Marginalized Men (Stefan Baral, Johns Hopkins University). This project was funded to validate gender-identity stigma metrics, compare key outcomes between transgender women and cisgender men who have sex with men (MSM), and gain insight into a larger and appropriately scaled online survey of transgender women with self-collection of biospecimens. The team will use the results of these aims to apply for an R01 focused on a statistically powered population-based survey of transgender women in the US with self-collection of biospecimens to answer fundamentally important questions on reasons driving inequalities in health outcomes and to provide insights into appropriate interventions to address these disparities.

Effect of Patient-Provider Sexual Communication Adjuvant Endocrine Therapy Adherence, Sexual Dysfunction Management, and Sexual Quality of Life Among Black Women with Breast Cancer (Ilana Gratez, University of Tennessee Health Science Center). This study examines communication patterns with medical oncology care teams, medication adherence, and side effects among lesbian, bisexual, queer (LBQ) women with breast cancer. Results will inform the development of LBQ-targeted text and graphic health messages that will be integrated into a parent intervention. The project would be the first to provide critical evidence to understand patient-provider communication and adjuvant endocrine therapy treatment adherence challenges among the LBQ breast cancer patient population.

Stigma, Cohesion and HIV Outcomes Among Vulnerable Women Across Epidemic Settings (Deanne Kerrigan, American University). This project is a unique opportunity to compare both qualitative and quantitative data from cisgender and trans women sex workers living with HIV in the Dominican Republic. These comparisons will further improve measurement of stigma and cohesion and understanding of these phenomena, which will inform tailored intervention strategies to more effectively promote optimal HIV outcomes and wellbeing across distinct settings.

Peer Recruitment Model in Anal Cancer Prevention (Ronald Mitsuyasu, University of California, Los Angeles). The peer recruitment strategy is based on the premise that members of social networks know and trust other members of their community, and often share similar health risk behaviors. The ANCHOR study has faced a number of hurdles in recruitment across

the United States because of the socio-cultural diversity of the HIV-epidemic across the country. Successful recruitment strategies used in San Francisco and New York may be inappropriate for other sites where homophobia and HIV stigma may deter potential participants from self-identifying as gay/transgender or HIV+. The ANCHOR study has a large, well established network of 21 sites across the United States. This network is unique and is staffed by providers that are culturally sensitive and also are certified to perform difficult interventional strategies. The Research Approach is strong and leverages the strengths of the team/study sites, and information obtained through the first third of the study's accrual. The proposal clearly outlines five criteria for selection of four sites within the network: (1) located in an urban center with a large LGBT population; (2) has not met enrollment targets to date; (3) less than half of the currently enrolled participants were community recruited; (4) staff expresses support and interest in PCR; and (5) can obtain institutional approval to implement the strategy. Their selection of PCRs is informed and appropriate and draws from people who have been motivated to be screened through ANCHOR but were screen ineligible. The education of the PCRs is sound. The proposed study has the potential to provide additional scientific knowledge regarding peer-driven recruitment approaches' effectiveness in overcoming barriers and reaching key populations. However, there is a secondary potential positive outcome of this research proposal, in that it could improve recruitment for the ANCHOR RCT and ensure appropriate representation of MSM and transgender women in a variety of embedded sub-studies of ANCHOR, specifically with development and validation of the Quality of Life tool.

Cardiometabolic Risk in HIV+ Transgender Women (Joseph Margolick, Johns Hopkins University). Feminizing hormone therapy (FHT) for transgender women (TW) modulates inflammatory, metabolic and coagulation pathways and causes fat gain and loss of lean mass, but the degree to which these perturbations translate into altered cardiometabolic disease risk is not well understood. Additionally, up to 44% of TW are HIV-infected (HIV+). Chronic HIV infection is characterized by persistent inflammation and immune activation that leads to metabolic disturbances, including increased cardiovascular disease (CVD) risk, that are leading causes of morbidity and mortality in HIV+ adults. It is currently unknown whether FHT exacerbates or ameliorates HIV-associated cardiometabolic disease risk in TW, and data is lacking that identifies specific inflammatory and metabolic pathways affected by FHT in HIV+ TW and/or how changes in these immunometabolic pathways translate to clinical disease burden. The Multicenter AIDS Cohort Study (MACS) is a long-term, observational cohort of HIV+ and HIV-uninfected men who have sex with men. Men enrolled in the MACS CVD2 sub-study have detailed cardiometabolic and inflammatory/metabolic biomarker profiling, and sociodemographic risk factors similar to many TW. In a cross-sectional study, we will enroll 40 TW 40-70 years of age on FHT, with and without HIV infection. TW will be age-, race-, body mass index- and HIV serostatusmatched (1:2) to HIV+ and HIV-uninfected MACS CVD2 control men, and will undergo similar cardiometabolic profiling to MACS CVD2 (cardiac computed tomography [CT] imaging including coronary angiography for coronary artery calcium scoring, calcified and non-calcified plaque burden, coronary artery stenosis assessment and epicardial fat quantification; non-contrast, single slice abdominal and thigh CT for visceral and subcutaneous fat and lean mass quantification; and blood collection for biomarker profiling). Using these data, we aim to determine in TW on FHT compared to HIV+ and HIV-uninfected MACS men: 1) the effects of HIV and FHT use on circulating metabolic, inflammatory and coagulation biomarker levels; 2) the effects of HIV and FHT use on CVD burden; 3) the effects of HIV and FHT use on central and peripheral fat and lean mass quantity and quality; and 4)

differences in relationships between biomarker levels and CVD burden and fat and lean mass quantity and quality, with the goal of identifying pathways unique to cardiometabolic disease pathogenesis in TW. This novel pilot project will expand understanding of cardiometabolic disease and immuno-metabolic perturbations in TW on FHT and help optimize care and improve quality of life for TW, a vulnerable and understudied population.

VIII. Funding Announcements Relevant to Women's Health And/Or the Influence of Sex on Disease

Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations (Admin Supp Clinical Trial Optional) – SGM populations include, but are not limited to, lesbian, gay, bisexual, and transgender people, and individuals with differences or disorders of sexual development (sometimes referred to as "intersex" or as specific diagnoses). This trans-NIH effort, which involves multiple Institutes, Centers and Offices from across NIH, is intended to encourage investigation in this growing, field of research. To increase our collective understanding of the broad range of research needed to address the unique health issues of SGM populations, the supplement will focus on areas of research interest, including, but not limited to: studies on increased disease risk; mental, behavioral and social health; approaches to personalized medicine; access to care; reproductive and sexual development; neurological and cognitive development; and resilience.

The SGMRO funded administrative supplements to expand existing research to focus on Sexual and Gender Minority (SGM) health. In 2017 and 2018 we funded a total of $1,291,233 and $1,459,016, respectively.

Research on the Health of Transgender and Gender Nonconforming Populations (R01 **&** R21**)** - This funding opportunity announcement (FOA) calls for research on the health of transgender and gender nonconforming people of all ages, including both youth and adults who are questioning their gender identity and those individuals who are making or who have made a transition from being identified as one gender to the other. This group encompasses individuals whose gender identity differs from the sex on their original birth certificate or whose gender expression varies significantly from what is traditionally associated with or typical for that sex.

The Health of Sexual and Gender Minority (SGM) Populations (R01**) (there are also R03, R15, and R21 companion announcements)** - The National Institutes of Health (NIH) is committed to supporting research that will increase scientific understanding of the health status of diverse population groups and thereby improve the effectiveness of health interventions and services for individuals within those groups. Priority is placed on understudied populations with distinctive health risk profiles. This funding opportunity announcement (FOA) focuses on sexual and gender minority (SGM) populations, including lesbian, gay, bisexual, transgender, and intersex populations. Basic, social, behavioral, clinical, and services research relevant to the missions of the sponsoring Institutes and Centers may be proposed.

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Appendix A. Coordinating Committee on Research on Women's Health (CCRWH) Roster

Fiscal Year 2017		
NIH ICO	**Primary Name**	**Alternate Name**
CSR	Denise Wiesch, Ph.D.	Elaine Sierra-Rivera, Ph.D.
FIC	Rachel Sturke, Ph.D., M.P.H., M.I.A.	Lydia Mann Kline
NCATS	Danilo Tagle, Ph.D., M.S.	
NCCIH	Lanay Mudd, Ph.D.	
NCI	Diane Palmieri, Ph.D.	
NEI	Lisa Neuhold, Ph.D.	
NHGRI	Jennifer Troyer, Ph.D.	Sonya Jooma, M.A.
NHLBI	Xenia Tigno, Ph.D., M.S.	Norbert Weber, Ph.D.
NIA	Kate Nagy, M.A.	Mia Lowden, Ph.D.
NIAAA	Ivana Grakalic, Ph.D.	Deidra Roach, M.D.
NIAID	Juliane Caviston, Ph.D.	Jane Lockmuller, M.S.
NIAMS	Lee Alekel, Ph.D.	Jonelle Drugan, Ph.D.
NIBIB	Steve Zullo, Ph.D.	
NICHD	Elizabeth (Liz) Wehr, J.D.	Candace Tingen, Ph.D.
NIDA	Cora Lee Wetherington, Ph.D.	
NIDCD	Susan Sullivan, Ph.D.	Lonnie L. Lisle
NIDCR	Dena Fischer, D.D.S., M.S.D., M.S.	Yolanda Vallejo-Estrada, Ph.D.
NIDDK	Eleanor Hoff, Ph.D.	Mary Hanlon-Tilghman, Ph.D.
NIEHS	Kelly Chandler, Ph.D.	Thaddeus Schug, Ph.D.
NIGMS	Nina Sidorova, Ph.D.	
NIMH	Tamara Lewis-Johnson, M.P.H., M.B.A.	Lauren Hill, Ph.D.
NIMHD	Jennifer Alvidrez, Ph.D.	Nathaniel Stinson Jr., Ph.D., M.D., M.P.H.
NINDS	Jim Koenig, Ph.D.	Dana Greene, Ph.D.
NINR	Sung Sug (Sarah) Yoon, RN, Ph.D.	Rebecca Henry, Ph.D., RN
OBSSR	Kathryn (Katie) Morris, M.P.H.	
OAR	Gina Brown, M.D.	
ODP	Ranell Myles, Ph.D., M.P.H.	Kate Winseck, M.S.W.
ODS	Barbara C. Sorkin, Ph.D.	

Fiscal Year 2018		
NIH ICO	**Primary Name**	**Alternate Name**
CC	Christine Grady, M.S.N., Ph.D.	Ann Berger, M.S.N., M.D.
CSR	Valerie Durrant, Ph.D.	
FIC	Rachel Sturke, Ph.D., M.P.H., M.I.A.	
NCATS	Jane Atkinson, D.D.S.	
NCCIH	Emmeline Edwards, Ph.D.	Lanay Mudd, Ph.D.
NCI	L. Michelle Bennett, Ph.D.	Diane Palmieri, Ph.D.
NEI	Paul Sheehy, Ph.D.	Lisa Neuhold, Ph.D.
NHGRI	Cristina Kapustij, M.S.	Jennifer Troyer, Ph.D.
NHLBI	Xenia T. Tigno, Ph.D., M.S.	Donna Marie Dimichele, M.D.
NIA	Kate Nagy, M.A.	Mia Lowden, Ph.D.
NIAAA	Ivana Grakalic, Ph.D.	Deidra Roach, M.D.
NIAID	Tara Schwetz, Ph.D.	Juliane Caviston, Ph.D.
NIAMS	Su-Yau Mao, Ph.D.	Jonelle Drugan, Ph.D.
NIBIB	David George, Ph.D.	
NICHD	Lisa Halvorson, M.D.	Candace Tingen, Ph.D.
NIDA	Cora Lee Wetherington, Ph.D.	
NIDCD	Susan L. Sullivan, Ph.D.	
NIDCR	Lillian Shum, Ph.D.	Dena Fischer, D.D.S., M.S.D., M.S.
NIDDK	Eleanor Hoff, Ph.D.	Mary Hanlon-Tilghman, Ph.D.
NIEHS	Gwen Collman, Ph.D.	Kelly Chandler, Ph.D.
NIGMS	Judith Greenberg, Ph.D.	
NIMH	Shelli Avenevoli, Ph.D.	
NIMHD	Joyce Hunter, Ph.D.	
NINDS	Nina Schor, M.D., Ph.D.	
NINR	Yvonne Bryan, Ph.D.	Sung Sug (Sarah) Yoon, RN, Ph.D.
NLM	David Landsman, Ph.D.	
OBSSR	Wendy Smith, M.A., Ph.D., B.C.B.	Kathryn (Katie) Morris, M.P.H.
ODP	Elizabeth Neilson, Ph.D., M.P.H., M.S.N.	Kate Winseck, M.S.W.
OCPL	Christen Sandoval, M.S.P.H., C.H.E.S.	
ODS	Barbara C. Sorkin, Ph.D.	LaVerne Brown, Ph.D.
ORIP	Stephanie Murphy, V.M.D., Ph.D., DACLAM	
Ex Officio Members		
NIH ICO	**Primary Name**	**Alternate Name**
DPCPSI	James M. Anderson, M.D., Ph.D.	
OD	Carrie Wolinetz, Ph.D.	

Appendix B. ORWH-Co-funded Research Summaries

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	The Nociceptin ORL1 System: Treatment Target for Relapse	Weiss, Friedbert	Scripps Research Institue	3 R01 AA014351-12S1	SGAS	9429426	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	EtOH Seeking and Relapse: Therapeutic Potential of Transdermal Cannabidiol	Weiss, Friedbert	Scripps Research Institue	3 R01 AA022082-04S1	SGAS	9429509	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Astrocyte-neuron interactions and sulfatases in Fetal Alcohol Spectrum Disorders	Guizetti, Marina	Oregon Health & Science University	3 R01 AA022948-03S1	SGAS	9413791	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Maternal genotype, choline intervention, & epigenetics in Fetal Alcohol Syndrome	Hamre, Kristin M	University of Tennessee Health Science Center	3 R01 AA023508-03S1	SGAS	9673551	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Sex Differences in Autonomic Nervous System Function and Depression Across Adolescence	Baker, Fiona C	SRI International	3 U01 AA021696-07S1	SGAS	9672810	RePORTER Proj. Info.
2018	Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54)	Sex-Appropriate Treatment Development for Alcohol Use Disorders	McKee, Sherry Ann	Yale University	9 P01 AA027473-06	SCORE	9689591	RePORTER Proj. Info.
2017	NIH Support for Conferences and Scientific Meetings (Parent R13)	Organization for the Study of Sex Differences Annual Meeting	Schwarz, Jaclyn Marie	University of Delaware	1 R13 AG056135-01A1	SRP	9398539	RePORTER Proj. Info.
2017	NIH Exploratory/ Developmental Research Grant Program (Parent R21)	Sleep, hot flashes and cognition: A nonhuman primate model for menopausal symptoms	Lacreuse, Agnes	University of Massachusetts Amherst	1 R21 AG053841-01A1	SRP	9323651	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on sex Differences (P50)	Sex-specific Risk for Vascular Dysfunction and Cognitive Decline	Miller, Virginia M	Mayo Clinic Rochester	3 P50 AG044170-05S1	SCORE	9503866	RePORTER Proj. Info.
2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	MsFLASH: Living a Healthy Menopause	Guthrie, Katherine Adams	Fred Hutchinson Cancer Research Center	3 R01 AG048209-03S1	U3	9449164	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	Chondrocyte Metabolic Stress in the Development of Osteoarthritis	Griffin, Timothy M	Oklahoma Medical Research Foundation	3 R01 AG049058-03S1	SGAS	9432273	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Role of FXR and TGR5 in Age Related Renal Disease as a function of sex	Levi, Moshe	University of Colorado Denver	3 R01 AG049493-02S1	SGAS	9429528	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Exercise-induced epigenetic mechanisms underlying neuronal plasticity and cognition	Wood, Marcelo Andres	University of California-Irvine	3 R01 AG051807-02S1	SGAS	9429416	RePORTER Proj. Info.
2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	Study of Women's Health Across the Nation (SWAN) V: UCLA Site	Greendale, Gail A	University of California Los Angeles	3 U01 AG012539-24S1	U3	9415899	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Multicenter Osteoarthritis Study (MOST) Second Renewal - Boston University	Felson, David Tobin	Boston University Medical Campus	3 U01 AG018820-16S1	SGAS	9428243	RePORTER Proj. Info.
2017	Biodemography of Aging (R01)	Biodemography of Aging in Wild Chimpanzees	Thompson, Melissa Emery	University of New Mexico	5 R01 AG049395-03	SRP	9340050	RePORTER Proj. Info.
2018	Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54)	Sex and Age Differences in Immunity to Influenza (SADII)	Klein, Sabra L	Johns Hopkins University	1 U54 AG062333-01	SCORE	9689747	RePORTER Proj. Info.
2018	Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54)	Emory Specialized Center of Research Excellence (SCORE) on Sex Differences	Ofotokun, Ighovwerha	Emory University	1 U54 AG062334-01	SCORE	9689730	RePORTER Proj. Info.
2018	Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54)	Sex-Specific Effects of Endocrine Disruption on Aging and Alzheimer's Disease	Mielke, Michelle M	Mayo Clinic Rochester	2 U54 AG044170-06	SCORE	9689202	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Changes in Multimorbidity and Disability Among Race/ Ethnic Older Adults (Administrative Supplement)	Quinones, Ana Roman	Oregon Health & Science University	3 R01 AG055681-02S2	SGAS	9673496	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Disparities in Patterns of Recurrent Stroke in the Elderly	Lichtman, Judith H	Yale University	3 R01 AG056628-01A1S2	SGAS	9793035	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Biodemography of Aging (R01)	Biodemography of Aging in Wild Chimpanzees	Thompson, Melissa Emery	University of New Mexico	5 R01 AG049395-04	SRP	9539714	RePORTER Proj. Info.
2018	Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54)	Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function	Kohrt, Wendy M	University of Colorado Denver	9 U54 AG062319-06	SCORE	9688828	RePORTER Proj. Info.
2017	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Developmental Pharmacology of Antiretroviral Metabolism in Mucosal Tissues	Bumpus, Namandje N	Johns Hopkins University	1 R01 AI128781-01	SRP	9244420	RePORTER Proj. Info.
2017	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Mucosal mechanisms of altered HIV susceptibility in Adolescents	Klatt, Nichole Rose	University of Washington	1 R01 AI128782-01	SRP	9244690	RePORTER Proj. Info.
2017	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Mucosal injury from sexual practices: Behavior and biology of South African Adolescents	Jaspan, Heather Beryl	Seattle Children's Hospital	1 R01 AI128792-01	SRP	9245165	RePORTER Proj. Info.
2017	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Maturation, Infectibility, and Trauma (MIT) Contributes to HIV Susceptibility in Adolescents	Aldrovandi, Grace M	University of California Los Angeles	1 R01 AI128796-01	SRP	9245320	RePORTER Proj. Info.
2017	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Sexual trauma and HIV susceptibility among women: the role of stress and genital immunity	Stockman, Jamila Kinshasa	University of California, San Diego	1 R01 AI128803-01	SRP	9245577	RePORTER Proj. Info.
2017	High Priority Immunology Grants (R01)	Role of Hofbauer Cells in Fetal Infection/ Inflammation	Guller, Seth M	Yale University	1 R01 AI131613-01	R56	9323669	RePORTER Proj. Info.
2017	NIH Exploratory/ Developmental Research Grant Program (Parent R21)	Impact of prenatal HDM exposure in severely asthmatic mothers on offspring asthma	Lekwowich, Ian Paul	Cincinnati Children's Hospital Medical Center	1 R21 AI119385-01A1	SRP	9243430	RePORTER Proj. Info.
2017	Immunity in Neonates and Infants (U01)	Lipid Regulation of the Development of Responsiveness to Allergen in Neonates and Infants	Cook-Mills, Joan M	Northwestern University at Chicago	1 U01 AI131337-01	SRP	9323656	RePORTER Proj. Info.
2017	Immunity in Neonates and Infants (U01)	Determining how macrophages regulate immunity to Zika virus infection at the maternal-fetal interface	Chakraborty, Rana	Emory University	1 U01 AI131566-01	SRP	9331920	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	Role of IL-1 in Bacterial ligand-induced vasculitis and myocarditis	Arditi, Moshe	Cedars-Sinai Medical Center	5 R01 AI072726-07	SRP	9212778	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Research Project Grant (Parent R01)	Genomic Epidemiology of Methicillin-Resistant Staphylococcus aureus in Jail	Popovich, Kyle Jeanne	Rush University Medical Center	5 R01 AI114688-03	U3	9192939	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	Interleukin-36 cytokines in antiviral immune responses	Jensen, Liselotte E	Temple University of the Commonwealth	5 R01 AI125111-02	SRP	9308835	RePORTER Proj. Info.
2017	Clinical Trials Units for NIAID Networks (UM1)	Case Clinical Trials Unit	Lederman, Michael Marcel	Case Western Reserve University	5 UM1 AI069501-11	SRP	9178619	RePORTER Proj. Info.
2018	High Priority Immunology Grants (R01)	Contribution of rigid matrix to allergic eosinophilic esophagitis pathogenesis	Aceves, Seema S	University of California, San Diego	5 R01 AI092135-08	SGAS	9519791	RePORTER Proj. Info.
2018	Basic Research on HIV Persistence (R01)	Developing Pathogen Recognition Receptor Agonists as Latency Reversing Agents	Bosque, Alberto	George Washington University	5 R01 AI124722-04	SGAS	9501675	RePORTER Proj. Info.
2018	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Developmental Pharmacology of Antiretroviral Metabolism in Mucosal Tissues	Bumpus, Namandje N	Johns Hopkins University	5 R01 AI128781-02	SRP	9411719	RePORTER Proj. Info.
2018	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Mucosal injury from sexual practices: Behavior and biology of South African Adolescents	Jaspan, Heather Beryl	Seattle Children's Hospital	5 R01 AI128792-02	SRP	9416076	RePORTER Proj. Info.
2018	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Maturation, Infectibility, and Trauma(MIT) Contributes to HIV Susceptibility in Adolescents	Aldrovandi, Grace M	University of California Los Angeles	5 R01 AI128796-02	SRP	9440980	RePORTER Proj. Info.
2018	Risk of Adolescence and Injury in HIV Susceptibility (RAIS) (R01)	Sexual trauma and HIV susceptibility among women: the role of stress and genital immunity	Stockman, Jamila Kinshasa	University of California, San Diego	5 R01 AI128803-02	U3	9512748	RePORTER Proj. Info.
2018	NIAID Resource-Related Research Projects (R24)	Primary Infection Resource Consortium (PIRC)	Little, Susan Janet	University of California, San Diego	5 R24 AI106039-06	U3	9547753	RePORTER Proj. Info.
2018	Systems Biology and Antibacterial Resistance (U01)	Systems Immunobiology of Antibiotic-Persistent MRSA Infection	Yeaman, Michael R	The Los Angeles Biomedical Research Institute / Harbor-UCLA Medical Center	5 U01 AI124319-03	SGAS	9440955	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Leadership Group for a Clinical Research Network on HIV/AIDS and HIV-Associated Infections in Pediatric and Maternal Populations (UM1)	International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Laboratory Center	Aldrovandi, Grace M	University of California Los Angeles	5 UM1 AI106716-06	U3	9390443	RePORTER Proj. Info.
2018	Change of Grantee Organization (Type 7 Parent Clinical Trial Optional)	Mucosal mechanisms of altered HIV susceptibility in Adolescents	Klatt, Nichole Rose	University of Miami School of Medicine	7 R01 AI128782-03	SRP	9693014	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Sex Differences in Musculoskeletal Conditions across the Lifespan	Lane, Nancy E	University of California at Davis	3 P50 AR063043-05S1	SCORE	9483803	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Role of IGF-I/integrin signaling in the periosteal response to load	Bikle, Daniel David	Northern California Institute for Research & Education	3 R01 AR055924-08S1	SGAS	9423436	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	Influence of PTSD Symptoms on Chronic Pain Development after Sexual Assault	McLean, Samuel A	University of North Carolina Chapel Hill	5 R01 AR064700-04	U3	9349461	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Incorporation of Dexamethasone Delivery within Engineered Cartilage	Hung, Clark T	Columbia University New York Morningside	3 R01 AR068133-03S2	SGAS	9667055	RePORTER Proj. Info.
2018	Research Project Grant (Parent R01)	Influence of PTSD Symptoms on Chronic Pain Development after Sexual Assault	McLean, Samuel A	University of North Carolina Chapel Hill	5 R01 AR064700-05	SRP	9548459	RePORTER Proj. Info.
2017	NIH-DOD-VA Pain Management Collaboratory - Coordinating Center (U24)	Pain Management Collaboratory Coordinating Center (PMC3)	Kerns, Robert D	Yale University	1 U24 AT009769-01	SRP	9446514	RePORTER Proj. Info.
2017	NIH-DOD-VA Pain Management Collaboratory - Pragmatic Clinical Trials Demonstration Projects (UG3/UH3)	Chiropractic Care for Veterans: A Pragmatic Randomized Trial Addressing Dose Effects for cLBP	Long, Cynthia R	Palmer College of Chiropractic	1 UG3 AT009761-01	SRP	9446039	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	Suppressing inflammation and boosting humoral immunity with n-3 PUFAs	Shaikh, Saame R	East Carolina University	3 R01 AT008375-03S1	SGAS	9488876	RePORTER Proj. Info.
2017	Mechanisms, Models, Measurement, & Management in Pain Research (R21)	Chronic Stress and Visceral Pain: Role of Intestinal Barrier Dysfunction	Wiley, John W	University of Michigan at Ann Arbor	3 R21 AT009253-02S1	SRP	9489492	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Change of Grantee Organization (Type 7 Parent)	Suppressing inflammation and boosting humoral immunity with n-3 PUFAs	Shaikh, Saame R	University of North Carolina Chapel Hill	7 R01 AT008375-04	SRP	9529033	RePORTER Proj. Info.
2017	Change of Grantee Organization (Type 7 Parent Clinical Trial Optional)	Phased Exploratory Clinical Studies of Harpagophytum procumbens Impact upon the Biological Signature of inflammatory Osteoarthritis.	Folk, William Robert	University of Missouri-Columbia	7 R21 AT009086-03	SRP	9771124	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Botanical Dietary Supplements for Women's Health	Paull, Guido F	University of Illinois at Chicago	3 P50 AT000155-19S2	SGAS	9755716	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Mechanisms underlying anabolic effects of cyclic compressive loading in muscle	Dupont-Versteegden, Esther E	University of Kentucky	3 R01 AT009268-02S1	SGAS	9760038	RePORTER Proj. Info.
2018	Research Project Grant (Parent R01)	Suppressing inflammation and boosting humoral immunity with n-3 PUFAs	Shaikh, Saame R	University of North Carolina Chapel Hill	5 R01 AT008375-05	SRP	9459317	RePORTER Proj. Info.
2018	NIH-DOD-VA Pain Management Collaboratory - Coordinating Center (U24)	Pain Management Collaboratory Coordinating Center (PMC3)	Kerns, Robert D	Yale University	5 U24 AT009769-02	SRP	9567930	RePORTER Proj. Info.
2018	NIH-DOD-VA Pain Management Collaboratory - Pragmatic Clinical Trials Demonstration Projects (UG3/UH3)	Cooperative Pain Education and Self-management: Expanding Treatment for Real-world Access (COPES ExTRA)	Heapy, Alicia	Yale University	5 UG3 AT009767-02	SRP	9567928	RePORTER Proj. Info.
2017	Innovative Research in Cancer Nanotechnology (IRCN) (U01)	Integrated Nano-Therapeutics to Overcome Tumor Plasticity and Resistance	Amiji, Mansoor M	Northeastern University	1 R56 CA198492-01A1	R56	9165227	RePORTER Proj. Info.
2017	Innovative Research in Cancer Nanotechnology (IRCN) (U01)	Nanoparticle Transport Through Tissues	Ruoslahti, Erkki	Sanford Burnham Prebys Medical Discovery Institute	1 R56 CA207839-01A1	R56	9262699	RePORTER Proj. Info.
2017	Innovative Research in Cancer Nanotechnology (IRCN) (U01)	Nanosensor-Based Phenotypic Screening for Precision Therapy of Cancer Stem Cells	Rotello, Vincent M	University of Massachusetts Amherst	1 R56 CA207932-01A1	R56	9371612	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Innovative Research in Cancer Nanotechnology (IRCN) (U01)	Biomimetic nanovesicles to overcome multiple physiological barriers for primary and metastatic triple-negative breast cancer therapy	Tasciotti, Ennio	Methodist Hospital Research Institute	1 R56 CA213859-01A1	R56	9372449	RePORTER Proj. Info.
2017	National Cancer Institute Program Project Applications (P01)	PDT Optimization and Mechanisms	Gollnick, Sandra O	Roswell Park Cancer Institute Corporation	3 P01 CA055791-23S1	SRP	9563622	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Neuroimmune Mechanisms of Cancer-Related Symptoms in Oral Squamous Cell Carcinoma	Dantzer, Robert	University of Texas MD Anderson Cancer Center	3 R01 CA193522-03S1	SGAS	9408393	RePORTER Proj. Info.
2017	Person-Centered Outcomes Research Resource (U2C)	The National Person-Centered Assessment Resource (PCAR)	Cella, David	Northwestern University at Chicago	5 U2C CA186878-04	SRP	9339979	RePORTER Proj. Info.
2018	NIH Research Project Grant (Parent R01)	In vivo methodology for the discovery and validation of miRNA biomarkers in cancer	Medarova, Zdravka O	Massachusetts General Hospital	1 R56 CA214464-01A1	R56	9443210	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	Risk-based Breast Cancer Screening and Surveillance in Community Practice	Miglioretti, Diana L	University of California at Davis	3 P01 CA154292-07S1	U3	9793047	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	Treatment decision making in low-risk thyroid cancer	Haymart, Megan RIST	University of Michigan at Ann Arbor	3 R01 CA201198-03S1	U3	9793049	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	An Imaging Technology for Intra-Operative Surgical margin assessment in oral and Head and Neck Cancers (OSCC)	St John, Maie A	University of California Los Angeles	3 R01 CA220663-02S1	SGAS	9672761	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	MIT/Mayo Physical Sciences Center for Drug Distribution and Efficacy in Brain Tumors	White, Forest M	Massachusetts Institute of Technology	3 U54 CA210180-03S1	SGAS	9673363	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	AIDS Malignancy Consortium (AMC)	Mitsuyasu, Ronald T	University of California Los Angeles	3 UM1 CA121947-12S1	U3	9787647	RePORTER Proj. Info.
2018	Innovative Approaches to Studying Cancer Communication in the New Media Environment (R01)	Communication App to Manage Symptoms and Improve Adjuvant Endocrine Therapy Adherence	Graetz, Ilana	University of Tennessee Health Science Center	5 R01 CA218155-02	SRP	9565527	RePORTER Proj. Info.
2017	NIH Research Project Grant (Parent R01)	Women's Response to E-Cigarette Cues	King, Andrea C	University of Chicago	1 R56 DA044210-01	R56	9545202	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Kentucky BIRCWH Program: Training the Next Generation of Womens Health Researchers	Curry, Thomas E	University of Kentucky	2 K12 DA035150-06	BIRCWH	9369244	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	Socio-moral processing in female stimulant abuse and psychopathy	Kiehl, Kent A	The Mind Research Network	2 R56 DA026505-06A1	R56	9545201	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Gender Differences in Mechanisms of Recovery from Opioid Use Disorder and Anxiety	McHugh, Rebecca Kathryn	McLean Hospital	3 K23 DA035297-04S1	SGAS	9428337	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Cognitive-Affective Substrates of Smoking: Targets for Maternal Behavior Change	Massey, Suena Huang	Northwestern University at Chicago	3 K23 DA037913-03S1	SGAS	9416374	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	ORWH: SCOR on Sex and Gender Factors Affecting Women's Health	Brady, Kathleen T	Medical University of South Carolina	3 P50 DA016511-15S1	SCORE	9481896	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Sex Differences and Progesterone Effects on Impulsivity, Smoking & Cocaine Abuse	Carroll, Marilyn E	University of Minnesota	3 P50 DA033942-05S1	SCORE	9483407	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Yale SCOR on Gender-Sensitive Treatment for Tobacco Dependence	McKee, Sherry Ann	Yale University	3 P50 DA033945-05S1	SCORE	9476462	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Neurodevelopmental Effects of Cannabis and its Epigenetic Regulation	Hurd, Yasmin L	Icahn School of Medicine at Mount Sinai	3 R01 DA030359-07S1	SGAS	9431764	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	Alpha 5 nAChR is a Risk Factor within the Dopamine System for Nicotine Addiction	Dani, John A	University of Pennsylvania	3 R01 DA036572-04S2	SGAS	9428198	RePORTER Proj. Info.
2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	Impact of Cocaine and Polydrug Use on Cranial Small Vessel Disease	Riley, Elise D	University of California, San Francisco	3 R01 DA037012-04S1	U3	9448208	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Sex differences in stress-potentiated cocaine seeking and the underlying mechanisms	Mantsch, John R	Marquette University	3 R01 DA038663-04S1	SGAS	9428935	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Indigenous Pathways of Substance Use and Mental Health through Early Adulthood	Walls, Melissa L	University of Minnesota	3 R01 DA039912-02S1	SGAS	9413635	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Ecological Momentary Assessment of Cannabis Use Effects in Young Adults	Ansell, Emily B	Syracuse University	3 R01 DA039924-02S1	SGAS	9430531	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Mechanisms Regulating Cocaine Memory Strength	Torregrossa, Mary M	University of Pittsburgh at Pittsburgh	3 R01 DA042029-02S1	SGAS	9408065	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Sex Dependent Recruitment of PKCdelta Neurons by Stress: Administrative Supplement for Noradrenergic Regulation in the BNST	Winder, Danny G	Vanderbilt University	3 R01 DA042475-02S1	SGAS	9430555	RePORTER Proj. Info.
2017	Adolescent Brain Cognitive Development (ABCD) Study - Research Project Sites (U01)	Adolescent Brain Cognitive Development (ABCD): FIU	Gonzalez, Raul	Florida International University	5 U01 DA041156-03	SRP	9281720	RePORTER Proj. Info.
2018	Health Services and Economic Research on the Prevention and Treatment of Drug, Alcohol, and Tobacco Abuse (R01)	Improving Access to Treatment for Women with Opioid Use Disorder	Patrick, Stephen W	Vanderbilt University Medical Center	1 R01 DA045729-01	SRP	9497115	RePORTER Proj. Info.
2018	Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54)	MUSC Specialized Center of Research Excellence on Sex Differences	McRae-Clark, Aimee L	Medical University of South Carolina	2 U54 DA016511-16	SCORE	9689643	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Epigenetic Control of Brain Reward Systems	Day, Jeremy J	University of Alabama at Birmingham	3 DP1 DA039650-04S1	SGAS	9672206	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	KOR agonist functional Selectivity in peripheral sensory neurons	Clarke, William P	University of Texas Health Science Center	3 R01 DA038645-04S2	SGAS	9673274	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	Development of Co-Morbid PTSD and Chronic Pain Among Inner City Women	Burns, John W	Rush University Medical Center	3 R01 DA039522-04S2	U3	9687205	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	Executive function and aggression in pre-school aged children exposed in utero to marijuana	Klebanoff, Mark A	Research Institute Nationwide Children's Hospital	3 R01 DA042948-02S1	U3	9669153	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	The Determining Effective Testing in Emergency Departments and Care Coordination on Treatment Outcomes (DETECT) for HCV Trial	Haukoos, Jason	Denver Health and Hospital Authority	3 R01 DA042982-01A1S1	SGAS	9673534	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	A Randomized Double-Blind Controlled Trial of Creatine in Female Methamphetamine Users	Renshaw, Perry Franklin	University of Utah	3 R01 DA043248-02S1	SGAS	9671194	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Sensitivity to Unpredictable Threat and Smoking Lapse Behavior	Zvolensky, Michael J	University of Houston	3 R21 DA045285-02S2	SGAS	9671715	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Defining the effects of biological sex on patterns inflammatory gene expression in HIV an HIV/HVC coinfection	Thomas, David L	Johns Hopkins University	3 R37 DA013806-19S1	SGAS	9673504	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Kentucky BIRCWH Program: Training the Next Generation of Women's Health Researchers	Curry, Thomas E	University of Kentucky	5 K12 DA035150-07	BIRCWH	9525321	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Adolescent Brain COGNITIVE DEVELOPMENT (ABCD) Study - Research PROJECT SITES (U01)	Adolescent Brain Cognitive Development (ABCD): FIU	Gonzalez, Raul	Florida International University	5 U01 DA041156-04	SRP	9509422	RePORTER Proj. Info.
2017	NIH Research Project Grant (Parent R01)	Analysis of MyD88-mediated immune activation in Sjogrens syndrome pathogenesis	Kramer, Jill Marie	State University of New York at Buffalo	1 R56 DE025218-01A1	R56	9530733	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	Non-viral gene therapy for cancer pain	Schmidt, Brian L	New York University	3 R01 DE025393-02S1	SGAS	9434015	RePORTER Proj. Info.
2017	Pharmacogenomics of Orofacial Pain Management (R01)	Chronic orofacial pain: genetics, cognitive-emotional factors, and endogenous modulatory systems	Colloca, Luana	University of Maryland Baltimore	5 R01 DE025946-02	SRP	9265070	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Novel Role for the P2Y2 Receptor in the Autoimmune Disease Sjogrens Syndrome	Weisman, Gary Andrew	University of Missouri-Columbia	3 R01 DE007389-28S2	SGAS	9663548	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Oral immune activation and alveolar bone loss in HIV-infected postmenopausal women	Yin, Michael T	Columbia University Health Sciences	3 R01 DE026924-02S1	SGAS	9673382	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Center for Neurovisceral Sciences & Women's Health	Mayer, Emeran A	University of California Los Angeles	3 P50 DK064539-15S1	SCORE	9508977	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Molecular and Epidemiologic Basis of UTI in Women	Hultgren, Scott J	Washington University	3 P50 DK064540-15S1	SCORE	9516050	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	The regulation and activation of STATs in adipocytes	Stephens, Jacqueline M	LSU Pennington Biomedical Research Center	3 R01 DK052968-17S1	SRP	9485669	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	Cellular Selenium Status and PGJ2 Metabolism (PA-17-078 supplement 2017)	Prabhu, Kumble Sandeep	Pennsylvania State University-University Park	3 R01 DK077152-07S1	SGAS	9431725	RePORTER Proj. Info.
2017	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Scientific and Data Coordinating Center (PLUS-SDCC) (U01)	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Scientific and Data Coordinating Center (PLUS-SDCC) (U01)	Rudser, Kyle	University of Minnesota	3 U01 DK106786-03S1	SRP	9545378	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Clinical Centers (PLUS-CCS) (U01)	PLUS Loyola Clinical Center	Mueller, Elizabeth Rose	Loyola University Chicago	3 U01 DK106898-03S1	SRP	9508482	RePORTER Proj. Info.
2017	George M. O'Brien Urology Cooperative Research Centers Program (U54)	The Genetic Origins and Complications of Urinary Tract Abnormalities	Mendelsohn, Cathy Lee	Columbia University Health Sciences	3 U54 DK104309-04S1	SRP	9491221	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	Follow-up Glucose Testing and Timely Transition to Primary Care After Gestational Diabetes	Bernstein, Judith APT	Boston University Medical Campus	5 R01 DK107528-02	SRP	9244016	RePORTER Proj. Info.
2017	Exploration of the Roles of Brown and Beige Adipose Tissue in Humans (R01)	The Impact of Estrogen Status on the Biological Function of Brown Adipose Tissue in Women Measured Using Quantitative PET/CT	Melanson, Edward L	University of Colorado Denver	5 R01 DK112260-02	SRP	9353399	RePORTER Proj. Info.
2017	Limited Competition for the Continuation of the Diabetes Prevention Program Outcomes Study (DPPOS) Biostatistics Research Center (Collaborative U01)	22/22 Diabetes Prevention Program Outcomes Study (DPPOS) Phase 3 - Biostatistics Center	Temprosa, Marinella	George Washington University	5 U01 DK048489-24	SRP	9210088	RePORTER Proj. Info.
2017	Limited Competition of the MAPP Research Network (U01)	University of Michigan MAPP Research Network Discovery Site	Clauw, Daniel J	University of Michigan at Ann Arbor	5 U01 DK082345-09	SRP	9315152	RePORTER Proj. Info.
2017	Limited Competition of the MAPP Research Network (U01)	MAPP Research Network Second Phase	Mayer, Emeran A	University of California Los Angeles	5 U01 DK082370-09	SRP	9315800	RePORTER Proj. Info.
2017	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Clinical Centers (PLUS-CCS) (U01)	LUTS Prevention in Adolescent Girls and Women Across the Lifespan	Sutcliffe, Siobhan	Washington University	5 U01 DK106853-03	SRP	9316601	RePORTER Proj. Info.
2017	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Clinical Centers (PLUS-CCS) (U01)	University of Pennsylvania+ PLUS Clinical Center (PENN+PLUS CC)	Newman, Diane K	University of Pennsylvania	5 U01 DK106892-03	SRP	9316592	RePORTER Proj. Info.
2018	NIH Research Project Grant (Parent R01)	Discerning the influence of maternal obesity, weight gain, and diet on the infant microbiota and programming of NAFLD	Friedman, Jacob E	University of Colorado Denver	1 R56 DK114711-01A1	R56	9761694	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	NIH Research Project Grant (Parent R01)	A Practice-based Intervention to Improve Care for Women with Urinary Incontinence	Anger, Jennifer Tash	Cedars-Sinai Medical Center	1 R56 DK117261-01	R56	9729900	RePORTER Proj. Info.
2018	Specialized Centers of Research Excellence (SCORE) on Sex Differences (U54)	Sex Differences in the Metabolic Syndrome	Reue, Karen	University of California Los Angeles	1 U54 DK120342-01	SCORE	9689782	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Calcium transport in kidney proximal tubule and calcium phosphate stone formation	Bandyopadhyay, Bidhan Chandra	Institute for Clinical Research, Inc.	3 R01 DK102043-04S1	SGAS	9784425	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Adipose Tissue Distribution Determines Microglial Regulation of Hippocampal Plasticity	Stranahan, Alexis M	Augusta University	3 R01 DK110586-02S1	SGAS	9657105	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	A Cluster-Randomized Trial of Pharmacist-Coordinated Implementation of the DPP	Duru, Obidiugwu Kenrik	University of California Los Angeles	3 R18 DK105464-04S1	U3	9758126	RePORTER Proj. Info.
2018	Limited Competition for the Continuation of the Hepatitis B Research Network Clinical Centers (U01)	Harvard Hepatitis B Consortium	Lau, Daryl T	Beth Israel Deaconess Medical Center	3 U01 DK082919-11S1	SRP	9746966	RePORTER Proj. Info.
2018	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Scientific and Data Coordinating Center (PLUS-SDCC) (U01)	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Scientific and Data Coordinating Center (PLUS-SDCC) (U01)	Rudser, Kyle	University of Minnesota	3 U01 DK106786-04S1	SRP	9775592	RePORTER Proj. Info.
2018	Limited Competition for the Continuation of the Diabetes Prevention Program Outcomes Study (DPPOS) Biostatistics Research Center (Collaborative U01)	22/22 Diabetes Prevention Program Outcomes Study (DPPOS) Phase 3 - Biostatistics Center	Temprosa, Marinella	George Washington University	5 U01 DK048489-25	SRP	9430411	RePORTER Proj. Info.
2018	Limited Competition of the MAPP Research Network (U01)	University of Michigan MAPP Research Network Discovery Site	Clauw, Daniel J	University of Michigan at Ann Arbor	5 U01 DK082345-10	SRP	9525960	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Limited Competition of the MAPP Research Network (U01)	MAPP Research Network Second Phase	Mayer, Emeran A	University of California Los Angeles	5 U01 DK082370-10	SRP	9533551	RePORTER Proj. Info.
2018	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Clinical Centers (PLUS-CCS) (U01)	LUTS Prevention in Adolescent Girls and Women Across the Lifespan	Sutcliffe, Siobhan	Washington University	5 U01 DK106853-04	SRP	9534603	RePORTER Proj. Info.
2018	Prevention of Lower Urinary Tract Symptoms in Women: Bladder Health Clinical Centers (PLUS-CCS) (U01)	University of Pennsylvania+ PLUS Clinical Center (PENN+PLUS CC)	Newman, Diane K	University of Pennsylvania	5 U01 DK106892-04	SRP	9534604	RePORTER Proj. Info.
2017	NIH Exploratory/ Developmental Research Grant Program (Parent R21)	A novel strategy to see and treat breast cancer: translation to intra-operative breast margin assessment	Ramanujam, Nirmala	Duke University	1 R21 EB025008-01	SRP	9387262	RePORTER Proj. Info.
2017	Centers of Eexcellence for Big Data Computing in the Biomedical Sciences (U54)	ENIGMA Center for Worldwide Medicine, Imaging & Genomics	Thompson, Paul M	University of Southern California	3 U54 EB020403-04S1	SRP	9517179	RePORTER Proj. Info.
2017	BRAIN Initiative: Theories, Models and Methods for Analysis of Complex Data from the Brain (R01).	Novel Bayesian linear dynamical systems-based methods for discovering human Brain circuit dynamics in health and disease	Menon, Vinod	Stanford University	5 R01 EB022907-02	SRP	9360103	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Differences in Immunological Response and Nutritional Status by Sex in Patients with Acute Dengue Virus Infection	Mehta, Saurabh	Cornell University	3 R01 EB021331-03S1	SGAS	9673527	RePORTER Proj. Info.
2017	Microphysiological Systems (MPS) for Disease Modeling and Efficacy Testing (UG3/ UH3)	PCOS and androgen-related disease modeling and drug testing in Multi-organ Integrated Microfluidic Reproductive Platform	Woodruff, Teresa K	Northwestern University at Chicago	1 UG3 ES029073-01	SRP	9398870	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	Prenatal endocrine-disrupting chemicals and social/cognitive risk in mothers and infants: Potential biologic pathways	Beebe, Beatrice A	New York State Psychiatric Institute	3 R01 ES027424-01A1S1	U3	9687384	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Early life ENM-exposure and the impact on neurobehavioral and cardiovascular Outcomes and biochemical mechanisms	Mortensen, Ninell Pollas	Research Triangle Institute	3 U01 ES027254-03S1	SGAS	9783922	RePORTER Proj. Info.
2018	MENTORED Clinical SCIENTIST Research CAREER DEVELOPMENT AWARD (Parent K08)	Sex disparity and estradiol in Fuchs endothelial corneal dystrophy	Patel, Sangita	State University of New York at Buffalo	1 K08 EY029007-01	SRP	9505347	RePORTER Proj. Info.
2018	NIH Research Project Grant (Parent R01)	The Impact of the Herpes Zoster Vaccine on Herpes Zoster Ophthalmicus	Acharya, Nisha	University of California, San Francisco	1 R01 EY028739-01	SRP	9424460	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	In vivo imaging of inhibitory circuit remodeling in mouse visual cortex	Nedivi, Elly	Massachusetts Institute of Technology	3 R01 EY025437-04S1	SGAS	9672749	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	A Novel Neuroprotective Approach for Glaucoma	Prokai, Katalin T	University of North Texas Health Science Center	3 R01 EY027005-03S1	SGAS	9793253	RePORTER Proj. Info.
2018	NIH Support for Conferences and Scientific Meetings (Parent R13)	Minority Pipeline Program in Ophthalmology: Rabb Venable Excellence in Research in conjunction with the Ophthalmology Section of the National Medical Association	Olivier, Mildred Marie Gerard	National Medical Association	5 R13 EY016936-10	SRP	9474132	RePORTER Proj. Info.
2017	Native American Research Centers for Health (NARCH) (S06)	Cherokee Nation Native American Research Center for Health	Khan, Sohail	Cherokee Nation	1 S06 GM123546-01	SRP	9321747	RePORTER Proj. Info.
2017	Native American Research Centers for Health (NARCH) (S06)	WMAT-JHU NARCH IX Application	Craig, Mariddie J	White Mountain Apache Tribe	1 S06 GM123547-01	SRP	9322031	RePORTER Proj. Info.
2017	Limited Competition: Centers of Biomedical Research Excellence (COBRE) Phase III — Transitional Centers [P30]	Center for Translational Neuroscience	Garcia-Rill, Edgar E	University of Arkansas for Medical Sciences	3 P30 GM110702-04S1	U3	9527896	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	PARylation in genotoxic stress-induced NF-kB activation Supplement for Research on Sex/ Gender Influences	Wan, Fengyi	Johns Hopkins University	3 R01 GM111682-03S1	SGAS	9431267	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Biogenesis of melanosomes and other lysosome-related organelles	Dell'Angelica, Esteban C	University of California Los Angeles	3 R01 GM112942-03S1	SGAS	9432373	RePORTER Proj. Info.
2018	Native American Research Centers for Health (NARCH) (S06)	ANTHC NARCH X	Ferucci, Elizabeth D	Alaska Native Tribal Health Consortium	1 S06 GM127911-01	SRP	9513860	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Myosin Gene Diversity and Function	Leinwand, Leslie Anne	University of Colorado	3 R01 GM029090-36S1	SGAS	9671161	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Admin Supplement: Healthy Volunteers as Model Organisms: Comparative Research Ethics and Policy for Phase I Trials	Fisher, Jill A	University of North Carolina Chapel Hill	3 R01 GM099952-07S1	SGAS	9671657	RePORTER Proj. Info.
2018	Research Project Grant (Parent R01)	Biogenesis of melanosomes and other lysosome-related organelles	Dell'Angelica, Esteban C	University of California Los Angeles	5 R01 GM112942-04	SRP	9380965	RePORTER Proj. Info.
2018	Native American Research Centers for Health (NARCH) (S06)	Cherokee Nation Native American Research Center for Health	Khan, Sohail	Cherokee Nation	5 S06 GM123546-02	SRP	9566248	RePORTER Proj. Info.
2018	Native American Research Centers for Health (NARCH) (S06)	WMAT-JHU NARCH IX Application	Craig, Mariddie J	White Mountain Apache Tribe	5 S06 GM123547-02	SRP	9568784	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Tufts BIRCWH Program	Freund, Karen	Tufts University Boston	1 K12 HD092535-01	BIRCWH	9368907	RePORTER Proj. Info.
2017	NIH Small Research Grant Program (Parent R03)	Cognitive deficits in Down syndrome: contributions from Hsa21 orthologs on mouse chromosome 10	Gardiner, Kathleen	University of Colorado Denver	1 R03 HD091639-01	SRP	9298396	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Research Project Grant (Parent R01)	Ovarian ultrasonography for the Clinical evaluation of polycystic ovary syndrome.	Lujan, Marla E	Cornell University	1 R56 HD089962-01	R56	9549164	RePORTER Proj. Info.
2017	NIH Research Project Grant (Parent R01)	The Genetics of Primary Ovarian Insufficiency	Welt, Corrine K	University of Utah	1 R56 HD090159-01A1	R56	9389173	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research Careers in Women's Health in Pittsburgh	Sadovsky, Yoel	Magee-Womens Research Institute and Foundation	2 K12 HD043441-16	BIRCWH	9369225	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research Careers in Women's Health	Andrews, Nancy Catherine	Duke University	2 K12 HD043446-16	BIRCWH	9369130	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research in Women's Health	Krousel-Wood, Marie A	Tulane University of Louisiana	2 K12 HD043451-16	BIRCWH	9366919	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research Careers in Women's Health	Hartmann, Katherine E	Vanderbilt University Medical Center	2 K12 HD043483-17	BIRCWH	9365944	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Oregon BIRCWH: Scholars in Women's Health Research Across the Lifespan	Guise, Jeanne-Marie	Oregon Health & Science University	2 K12 HD043488-16	BIRCWH	9367498	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Women's Health at MUSC	McGinty, Jacqueline F	Medical University of South Carolina	2 K12 HD055885-11	BIRCWH	9373582	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	University of MN Building Interdisciplinary Research Careers in Women's Health	Vinogradov, Sophia	University of Minnesota	2 K12 HD055887-11	BIRCWH	9368939	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	The Colorado Building Interdisciplinary Research Careers in Women's Health Program	Regensteiner, Judith G	University of Colorado Denver	2 K12 HD057022-11	BIRCWH	9365638	RePORTER Proj. Info.
2017	NIH Research Project Grant (Parent R01)	Cytoplasmic Maturation in Mouse Oocytes	Mehlmann, Lisa M	University of Connecticut School of Medicine/DNT	2 R56 HD056366-06A1	R56	9381070	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	UNC BIRCWH	Boggess, Kim A	University of North Carolina Chapel Hill	3 K12 HD001441-18S1	BIRCWH	9504281	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	Building Interdisciplinary Research Careers in Women's Health at UC Davis - Administrative Supplement	Gold, Ellen B	University of California at Davis	3 K12 HD051958-13S1	BIRCWH	9514685	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	Hormones and Genes in Women's Health: Bench to Bedside	Goldstein, Jill M	Brigham and Women's Hospital	3 K12 HD051959-13S1	BIRCWH	9513871	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	UTMB Women's Health Research Scholars Program	Berenson, Abbey B	University of Texas Medical Branch Galveston	3 K12 HD052023-13S1	BIRCWH	9511050	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	UCSF-Kaiser Building Interdisciplinary Research Careers in Women's Health Program	Brindis. Claire D	University of California, San Francisco	3 K12 HD052163-18S1	BIRCWH	9514684	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	Mayo Clinic Building Interdisciplinary Research Careers in Women's Health	Miller, Virginia M	Mayo Clinic Rochester	3 K12 HD065987-08S1	BIRCWH	9513708	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	The Johns Hopkins Clinical Research Scholars in Women's Health (BIRCWH)	Ford, Daniel Ernest	Johns Hopkins University	3 K12 HD085845-03S1	BIRCWH	9509866	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	Training in Sex and Gender Differences Research to Improve Women's Health	Epperson, C Neill	University of Pennsylvania	3 K12 HD085848-03S1	BIRCWH	9512012	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	Emory BIRCWH Program - Administrative Supplement	Ofotokun, Ighovwerha	Emory University	3 K12 HD085850-03S1	BIRCWH	9515372	RePORTER Proj. Info.
2017	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Admin Supp)	Utah Building Interdisciplinary Research Careers in Women's Health Career Development Program	Varner, Michael W	University of Utah	3 K12 HD085852-03S1	BIRCWH	9514563	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Genes, Androgens and Intrauterine Environment in PCOS	Dunaif, Andrea E	Northwestern University at Chicago	3 P50 HD044405-15S1	SCORE	9527916	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Birth, Muscle Injury and Pelvic Floor Dysfunction	Delancey, John O L	University of Michigan at Ann Arbor	3 P50 HD044406-15S1	SCORE	9547564	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function	Kohrt, Wendy M	University of Colorado Denver	3 P50 HD073063-05S1	SCORE	9502000	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	Kisspeptin and Neurokinin B: Physiology in Monkey to Pathophysiology in Human	Seminara, Stephanie Beth	Massachusetts General Hospital	3 R01 HD043341-15S1	SGAS	9431349	RePORTER Proj. Info.
2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	Reducing disparities in health and safety for young sexual minority women in abusive relationships	Glass, Nancy E	Johns Hopkins University	3 R01 HD076881-04S1	U3	9447618	RePORTER Proj. Info.
2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	Identity Development, Risk, and Resilience among Gender Diverse populations	Bockting, Walter O	New York State Psychiatric Institute	3 R01 HD079603-04S1	U3	9448589	RePORTER Proj. Info.
2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	Women's Health and Disability: Building a Clinically Relevant Outcome Measure	Kalpakjian, Claire Zabelle	University of Michigan at Ann Arbor	3 R01 HD082122-03S1	U3	9446531	RePORTER Proj. Info.
2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	Enhancing Recruitment and Retention of Underrepresented Pregnant Hispanic Women in a Phase III Randomized Clinical Trial	Carlson, Susan E	University of Kansas Medical Center	3 R01 HD083292-02S1	U3	9446350	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Maternal nutrition and oocyte programming	Moley, Kelle H	Washington University	3 R01 HD083895-03S1	SGAS	9430774	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	Prophylactic Negative Pressure Wound Therapy in Obese Women at Cesarean Multicenter Randomized Trial	Tuuli, Methodius Gamuo	Washington University	3 R01 HD086007-02S1	U3	9443985	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	Gender Bias in Mammalian DNA Replication During Development	Schimenti, John C	Cornell University	3 R01 HD086609-01A1S1	SGAS	9430547	RePORTER Proj. Info.
2017	2014 NIH Pioneer Award Program (DP1)	Single cell mapping of developmental trajectories underlying health and disease	Pe'er, Dana	Sloan Kettering Institute Cancer Research	5 DP1 HD084071-05	SRP	9312128	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	UNC BIRCWH	Boggess, Kim A	University of North Carolina Chapel Hill	5 K12 HD001441-18	BIRCWH	9325030	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research Careers in Women's Health at UC Davis	Gold, Ellen B	University of California at Davis	5 K12 HD051958-13	BIRCWH	9333128	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Hormones and Genes in Women's Health: Bench to Bedside	Goldstein, Jill M	Brigham and Women's Hospital	5 K12 HD051959-13	BIRCWH	9333132	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	UTMB Women's Health Research Scholars Program	Berenson, Abbey B	University of Texas Medical Branch Galveston	5 K12 HD052023-13	BIRCWH	9329432	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	UCSF-Kaiser Building Interdisciplinary Research Careers in Women's Health Program	Brindis. Claire D	University of California, San Francisco	5 K12 HD052163-18	BIRCWH	9330869	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Mayo Clinic Building Interdisciplinary Research Careers in Women's Health	Miller, Virginia M	Mayo Clinic Rochester	5 K12 HD065987-08	BIRCWH	9329447	RePORTER Proj. Info.
2017	Women's Reproductive Health Research (WRHR) Career Development Program (K12)	OHSU Women's Reproductive Health Research K12 Program	Caughey, Aaron B	Oregon Health & Science University	5 K12 HD085809-03	SRP	9297347	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	The Johns Hopkins Clinical Research Scholars in Women's Health (BIRCWH)	Ford, Daniel Ernest	Johns Hopkins University	5 K12 HD085845-03	BIRCWH	9349357	RePORTER Proj. Info.

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2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Training in Sex and Gender Differences Research to Improve Women's Health	Epperson, C Neill	University of Pennsylvania	5 K12 HD085848-03	BIRCWH	9325550	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Emory University BIRCWH Program	Ofotokun, Ighovwerha	Emory University	5 K12 HD085850-03	BIRCWH	9344672	RePORTER Proj. Info.
2017	Building Interdisciplinary Research Careers in Women's Health (K12)	Utah Building Interdisciplinary Research Careers in Women's Health Career Development Program	Varner, Michael W	University of Utah	5 K12 HD085852-03	BIRCWH	9330198	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	Pediatric CFS in a Community-Based Sample	Jason, Leonard A	DePaul University	5 R01 HD072208-05	SRP	9315183	RePORTER Proj. Info.
2017	Pelvic Floor Disorders Network Data Coordinating Center (U24)	Pelvic Floor Disorders Network Data Coordinating Center: (2016-2021)	Gantz, Marie G	Research Triangle Institute	5 U24 HD069031-07	SRP	9352695	RePORTER Proj. Info.
2018	Integrative Research in Gynecologic Health (R01)	Small molecule GPR10 antagonists for the treatment of uterine fibroids	Chennathukuzhi, Vargheese Mani	University of Kansas Medical Center	1 R01 HD094373-01	SRP	9463147	RePORTER Proj. Info.
2018	NIH Support for Conferences and Scientific Meetings (Parent R13)	2018 Turner Resource Network Symposium Turner Science in the 21st Century	Silberbach, Gary Michael	Oregon Health & Science University	1 R13 HD096857-01	SRP	9612895	RePORTER Proj. Info.
2018	NIH Research Project Grant (Parent R01)	Role of the DNA Helicase LSH in female meiosis	De La Fuente, Rabindranath	University of Georgia	1 R56 HD093383-01A1	R56	9766132	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	Demographic and Health Disparities in Recovery from Hurricane Katrina: KATRINA@10	Vanlandingham, Mark J	Tulane University of Louisiana	3 P01 HD082032-04S2	U3	9686116	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Administrative Supplement Diabetic Pregnancies and Gastrulation	Salbaum, J Michael	LSU Pennington Biomedical Research Center	3 R01 HD085017-04S1	SGAS	9673457	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	A mechanistic Study of the association between poverty and executive functions in early childhood: Contributions of early Brain development and the early caregiving environment	Propper, Cathi Barbra	University of North Carolina Chapel Hill	3 R01 HD091148-01A1S1	U3	9774608	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Novel Roles of Placental Allopregnanolone in Brain Development and Injury	Penn, Anna A	Children's Research Institute	3 R01 HD092593-02S1	SGAS	9670000	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Regenerative nanotherapeutics for tissue repair in proteolytic disorders	Ramamurthi, Anand	Cleveland Clinic Lerner College of Medicine-CWRU	3 R21 HD095521-02S1	SGAS	9672038	RePORTER Proj. Info.
2018	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp - Clinical Trial Optional)	Pelvic Floor Disorders Network Data Coordinating Center: (2016-2021)	Gantz, Marie G	Research Triangle Institute	3 U24 HD069031-08S1	SRP	9771797	RePORTER Proj. Info.
2018	2014 NIH PIONEER AWARD Program (DP1)	Single cell mapping of developmental trajectories underlying health and disease	Pe'er, Dana	Sloan Kettering Institute Cancer Research	5 DP1 HD084071-06	SRP	9562115	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	UNC BIRCWH	Boggess, Kim A	University of North Carolina Chapel Hill	5 K12 HD001441-19	BIRCWH	9536057	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research Careers in Women's Health in Pittsburgh	Sadovsky, Yoel	Magee-Womens Research Institute and Foundation	5 K12 HD043441-17	BIRCWH	9551652	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research Careers in Women's Health	Andrews, Nancy Catherine	Duke University	5 K12 HD043446-17	BIRCWH	9564145	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research in Women's Health	Krousel-Wood, Marie A	Tulane University of Louisiana	5 K12 HD043451-17	BIRCWH	9554962	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research Careers in Women's Health	Hartmann, Katherine E	Vanderbilt University Medical Center	5 K12 HD043483-18	BIRCWH	9552905	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Oregon BIRCWH: Scholars in Women's Health Research Across the Lifespan	Guise, Jeanne-Marie	Oregon Health & Science University	5 K12 HD043488-17	BIRCWH	9552882	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Research Careers in Women's Health at UC Davis	Gold, Ellen B	University of California at Davis	5 K12 HD051958-14	BIRCWH	9537270	RePORTER Proj. Info.

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2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Hormones and Genes in Women's Health: Bench to Bedside	Goldstein, Jill M	Brigham and Women's Hospital	5 K12 HD051959-14	BIRCWH	9536056	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	UTMB Women's Health Research Scholars Program	Berenson, Abbey B	The University of Texas Medical Branch at Galveston	5 K12 HD052023-14	BIRCWH	9533879	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	UCSF-Kaiser Building Interdisciplinary Research Careers in Women's Health Program	Brindis, Claire D	University of California, San Francisco	5 K12 HD052163-19	BIRCWH	9537278	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Building Interdisciplinary Women's Health at MUSC	McGinty, Jacqueline F	Medical University of South Carolina	5 K12 HD055885-12	BIRCWH	9563308	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	University of MN Building Interdisciplinary Research Careers in Women's Health	Vinogradov, Sophia	University of Minnesota	5 K12 HD055887-12	BIRCWH	9552233	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	The Colorado Building Interdisciplinary Research Careers in Women's Health Program	Regensteiner, Judith G	University of Colorado Denver	5 K12 HD057022-12	BIRCWH	9555014	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Mayo Clinic Building Interdisciplinary Research Careers in Women's Health	Miller, Virginia M	Mayo Clinic Rochester	5 K12 HD065987-09	BIRCWH	9536058	RePORTER Proj. Info.
2018	Women's Reproductive Health Research (WRHR) Career Development Program (K12)	OHSU Women's Reproductive Health Research K12 Program	Caughey, Aaron B	Oregon Health & Science University	5 K12 HD085809-04	SRP	9521395	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	The Johns Hopkins Clinical Research Scholars in Women's Health (BIRCWH)	Ford, Daniel Ernest	Johns Hopkins University	5 K12 HD085845-04	BIRCWH	9543510	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Training in Sex and Gender Differences Research to Improve Women's Health	Epperson, C Neill	University of Pennsylvania	5 K12 HD085848-04	BIRCWH	9534151	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Emory University BIRCWH Program	Ofotokun, Ighovwerha	Emory University	5 K12 HD085850-04	BIRCWH	9555822	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Utah Building Interdisciplinary Research Careers in Women's Health Career Development Program	Varner, Michael W	University of Utah	5 K12 HD085852-04	BIRCWH	9538790	RePORTER Proj. Info.
2018	Building Interdisciplinary Research Careers in Women's Health (K12)	Tufts BIRCWH Program	Freund, Karen	Tufts University Boston	5 K12 HD092535-02	BIRCWH	9563314	RePORTER Proj. Info.
2017	Human Heredity and Health in Africa (H3AFRICA): Research Projects (U01)	African Female Breast Cancer Epidermiology (AFBRECANE) Study	Adebamowo, Clement Adebayo	Institute of Human Virology	1 U01 HG009784-01	SRP	9386289	RePORTER Proj. Info.
2017	Human Heredity and Health in Africa (H3 AFRICA): Collaborative Centers (U54)	AWI-Gen Phase 2: Genomic and environmental risk factors for cardiometabolic disease in Africans	Ramsay, Michele	Wits Health Consortium (PTY), LTD	2 U54 HG006938-06	SRP	9386866	RePORTER Proj. Info.
2017	Limited Competition: Knockout Mouse Production and Phenotyping Project (UM1)	Consortium for large-scale production and phenotyping of knockout mice (UM1)	Beaudet, Arthur L	Baylor College of Medicine	5 UM1 HG006348-07	SRP	9360142	RePORTER Proj. Info.
2018	Human Heredity and Health in Africa (H3AFRICA): Research Projects (U01)	African Female Breast Cancer Epidermiology (AFBRECANE) Study	Adebamowo, Clement Adebayo	Institute of Human Virology	5 U01 HG009784-02	SRP	9555927	RePORTER Proj. Info.
2018	Human Heredity and Health in Africa (H3 AFRICA): Collaborative Centers (U54)	AWI-Gen Phase 2: Genomic and environmental risk factors for cardiometabolic disease in Africans	Ramsay, Michele	Wits Health Consortium (PTY), LTD	5 U54 HG006938-07	SRP	9565621	RePORTER Proj. Info.
2018	Limited Competition: Knockout Mouse Production and Phenotyping Project (UM1)	Consortium for large-scale production and phenotyping of knockout mice (UM1)	Beaudet, Arthur L	Baylor College of Medicine	5 UM1 HG006348-08	SRP	9551060	RePORTER Proj. Info.
2017	Pulmonary and Cardiovascular Consequences of Inhaled Nicotine (R01)	Effects of Inhaled Nicotine on Vascular miR-24 Activity and AAA Formation	Tsao, Philip S	Palo Alto Veterans Institute for Research	1 R56 HL135654-01	R56	9513662	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	Mechanisms of IL-17A-mediated enhancement of asthma severity	Lewkowich, Ian Paul	Cincinnati Children's Hospital Medical Center	3 R01 HL122300-04S1	SGAS	9537174	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Latexin function in the maintenance and regeneration of the hematopoietic system	Liang, Ying	University of Kentucky	3 R01 HL124015-02S1	SGAS	9537135	RePORTER Proj. Info.

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2017	Research on the Health of Women of Underrepresented, Understudied and Underreported (U3) Populations An ORWH FY17 Administrative Supplement (Admin Supp)	Expectations of Discrimination and CVD Risk in African-American Women	Lewis, Tené T	Emory University	3 R01 HL130471-02S1	U3	9507308	RePORTER Proj. Info.
2017	Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (Admin Supp)	NIH - NHLBI - Re-Entry Supplement to Existing R01 Variant surface antigens in cerebral malaria pathogenesis	Plowe, Christopher V	University of Maryland Baltimore	3 R01 HL130750-03S1	SRP	9443388	RePORTER Proj. Info.
2017	Limited Competition: Pregnancy as a Window to Future Cardiovascular Health: Adverse Pregnancy Outcomes as Predictors of Increased Risk Factors for Cardiovascular Disease (U10)	Pregnancy as a Window to Future Cardiovascular Health: Adverse Pregnancy Outcomes	Parker, Corette Breeden	Research Triangle Institute	3 U10 HL119991-04S1	SRP	9548384	RePORTER Proj. Info.
2018	NIH Research Project Grant (Parent R01)	Hypertension in Adult IUGR Offspring: Beneficial Effects of Perinatal Intervention	Alexander, Barbara T	University of Mississippi Medical Center	1 R56 HL143459-01	R56	9761083	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Mechanisms of sex specific differences in neonatal hyperoxic lung injury	Lingappan, Krithika	Baylor College of Medicine	3 K08 HL127103-04S1	SGAS	9752710	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Molecular characterization of cardiomyopathy mutations in human cardiac myosin	Leinwand, Leslie Anne	University of Colorado	3 R01 HL117138-05S1	SGAS	9771013	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Conjugated linoleic acid nitration in vascular inflammation and atherosclerosis	Villacorta, Luis	University of Michigan at Ann Arbor	3 R01 HL123333-04S1	SGAS	9771088	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Eliciting Estrogens Protective Vascular Effects	Lindsey, Sarah H	Tulane University of Louisiana	3 R01 HL133619-02S1	SGAS	9753461	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	SPIROMICS II: Biological underpinnings of COPD heterogeneity and progression	Woodruff, Prescott G	University of California, San Francisco	3 U01 HL137880-02S1	SGAS	9753557	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp - Clinical Trial Optional)	Pregnancy as a Window to Future Cardiovascular Health: Adverse Pregnancy Outcomes	Parker, Corette Breeden	Research Triangle Institute	3 U10 HL119991-04S4	SRP	9759242	RePORTER Proj. Info.
2017	Advancing Health Disparities Interventions through Community-Based Participatory Research (U01)	Promoting Healthy Lifestyle Behaviors to Address Obesity Related Complications of African Americans with Severe Mental Illness Using Peer Navigators	Corrigan, Patrick W	Illinois Institute of Technology	3 U01 MD010541-02S1	U3	9506106	RePORTER Proj. Info.
2018	Change of Grantee Organization (Type 7 Parent Clinical Trial Optional)	Epigenomic Predictors of PTSD and Traumatic Stress in an African American Cohort	Uddin, Monica	University of South Florida	7 R01 MD011728-03	SGAS	9784362	RePORTER Proj. Info.
2017	Research Project Grant (Parent R01)	Ovarian Effects on Intrinsic Connectivity and the Affective Enhancement of Memory	Barrett, Lisa Feldman	Massachusetts General Hospital	1 R01 MH109464-01A1	SRP	9240048	RePORTER Proj. Info.
2017	Human Heredity and Health in Africa (H3AFRICA): Research Projects (U01)	Transgenerational Effects of Maternal Stressors: Investigating the Role of Infant Gene Expression	Stein, Dan Joseph	University of Cape Town	1 U01 MH115484-01	SRP	9386805	RePORTER Proj. Info.
2017	Specialized Centers of Research (SCOR) on Sex Differences (P50)	Prepubertal Stress, Windows of Risk & Sex Bias for Affective Disturbance	Epperson, C Neill	University of Pennsylvania	3 P50 MH099910-05S1	SCORE	9484360	RePORTER Proj. Info.
2017	Silvio O. Conte Centers for Basic or Translational Mental Health Research (P50)	Neuroimmune Mechanisms of Psychiatric Disorders	Carter, Cameron S	University of California at Davis	3 P50 MH106438-03S1	SRP	9496290	RePORTER Proj. Info.
2017	Innovative Measures of Oral Medication Adherence for HIV Treatment and Prevention (R01)	Next generation real-time monitoring for PrEP adherence in young Kenyan women	Haberer, Jessica Elizabeth	Massachusetts General Hospital	3 R01 MH109309-02S1	SRP	9485505	RePORTER Proj. Info.
2018	NIH Research Project Grant (Parent R01)	ENIGMA-SD: Understanding Sex Differences in Global Mental Health through ENIGMA	Thompson, Paul M	University of Southern California	1 R01 MH116147-01	SRP	9497565	RePORTER Proj. Info.
2018	Academic Research Enhancement Award (Parent R15)	Efficacy Trial of a Dissonance Based Eating Disorder Program	Green, Melinda Ann	Cornell College	1 R15 MH113044-01A1	SRP	9513808	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Gender differences in quantitative measures of autonomic function and Clinical features of the autism phenotype	Martin, Christa Lese	Geisinger Clinic	3 R01 MH107431-04S1	SGAS	9673477	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Ovarian Effects on Intrinsic Connectivity and the Affective Enhancement of Memory	Barrett, Lisa Feldman	Massachusetts General Hospital	3 R01 MH109464-02S1	SGAS	9670417	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	A Novel Wireless Ingestible Sensor System for Measurement of Medication Adherence in HIV Treatment and Prevention	Browne, Sara H	University of California, San Diego	3 R01 MH110057-04S1	U3	9763073	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	The role of cultural risk and resiliency factors and the built neighborhood environment on maternal depressive Symptoms in pregnant Mexican-American women	D'Anna-Hernandez, Kimberly Lynn	California State University San Marcos	3 R15 MH112091-01S1	U3	9687602	RePORTER Proj. Info.
2017	Centers of Excellence in Self-Management of Symptoms (P30)	Precision in Symptom Self-Management (PriSSM) Center	Bakken, Suzanne	Columbia University Health Sciences	3 P30 NR016587-02S1	SRP	9484756	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Gender Differences in Response to Diabetes Self-Management Education among Mexican American Adults	Kopelowicz, Alex J	University of California Los Angeles	3 R01 NR015809-02S1	SGAS	9430664	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Sex differences in exercise-related post-exertional malaise in ME/CFS	Friedberg, Fred	State University New York Stony Brook	3 R01 NR015850-02S1	SGAS	9431634	RePORTER Proj. Info.
2018	Maternal Nutrition and Pre-pregnancy Obesity: Effects on Mothers, Infants and Children (R01)	Severe Maternal Morbidity: An Investigation of Racial-Ethnic Disparities, Social Disadvantage & Maternal Weight	Carmichael, Suzan L	Stanford University	1 R01 NR017020-01A1	SRP	9447974	RePORTER Proj. Info.
2018	NIH Research Project Grant (Parent R01)	Sex-specific Brain injury and Symptoms in sleep apnea	Macey, Paul M	University of California Los Angeles	1 R56 NR017435-01A1	R56	9765453	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	NIH Research Project Grant (Parent R01)	Technology Enhanced Community Health Nursing to Reduce Recurrent STIs after PID	Trent, Maria E	Johns Hopkins University	2 R01 NR013507-06	SRP	9409377	RePORTER Proj. Info.
2018	Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations An ORWH FY18 Administrative Supplement (Admin Supp - Clinical Trial Optional)	Building Evidence for Effective Palliative/ End of Life Care for Teens with Cancer	Lyon, Maureen Ellen	Children's Research Institute	3 R01 NR015458-04S1	U3	9751574	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp)	Epileptogenesis following FSE: mechanisms, biomarkers, prevention	Baram, Tallie Z	University of California-Irvine	3 R01 NS035439-19S1	SGAS	9424530	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Vascular Injury and Recovery in Diabetic Ischemic Stroke	Ergul, Adviye	Augusta University	3 R01 NS083559-04S1	SGAS	9429297	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Role of the limbic-hypothalamic-pituitary-adrenal axis and gamma-aminobutyric acid type A receptor-mediated excitation in the developmental central and systemic effects of neonatal anesthesia	Martynyuk, Anatoly E	University of Florida	3 R01 NS091542-03S1	SGAS	9416273	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	MicroRNA-mediated silencing of the Kv4.2 complex in epilepsy	Gross Christina	Cincinnati Children's Hospital Medical Center	3 R01 NS092705-02S1	SGAS	9414624	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Sleep state-dependent mechanisms of seizure-induced death	Buchanan, Gordon Frank	University of Iowa	3 R01 NS095842-02S1	SGAS	9428205	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Sex, Stress and Immunity in the Acute to Chronic Pain Transition	Yaksh, Tony L	University of California, San Diego	3 R01 NS099338-01S1	SGAS	9431570	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Age-Dependence of Cerebral Oxygen Metabolism and Stroke Risk in Pediatric Sickle Cell Disease	Guilliams, Kristin	Washington University	3 K23 NS099472-02S1	SGAS	9673357	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Administrative Supplement for Research on Sex/Gender Influences (Admin Supp - Clinical Trial Optional)	Cellular mechanisms of fetal white matter injury	Back, Stephen Arthur	Oregon Health & Science University	3 R01 NS045737-15S1	SGAS	9673295	RePORTER Proj. Info.
2017	NIH Research Project Grant (Parent R01)	Drying, Storing, and Reanimating Egg Germinal Vesicles to Preserve Fertility	Comizzoli, Pierre	Smithsonian Institution	1 R01 OD023139-01A1	SRP	9382420	RePORTER Proj. Info.
2017	Animal and Biological Material Resource Centers (P40)	Rat Resource and Research Center	Bryda, Elizabeth C	University of Missouri-Columbia	3 P40 OD011062-17S1	SRP	9537764	RePORTER Proj. Info.
2017	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp)	Sex Differences in TAAR1: A New Participant in Methamphetamine Abuse	Robertson, Joseph E	Oregon Health & Science University	3 P51 OD011092-58S1	SGAS	9429530	RePORTER Proj. Info.
2017	Rapid Assessment of Zika Virus (ZIKV) Complications (R21)	Leveraging Established Fetal Primate Models to Expedite ZIKV Investigations	Tarantal, Alice F	University of California at Davis	3 R21 OD023716-02S1	SRP	9543066	RePORTER Proj. Info.
2018	Administrative Supplement for Research on Sex/ Gender Influences (Admin Supp - Clinical Trial Optional)	Enhanced Development of the Xiphophorus Model System	Walter, Ronald	Texas State University	3 R24 OD011120-11S2	SGAS	9753426	RePORTER Proj. Info.
2018	NIH Research Project Grant (Parent R01)	Drying, Storing, and Reanimating Egg Germinal Vesicles to Preserve Fertility	Comizzoli, Pierre	Smithsonian Institution	5 R01 OD023139-02	SRP	9545098	RePORTER Proj. Info.
2017	Fogarty Global Health Training Program (D43)	University of California Global Health Institute Program for Fellows and Scholars	Cohen, Craig R	University of California, San Francisco	2 D43 TW009343-06	SRP	9333660	RePORTER Proj. Info.
2017	Fogarty Global Injury and Trauma Research Training Program (D43)	Biobehavioral Research Approaches to reduce Effects of Trauma on Mental and Physical Health and Cognitive Outcomes in South Africa	Wyatt, Gail E	University of California Los Angeles	5 D43 TW007278-12	SRP	9353487	RePORTER Proj. Info.
2017	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	NURTURE: Research Training and Mentoring Program for Career Development of Faculty at Makerere University College of Health Sciences	Sewankambo, Nelson K	Makerere University	5 D43 TW010132-03	SRP	9328191	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2017	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Building Research And Innovation in Nigeria's Science - (BrainS)	Ogunsola, Folasade Tolulope	University of LAGOS - College of Medicine	5 D43 TW010134-03	SRP	9328188	RePORTER Proj. Info.
2017	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	UZCHS-Promote Excellence in Research and Faculty Enhanced Career Training (PERFECT Program)	Hakim, James Gita	College of Health SCIS University of Zimbabwe	5 D43 TW010137-03	SRP	9330250	RePORTER Proj. Info.
2017	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Strengthening of Research Capacity for Junior Faculty in Tanzania	Mteta, Alfred Kien	Kilimanjaro Christian Medical College	5 D43 TW010138-03	SRP	9336370	RePORTER Proj. Info.
2017	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Partnership for Health Research Training in Kenya (P-HERT)	Wamalwa, Dalton Chekoko	University of Nairobi	5 D43 TW010141-03	SRP	9328187	RePORTER Proj. Info.
2018	Fogarty Global Injury and Trauma Research Training Program (D43)	Biobehavioral Research Approaches to reduce Effects of Trauma on Mental and Physical Health and Cognitive Outcomes in South Africa	Wyatt, Gail E	University of California Los Angeles	5 D43 TW007278-13	SRP	9563334	RePORTER Proj. Info.
2018	Fogarty Global Health Training Program (D43)	University of California Global Health Institute Program for Fellows and Scholars	Cohen, Craig R	University of California, San Francisco	5 D43 TW009343-07	SRP	9475656	RePORTER Proj. Info.
2018	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	NURTURE: Research Training and Mentoring Program for Career Development of Faculty at Makerere University College of Health Sciences	Sewankambo, Nelson K	Makerere University	5 D43 TW010132-04	SRP	9564001	RePORTER Proj. Info.
2018	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Building Research And Innovation in Nigeria's Science - (Brains)	Ogunsola, Folasade Tolulope	University of Lagos - College of Medicine	5 D43 TW010134-04	SRP	9562974	RePORTER Proj. Info.

FY	RFA Title	Title	PI Name	Institution	Grant	ORWH Program	Appl Id	RePORTER Project Info
2018	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	UZCHS-Promote Excellence in Research and Faculty Enhanced Career Training (PERFECT Program)	Hakim, James Gita	College of Health SCIS University of Zimbabwe	5 D43 TW010137-04	SRP	9563338	RePORTER Proj. Info.
2018	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Strengthening of Research Capacity for Junior Faculty in Tanzania	Mteta, Alfred Kien	Kilimanjaro Christian Medical College	5 D43 TW010138-04	SRP	9562154	RePORTER Proj. Info.
2018	Limited Competition: Research Training for Career Development of Junior Faculty in Medical Education Partnership Initiative (MEPI) Institutions (D43)	Partnership for Health Research Training in Kenya (P-HERT)	Wamalwa, Dalton Chekoko	University of Nairobi	5 D43 TW010141-04	SRP	9563337	RePORTER Proj. Info.

Appendix C. Members of the NIH Working Group on Women in Biomedical Careers

Fiscal Years 2017–2018

Co-chairs

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

Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health (NIH)

Institute and Center Directors

Linda S. Birnbaum, Ph.D., DABT, ATS, Director, National Institute of Environmental Health Sciences (NIEHS)

Joshua A. Gordon, M.D., Ph.D., Director, National Institute of Mental Health (NIMH)

Patricia A. Grady, Ph.D., RN, FAAN, Director, National Institute of Nursing Research (NINR)

Griffin P. Rodgers, M.D., M.A.C.P., Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Office of the Director

Benjamin Butler, J.D., Senior Attorney, Office of General Council (OGC) (Ex Officio)

Debra C. Chew, J.D., Director, Office of Equity, Diversity, and Inclusion (EDI)

Hannah Valantine, M.D., MRCP, Chief Officer for Scientific Workforce Diversity (SWD)

Intramural Research

M. Catherine Bushnell, Ph.D., Scientific Director and Chief, Pain and Integrative Neuroscience Branch, National Center for Complementary and Integrative Health (NCCIH)

Edward Giniger, Ph.D., Senior Investigator, National Institute of Neurological Disorders and Stroke (NINDS)

Michael Gottesman, M.D., Deputy Director for Intramural Research, Office of Intramural Research (OIR)

Elizabeth Murphy, Ph.D., Senior Investigator, National Heart, Lung, and Blood Institute (NHLBI)

Elaine Ostrander, Ph.D., Chief & Senior Investigator, Cancer Genetics and Comparative Genomics Branch, National Human Genome Research Institute (NHGRI)

Joan Schwartz, Ph.D., Special Volunteer, Office of Intramural Research (OIR)

Kathryn Zoon, Ph.D., Scientist Emeritus, National Institute of Allergy and Infectious Diseases (NIAID)

Extramural Research

Marie A. Bernard, M.D., Deputy Director, National Institute on Aging (NIA)

Jodi Black, Ph.D., Deputy Director, Office of Extramural Research (OER)

Judith H. Greenberg, Ph.D., Deputy Director, National Institute of General Medical Sciences (NIGMS)

Joyce Hunter, Ph.D., Deputy Director, National Institute on Minority Health and Health Disparities (NIMHD)

Michael S. Lauer, M.D., Deputy Director, Office of Extramural Research (OER)

P. Kay Lund, Ph.D., Director, Division of Biomedical Research Workforce, Office of Extramural Research (OER)

Pamela A. Marino, Ph.D., Chief, Biochemistry and Bio-related Chemistry Branch, Division of Pharmacology, Physiology, and Biological Chemistry, National Institute of General Medical Sciences (NIGMS)

Belinda Seto, Ph.D., Deputy Director, National Eye Institute (NEI)

Catherine Spong, M.D., Deputy Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Appendix D. Aggregate Enrollment Data and Tables

Section 1: Metrics Based on Aggregate Enrollment by Sex/Gender

Table 1A: Total Enrollment for All National Institutes of Health (NIH) Clinical Research from FY 2008-2018

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2008	15,412,355	9,243,966	60.0	5,991,739	38.9	176,650	1.1	7,507,149	48.7	361,434	2.3	1,736,817	11.3	5,630,305	36.5
2009	19,138,738	11,439,143	59.8	7,570,646	39.6	128,949	0.7	4,830,093	25.2	396,076	2.1	6,609,050	34.5	7,174,570	37.5
2010	23,363,635	13,102,832	56.1	10,044,444	43.0	216,359	0.9	4,440,402	19.0	1,328,551	5.7	8,662,430	37.1	8,715,893	37.3
2011	15,992,456	9,499,682	59.4	6,287,306	39.3	205,468	1.3	4,562,652	28.5	1,210,876	7.6	4,937,030	30.9	5,076,430	31.7
2012	17,655,238	10,071,897	57.0	7,382,884	41.8	200,457	1.1	3,713,994	21.0	1,096,914	6.2	6,357,903	36.0	6,285,970	35.6
2013	17,580,725	9,961,014	56.7	7,397,295	42.1	222,416	1.3	3,522,251	20.0	1,174,274	6.7	6,438,763	36.6	6,223,021	35.4
2014	28,565,995	16,353,416	57.2	11,038,679	38.6	1,173,900	4.1	3,550,006	12.4	429,440	1.5	12,803,410	44.8	10,609,239	37.1
2015	21,453,866	13,278,481	61.9	7,829,861	36.5	345,524	1.6	3,828,704	17.8	280,567	1.3	9,449,777	44.0	7,549,294	35.2
2016	39,712,265	20,983,081	52.8	17,865,381	45.0	863,803	2.2	2,985,796	7.5	217,876	0.5	17,997,285	45.3	17,647,505	44.4
2017	20,068,789	9,470,264	47.2	10,127,155	50.5	471,370	2.3	1,299,004	6.5	919,239	4.6	8,171,260	40.7	9,207,916	45.9
2018	12,814,162	6,711,564	52.4	5,668,475	44.2	434,123	3.4	1,445,846	11.3	918,805	7.2	5,265,718	41.1	4,749,670	37.1

Table 1B: Total Enrollment for NIH Clinical Research at U.S. Sites from FY 2013-2018

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2013	14,766,330	8,160,136	55.3	6,406,256	43.4	199,938	1.4	3,118,017	21.1	1,100,347	7.5	5,042,119	34.1	5,305,909	35.9
2014	25,209,874	14,395,132	57.1	9,944,895	39.4	869,847	3.5	3,120,777	12.4	335,703	1.3	11,274,355	44.7	9,609,192	38.1
2015	17,212,103	10,529,683	61.2	6,404,104	37.2	278,316	1.6	3,569,721	20.7	209,567	1.2	6,959,962	40.4	6,194,537	36.0
2016	30,710,848	16,594,940	54.0	13,311,968	43.3	803,940	2.6	2,722,586	8.9	163,430	0.5	13,872,354	45.2	13,148,538	42.8
2017	13,231,166	6,491,639	49.1	6,302,343	47.6	437,184	3.3	1,010,384	7.6	871,532	6.6	5,481,255	41.4	5,430,811	41.0
2018	10,578,286	5,413,405	51.2	4,775,856	45.1	389,025	3.7	1,147,146	10.8	886,491	8.4	4,266,259	40.3	3,889,365	36.8

Table 1C: Total Enrollment for Extramural NIH Clinical Research at U.S. Sites from FY 2013-2018

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2013	10,757,737	5,867,799	54.5	4,760,618	44.3	129,320	1.2	1,754,752	16.3	1,088,973	10.1	4,113,047	38.2	3,671,645	34.1
2014	21,897,331	12,126,129	55.4	8,960,001	40.9	811,201	3.7	1,754,275	8.0	324,567	1.5	10,371,854	47.4	8,635,434	39.4
2015	14,149,649	8,427,534	59.6	5,525,413	39.0	196,702	1.4	2,277,591	16.1	199,298	1.4	6,149,943	43.5	5,326,115	37.6
2016	27,510,129	14,418,631	52.4	12,415,288	45.1	676,210	2.5	1,377,694	5.0	153,472	0.6	13,040,937	47.4	12,261,816	44.6
2017	10,730,843	5,264,128	49.1	5,136,833	47.9	329,882	3.1	868,102	8.1	861,158	8.0	4,396,026	41.0	4,275,675	39.8
2018	9,074,769	4,650,602	51.2	4,068,126	44.8	356,041	3.9	1,065,792	11.7	876,842	9.7	3,584,810	39.5	3,191,284	35.2

Table 1D: Total Enrollment for Intramural NIH Clinical Research at U.S. Sites from FY 2013-2018

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2013	4,008,593	2,292,337	57.2	1,645,638	41.1	70,618	1.8	1,363,265	34.0	11,374	0.3	929,072	23.2	1,634,264	40.8
2014	3,312,543	2,269,003	68.5	984,894	29.7	58,646	1.8	1,366,502	41.3	11,136	0.3	902,501	27.2	973,758	29.4
2015	3,062,454	2,102,149	68.6	878,691	28.7	81,614	2.7	1,292,130	42.2	10,269	0.3	810,019	26.4	868,422	28.4
2016	3,200,719	2,176,309	68.0	896,680	28.0	127,730	4.0	1,344,892	42.0	9,958	0.3	831,417	26.0	886,722	27.7
2017	2,500,323	1,227,511	49.1	1,165,510	46.6	107,302	4.3	142,282	5.7	10,374	0.4	1,085,229	43.4	1,155,136	46.2
2018	1,503,517	762,803	50.7	707,730	47.1	32,984	2.2	81,354	5.4	9,649	0.6	681,449	45.3	698,081	46.4

Table 1E: Total Enrollment for All NIH-Defined Phase III Clinical Trials from FY 2008-2018

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2008	792,578	455,612	57.5	319,732	40.3	17,234	2.2	219,673	27.7	79,613	10.0	235,939	29.8	240,119	30.3
2009	652,300	345,748	53.0	276,159	42.3	30,393	4.7	141,892	21.8	65,516	10.0	203,856	31.3	210,643	32.3
2010	769,885	408,181	53.0	330,808	43.0	30,896	4.0	119,103	15.5	62,315	8.1	289,078	37.5	268,493	34.9
2011	584,278	333,293	57.0	222,060	38.0	28,925	5.0	82,315	14.1	26,229	4.5	250,978	43.0	195,831	33.5
2012	603,136	374,819	62.1	197,019	32.7	31,298	5.2	58,916	9.8	10,288	1.7	315,903	52.4	186,731	31.0
2013	691,023	506,732	73.3	179,220	25.9	5,071	0.7	217,869	31.5	12,406	1.8	288,863	41.8	166,814	24.1
2014	797,264	478,222	60.0	314,310	39.4	4,732	0.6	32,310	4.1	4,267	0.5	445,912	55.9	309,951	38.9
2015	1,619,508	1,091,910	67.4	507,561	31.3	20,037	1.2	29,368	1.8	4,267	0.3	1,062,542	65.6	503,294	31.1
2016	2,130,389	1,396,503	65.6	710,818	33.4	23,068	1.1	35,463	1.7	7,480	0.4	1,361,040	63.9	703,338	33.0
2017	907,643	535,440	59.0	371,636	40.9	567	0.1	154,733	17.0	10,800	1.2	380,707	41.9	360,836	39.8
2018	417,713	260,652	62.4	155,960	37.3	1,101	0.3	116,019	27.8	10,131	2.4	144,633	34.6	145,829	34.9

Table 1F: Total Enrollment for All NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 2013-2018

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2013	236,692	137,062	57.9	98,753	41.7	877	0.4	56,821	24.0	12,133	5.1	80,241	33.9	86,620	36.6
2014	254,263	132,354	52.1	121,366	47.7	543	0.2	23,389	9.2	4,282	1.7	108,965	42.9	117,084	46.0
2015	173,640	83,932	48.3	89,228	51.4	480	0.3	17,089	9.8	3,361	1.9	66,843	38.5	85,867	49.5
2016	169,893	83,278	49.0	86,425	50.9	190	0.1	22,733	13.4	6,092	3.6	60,545	35.6	80,333	47.3
2017	550,782	330,307	60.0	220,245	40.0	230	0.0	138,934	25.2	8,207	1.5	191,373	34.7	212,038	38.5
2018	335,391	209,985	62.6	124,830	37.2	576	0.2	98,685	29.4	7,468	2.2	111,300	33.2	117,362	35.0

Table 1G: Total Enrollment for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 2013-2018

Fiscal Year	Totals Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2013	226,204	129,126	57.1	96,201	42.5	877	0.4	50,850	22.5	11,972	5.3	78,276	34.6	84,229	37.2
2014	245,611	125,118	50.9	119,950	48.8	543	0.2	17,379	7.1	4,112	1.7	107,739	43.9	115,838	47.2
2015	161,030	74,759	46.4	85,794	53.3	477	0.3	11,067	6.9	3,181	2.0	63,692	39.6	82,613	51.3
2016	158,741	74,969	47.2	83,586	52.7	186	0.1	16,713	10.5	5,911	3.7	58,256	36.7	77,675	48.9
2017	540,640	322,436	59.6	217,976	40.3	228	0.0	132,912	24.6	8,191	1.5	189,524	35.1	209,785	38.8
2018	327,633	206,817	63.1	120,274	36.7	542	0.2	98,429	30.0	7,468	2.3	108,388	33.1	112,806	34.4

Table 1H: Total Enrollment for Intramural NIH-Defined Phase III Clinical Trials at U.S. Sites from FY 2013-2018

Fiscal Year	Total Enrollment	Total Females	% Females	Total Males	% Males	Total Unknown	% Unknown	Enrollment in Female-only	% Female-only	Enrollment in Male-only	% Male-only	Females, Excluding Female-only	% Females, Excluding Female-only	Males, Excluding Male-only	% Males, Excluding Male-only
2013	10,488	7,936	75.7	2,552	24.3	0	0.0	5,971	56.9	161	1.5	1,965	18.7	2,391	22.8
2014	8,652	7,236	83.6	1,416	16.4	0	0.0	6,010	69.5	170	2.0	1,226	14.2	1,246	14.4
2015	12,610	9,173	72.7	3,434	27.2	3	0.0	6,022	47.8	180	1.4	3,151	25.0	3,254	25.8
2016	11,152	8,309	74.5	2,839	25.5	4	0.0	6,020	54.0	181	1.6	2,289	20.5	2,658	23.8
2017	10,142	7,871	77.6	2,269	22.4	2	0.0	6,022	59.4	16	0.2	1,849	18.2	2,253	22.2
2018	7,758	3,168	40.8	4,556	58.7	34	0.4	256	3.3	0	0.0	2,912	37.5	4,556	58.7

Section 2: Aggregate Enrollment of Race and Ethnicity: Clinical Research

Table 2A: Total Enrollment and Minority Enrollment for all NIH Clinical Research from FY 2008 to 2018

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2008	15,412,355	4,412,106	28.6
2009	19,138,738	5,783,543	30.2
2010	23,363,635	7,510,763	32.1
2011	15,992,456	6,488,223	40.6
2012	17,655,238	6,446,175	36.5
2013	17,580,725	6,687,678	38.0
2014	28,565,995	9,582,978	33.5
2015	21,453,866	8,602,086	40.1
2016	39,712,265	14,987,425	37.7
2017	20,068,789	10,075,058	50.2
2018	12,814,162	4,621,528	36.1

Table 2B: Total Enrollment and Minority Enrollment for NIH Clinical Research at U.S. Sites from FY 2013 to 2018

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2013	14,766,330	4,322,007	29.3
2014	25,209,874	6,607,207	26.2
2015	17,212,103	4,778,010	27.8
2016	30,710,848	11,179,772	36.4
2017	13,231,166	3,742,781	28.3
2018	10,578,286	3,094,979	29.3

Table 2C: Total Enrollment and Minority Enrollment for Extramural NIH Clinical Research at U.S. Sites from FY 2013 to 2018

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2013	10,757,737	3,666,833	34.1
2014	21,897,331	6,173,549	28.2
2015	14,149,649	4,421,098	31.3
2016	27,510,129	10,770,168	39.1
2017	10,730,843	3,240,677	30.2
2018	9,074,769	2,863,823	31.6

Table 2D: Total Enrollment and Minority Enrollment for Intramural NIH Clinical Research at U.S. Sites from FY 2013 to 2018

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2013	4,008,593	655,174	16.3
2014	3,312,543	433,658	13.1
2015	3,062,454	356,912	11.7
2016	3,200,719	409,604	12.8
2017	2,500,323	502,104	20.1
2018	1,503,517	231,156	15.4

Table 2E: Total Enrollment for All NIH Clinical Research Racial Categories from FY 2013 to 2018

2013	17,578,991	10,570	6,686,903	38.0	371,013	2.1	2,474,126	14.1	2,266,772	12.9	43,589	0.2	9,450,454	53.8	209,669	1.2	2,763,368	15.7
2014	28,565,295	10,074	9,582,434	33.5	271,211	0.9	3,330,083	11.7	3,406,343	11.9	97,329	0.3	17,602,822	61.6	370,181	1.3	3,487,326	12.2
2015	21,453,866	11,082	8,602,086	40.1	488,167	2.3	3,403,915	15.9	2,546,765	11.9	40,321	0.2	10,367,705	48.3	339,308	1.6	4,267,685	19.9
2016	39,712,265	13,069	14,987,425	37.7	618,188	1.6	4,466,346	11.2	4,502,686	11.3	261,649	0.7	19,893,061	50.1	875,399	2.2	9,094,936	22.9
2017	20,068,789	14,580	10,075,058	50.2	130,608	0.7	6,041,535	30.1	2,325,409	11.6	27,863	0.1	9,399,014	46.8	438,059	2.2	1,706,301	8.5
2018	12,814,162	16,209	4,621,528	36.1	124,447	1.0	1,158,703	9.0	2,045,956	16.0	31,054	0.2	7,500,227	58.5	360,906	2.8	1,592,869	12.4

Table 2F: Total Enrollment for All NIH Clinical Research Ethnic Categories FY 2013 to 2018

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2013	12,895,326	73.4	1,798,501	10.2	2,885,164	16.4
2014	23,270,093	81.5	2,442,998	8.6	2,852,204	10.0
2015	15,298,198	71.3	2,332,328	10.9	3,823,340	17.8
2016	26,831,115	67.6	4,841,284	12.2	8,039,866	20.2
2017	16,920,869	84.3	1,378,631	6.9	1,769,289	8.8
2018	10,033,964	78.3	1,190,849	9.3	1,589,349	12.4

Table 2G: Total Enrollment for All NIH Clinical Research at U.S. Sites Racial Categories from FY 2013 to 2018

2013	14,764,596	4,321,232	29.3	136,416	0.9	1,008,180	6.8	1,765,689	12.0	41,242	0.3	9,035,020	61.2	190,838	1.3	2,587,211	17.5
2014	25,209,174	6,606,663	26.2	187,224	0.7	1,289,490	5.1	2,790,849	11.1	89,184	0.4	17,212,956	68.3	339,596	1.3	3,299,875	13.1
2015	17,212,103	4,778,010	27.8	139,377	0.8	970,862	5.6	1,672,975	9.7	31,675	0.2	9,950,746	57.8	288,773	1.7	4,157,695	24.2
2016	30,710,848	11,179,772	36.4	321,625	1.0	2,395,431	7.8	3,249,188	10.6	252,436	0.8	19,415,746	63.2	829,095	2.7	4,247,327	13.8
2017	13,231,166	3,742,781	28.3	117,270	0.9	422,203	3.2	1,808,949	13.7	27,601	0.2	8,859,771	67.0	390,899	3.0	1,604,473	12.1
2018	10,578,286	3,094,979	29.3	97,257	0.9	423,422	4.0	1,488,023	14.1	30,573	0.3	6,792,076	64.2	297,436	2.8	1,449,499	13.7

Table 2H: Total Enrollment for All NIH Clinical Research at U.S. Sites Ethnic Categories FY 2013 to 2018

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2013	10,639,126	72.1	1,313,858	8.9	2,811,612	19.0
2014	20,332,636	80.7	2,082,077	8.3	2,794,461	11.1
2015	11,678,565	67.9	1,834,210	10.7	3,699,328	21.5
2016	23,183,045	75.5	4,373,479	14.2	3,154,324	10.3
2017	10,416,536	78.7	1,199,711	9.1	1,614,919	12.2
2018	8,207,889	77.6	983,148	9.3	1,387,249	13.1

Table 2I: Total Enrollment for Extramural NIH Clinical Research at U.S. Sites Racial Categories from FY 2013 to 2018

2013	10,756,003	3,666,058	34.1	108,611	1.0	877,176	8.2	1,425,734	13.3	35,395	0.3	7,116,662	66.2	180,878	1.7	1,011,547	9.4
2014	21,896,631	6,173,005	28.2	160,605	0.7	1,222,199	5.6	2,592,096	11.8	83,039	0.4	15,636,146	71.4	328,422	1.5	1,874,124	8.6
2015	14,149,649	4,421,098	31.3	112,119	0.8	931,086	6.6	1,481,082	10.5	26,466	0.2	8,593,188	60.7	278,313	2.0	2,727,395	19.3
2016	27,510,129	10,770,168	39.1	293,887	1.1	2,352,180	8.6	3,028,871	11.0	247,061	0.9	18,012,861	65.5	817,320	3.0	2,757,949	10.0
2017	10,730,843	3,240,677	30.2	86,996	0.8	361,873	3.4	1,543,732	14.4	22,115	0.2	6,997,681	65.2	377,235	3.5	1,341,211	12.5
2018	9,074,769	2,863,823	31.6	70,274	0.8	398,335	4.4	1,363,141	15.0	26,622	0.3	5,611,705	61.8	287,841	3.2	1,316,851	14.5

Table 2J: Total Enrollment for Extramural NIH Clinical Research at U.S. Sites Ethnic Categories FY 2013 to 2018

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2013	8,478,293	78.8	1,166,466	10.8	1,111,244	10.3
2014	18,702,141	85.4	1,952,648	8.9	1,241,842	5.7
2015	10,250,999	72.5	1,745,814	12.3	2,152,836	15.2
2016	21,757,302	79.1	4,265,923	15.5	1,486,904	5.4
2017	8,519,353	79.4	1,065,979	9.9	1,145,511	10.7
2018	6,866,982	75.7	938,306	10.3	1,269,481	14.0

Table 2K: Total Enrollment for Intramural NIH Clinical Research at U.S. Sites Racial Categories from FY 2013 to 2018

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2013	4,008,593	655,174	16.3	27,805	0.7	131,004	3.3	339,955	8.5	5,847	0.1	1,918,358	47.9	9,960	0.2	1,575,664	39.3
2014	3,312,543	433,658	13.1	26,619	0.8	67,291	2.0	198,753	6.0	6,145	0.2	1,576,810	47.6	11,174	0.3	1,425,751	43.0
2015	3,062,454	356,912	11.7	27,258	0.9	39,776	1.3	191,893	6.3	5,209	0.2	1,357,558	44.3	10,460	0.3	1,430,300	46.7
2016	3,200,719	409,604	12.8	27,738	0.9	43,251	1.4	220,317	6.9	5,375	0.2	1,402,885	43.8	11,775	0.4	1,489,378	46.5
2017	2,500,323	502,104	20.1	30,274	1.2	60,330	2.4	265,217	10.6	5,486	0.2	1,862,090	74.5	13,664	0.5	263,262	10.5
2018	1,503,517	231,156	15.4	26,983	1.8	25,087	1.7	124,882	8.3	3,951	0.3	1,180,371	78.5	9,595	0.6	132,648	8.8

Table 2L: Total Enrollment for Intramural NIH Clinical Research at U.S. Sites Ethnic Categories FY 2013 to 2018

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2013	2,160,833	53.9	147,392	3.7	1,700,368	42.4
2014	1,630,495	49.2	129,429	3.9	1,552,619	46.9
2015	1,427,566	46.6	88,396	2.9	1,546,492	50.5
2016	1,425,743	44.5	107,556	3.4	1,667,420	52.1
2017	1,897,183	75.9	133,732	5.3	469,408	18.8
2018	1,340,907	89.2	44,842	3.0	117,768	7.8

Section 3: Aggregate Enrollment of Race and Ethnicity: NIH-Defined Phase III Clinical Trials

Table 3A: Total Enrollment and Minority Enrollment for All NIH Defined Phase III Clinical Trials from FY 2008 to 2018

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2008	792,578	270,899	34.2
2009	652,300	291,949	44.8
2010	769,885	447,187	58.1
2011	584,278	347,770	59.5
2012	603,136	396,714	65.8
2013	691,023	526,422	76.2
2014	797,264	627,456	78.7
2015*	1,619,508	1,492,248	92.1
2016*	2,130,389	1,992,237	93.5
2017	907,643	459,046	50.6
2018	417,714	160,615	38.5

**FY2015 and FY2016 includes data from large foreign Phase III trials which tend to have larger numbers of participants than domestic Phase III trials.*

Table 3B: Total Enrollment and Minority Enrollment at U.S. Sites for All NIH Defined Phase III Clinical Trials from FY 2013 to 2018

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2013	236,692	79,608	33.6
2014	254,263	95,934	37.7
2015	173,640	70,361	40.5
2016	169,893	72,318	42.6
2017	550,782	123,247	22.4
2018	335,391	104,170	31.1

Table 3C: Total Enrollment and Minority Enrollment at U.S. Sites for Extramural NIH Defined Phase III Clinical Trials from FY 2013 to 2018

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2013	226,204	76,030	33.6
2014	245,611	92,457	37.6
2015	161,030	66,176	41.1
2016	158,741	68,176	42.9
2017	540,640	119,772	22.2
2018	327,633	102,285	31.2

Table 3D: Total Enrollment and Minority Enrollment at U.S. Sites for Intramural NIH Defined Phase III Clinical Trials from FY 2013 to 2018

Fiscal Year	Total Enrollees	Minority Enrollees	% Minority Enrollees
2013	10,488	3,578	34.1
2014	8,652	3,477	40.2
2015	12,610	4,185	33.2
2016	11,152	4,142	37.1
2017	10,142	3,475	34.3
2018	7,758	1,885	24.3

Table 3E: Total Enrollment for All NIH-Defined Phase III Clinical Trials Racial Categories from FY 2013 to 2018

Fiscal Year	Total Enrollment	No. Inclusion Data Record	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2013	691,023	570	526,422	76.2	26,834	3.9	341,188	49.4	110,861	16.0	595	0.1	173,672	25.1	3,500	0.5	34,373	5.0
2014	797,264	525	627,456	78.7	30,119	3.8	409,983	51.4	135,630	17.0	490	0.1	184,372	23.1	3,697	0.5	32,973	4.1
2015*	1,619,508	498	1,492,248	92.1	124,444	7.7	976,701	60.3	360,471	22.3	300	0.0	124,641	7.7	2,113	0.1	30,838	1.9
2016*	2,130,389	574	1,992,237	93.5	150,019	7.0	1,037,057	48.7	772,419	36.3	320	0.0	139,940	6.6	2,096	0.1	28,538	1.3
2017	907,643	618	459,046	50.6	2,410	0.3	274,218	30.2	133,842	14.7	618	0.1	451,173	49.7	4,341	0.5	41,041	4.5
2018	417,714	717	160,615	38.5	2,390	0.6	18,961	4.5	79,604	19.1	847	0.2	269,943	64.6	15,298	3.7	30,670	7.3

**FY2015 and FY2016 includes data from large foreign Phase III trials which tend to have larger numbers of participants than domestic Phase III trials.*

Table 3F: Total Enrollment for All NIH-Defined Phase III Clinical Trials Ethnic Categories for FY 2013 to 2018

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2013	608,564	88.1	71,744	10.4	10,715	1.6
2014	703,877	88.3	77,152	9.7	16,235	2.0
2015	1,457,366	90.0	154,371	9.5	7,771	0.5
2016	1,941,923	91.2	181,121	8.5	7,345	0.3
2017	790,092	87.0	49,999	5.5	67,552	7.4
2018	354,752	84.9	49,446	11.8	13,515	3.2

Table 3G: Total Enrollment for All NIH-Defined Phase III Clinical Trials at U.S. Sites Racial Categories from FY 2013 to 2018

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2013	236,692	79,608	33.6	1,868	0.8	5,302	2.2	45,303	19.1	553	0.2	166,186	70.2	2,963	1.3	14,517	6.1
2014	254,263	95,934	37.7	5,129	2.0	4,150	1.6	58,170	22.9	457	0.2	173,719	68.3	3,053	1.2	9,585	3.8
2015	173,640	70,361	40.5	1,996	1.2	7,632	4.4	41,046	23.6	268	0.2	114,014	65.7	1,742	1.0	6,942	4.0
2016	169,893	72,318	42.6	1,259	0.7	19,470	11.5	29,367	17.3	276	0.2	110,836	65.2	1,973	1.2	6,712	4.0
2017	550,782	123,247	22.4	2,305	0.4	12,042	2.2	71,387	13.0	551	0.1	431,587	78.4	4,223	0.8	28,687	5.2
2018	335,391	104,170	31.1	2,249	0.7	8,992	2.7	49,346	14.7	769	0.2	249,110	74.3	11,905	3.5	13,020	3.9

Table 3H: Total Enrollment for All NIH-Defined Phase III Clinical Trials at U.S. Sites Ethnic Categories for FY 2013 to 2018

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2013	200,126	84.6	26,015	11.0	10,551	4.5
2014	214,559	84.4	28,814	11.3	10,890	4.3
2015	150,486	86.7	20,845	12.0	2,309	1.3
2016	144,849	85.3	21,801	12.8	3,243	1.9
2017	449,879	81.7	38,480	7.0	62,423	11.3
2018	293,131	87.4	35,741	10.7	6,519	1.9

Table 3I: Total Enrollment for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites Racial Categories from FY 2013 to 2018

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2013	226,204	76,030	33.6	1,554	0.7	5,001	2.2	42,994	19.0	547	0.2	158,999	70.3	2,942	1.3	14,167	6.3
2014	245,611	92,457	37.6	4,788	1.9	3,868	1.6	55,899	22.8	451	0.2	168,262	68.5	3,016	1.2	9,327	3.8
2015	161,030	66,176	41.1	1,537	1.0	7,340	4.6	38,110	23.7	261	0.2	105,555	65.6	1,705	1.1	6,522	4.1
2016	158,741	68,176	42.9	859	0.5	19,172	12.1	26,438	16.7	271	0.2	103,776	65.4	1,924	1.2	6,301	4.0
2017	540,640	119,772	22.2	1,842	0.3	11,726	2.2	69,164	12.8	545	0.1	424,758	78.6	4,174	0.8	28,431	5.3
2018	327,633	102,285	31.2	1,975	0.6	8,711	2.7	48,436	14.8	768	0.2	243,227	74.2	11,681	3.6	12,835	3.9

Table 3J: Total Enrollment for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites Ethnic Categories for FY 2013 to 2018

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2013	190,444	84.2	25,325	11.2	10,435	4.6
2014	206,640	84.1	28,202	11.5	10,769	4.4
2015	138,597	86.1	20,303	12.6	2,130	1.3
2016	134,461	84.7	21,238	13.4	3,042	1.9
2017	440,370	81.5	37,948	7.0	62,322	11.5
2018	285,642	87.2	35,502	10.8	6,489	2.0

Table 3K: Total Enrollment for Intramural NIH-Defined Phase III Clinical Trials at U.S. Sites Racial Categories from FY 2013 to 2018

Fiscal Year	Total Enrollment	Minority Enrollment	% Minority Enrollment	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black/ African American	% Black/ African American	Native Hawaiian/ Pacific Islander	% Native Hawaiian/ Pacific Islander	White	% White	More Than One Race	% More Than One Race	Unknown/ Not Reported	% Unknown/ Not Reported
2013	10,488	3,578	34.1	314	3.0	301	2.9	2,309	22.0	6	0.1	7,187	68.5	21	0.2	350	3.3
2014	8,652	3,477	40.2	341	3.9	282	3.3	2,271	26.2	6	0.1	5,457	63.1	37	0.4	258	3.0
2015	12,610	4,185	33.2	459	3.6	292	2.3	2,936	23.3	7	0.1	8,459	67.1	37	0.3	420	3.3
2016	11,152	4,142	37.1	400	3.6	298	2.7	2,929	26.3	5	0.0	7,060	63.3	49	0.4	411	3.7
2017	10,142	3,475	34.3	463	4.6	316	3.1	2,223	21.9	6	0.1	6,829	67.3	49	0.5	256	2.5
2018	7,758	1,885	24.3	274	3.5	281	3.6	910	11.7	1	0.0	5,883	75.8	224	2.9	185	2.4

Table 3L: Total Enrollment for Intramural NIH-Defined Phase III Clinical Trials at U.S. Sites Ethnic Categories for FY 2013 to 2018

Fiscal Year	Not Hispanic	% Not Hispanic	Hispanic/ Latino	% Hispanic/ Latino	Unknown/ Not Reported	% Unknown/ Not Reported
2013	9,682	92.3	690	6.6	116	1.1
2014	7,919	91.5	612	7.1	121	1.4
2015	12,610	94.3	542	4.3	179	1.4
2016	10,388	93.1	563	5.0	201	1.8
2017	9,509	93.8	532	5.2	101	1.0
2018	7,489	96.5	239	3.1	30	0.4

Section 4: Aggregate Enrollment: Sex/Gender by Race and Ethnicity for NIH Clinical Research

Table 4A: Minority Enrollment by Sex/Gender for All NIH Clinical Research from FY2013 to 2018

Fiscal Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2013	Female	3,861,247	38.8	9,961,014	56.7
	Male	2,767,206	27.8	7,397,295	42.1
	Unknown	59,225	0.6	222,416	1.3
2014	Female	5,264,659	32.2	16,353,416	57.2
	Male	3,899,441	23.8	11,038,679	38.6
	Unknown	418,878	2.6	1,173,900	4.1
2015	Female	5,255,224	39.6	13,278,481	61.9
	Male	3,175,954	23.9	7,829,861	36.5
	Unknown	170,908	1.3	345,524	1.6
2016	Female	8,226,149	39.2	20,983,081	52.8
	Male	6,649,220	37.2	17,865,381	45.0
	Unknown	112,056	13.0	863,803	2.2
2017	Female	4,664,388	49.3	9,470,264	47.2
	Male	5,364,942	53.0	10,127,155	50.5
	Unknown	45,728	9.7	471,370	2.3
2018	Female	2,610,070	38.9	6,711,564	52.4
	Male	1,967,116	34.7	5,668,475	44.2
	Unknown	44,342	10.2	434,123	3.4

Table 4B: Minority Enrollment by Sex/Gender for All NIH Clinical Research at U.S. Sites from FY2013 to 2018

Fiscal Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2013	Female	2,316,451	28.4	8,160,136	55.3
	Male	1,961,559	24.0	6,406,256	43.4
	Unknown	43,997	0.5	199,938	1.4
2014	Female	3,534,913	24.6	14,395,132	57.1
	Male	2,946,342	20.5	9,944,895	39.4
	Unknown	125,952	0.9	869,847	3.5
2015	Female	2,737,095	26.0	10,529,683	61.2
	Male	1,921,639	30.0	6,404,104	37.2
	Unknown	119,276	42.9	278,316	1.6
2016	Female	5,855,133	35.3	16,594,940	54.0
	Male	5,256,810	39.5	13,311,968	43.3
	Unknown	67,829	8.4	803,940	2.6
2017	Female	1,962,988	30.2	6,491,639	49.1
	Male	1,751,515	27.8	6,302,343	47.6
	Unknown	28,278	6.5	437,184	3.3
2018	Female	1,715,543	31.7	5,413,405	51.2
	Male	1,360,919	28.5	4,775,856	45.1
	Unknown	18,517	4.8	389,025	3.7

Table 4C: Minority Enrollment by Sex/Gender for Extramural NIH Clinical Research at U.S. Sites from FY2013 to 2018

Fiscal Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2013	Female	2,050,457	34.9	5,867,799	54.5
	Male	1,582,377	27.0	4,760,618	44.3
	Unknown	33,999	0.6	129,320	1.2
2014	Female	3,294,588	27.2	12,126,129	55.4
	Male	2,762,889	22.8	8,960,001	40.9
	Unknown	116,072	1.0	811,201	3.7
2015	Female	2,545,119	30.2	8,427,534	59.6
	Male	1,761,708	31.9	5,525,413	39.0
	Unknown	114,271	58.1	196,702	1.4
2016	Female	5,623,816	39.0	14,418,631	52.4
	Male	5,083,588	40.9	12,415,288	45.1
	Unknown	62,764	9.3	676,210	2.5
2017	Female	1,685,598	32.0	5,264,128	49.1
	Male	1,528,194	29.7	5,136,833	47.9
	Unknown	26,885	8.1	329,882	3.1
2018	Female	1,581,696	34.0	4,650,602	51.2
	Male	1,264,241	31.1	4,068,126	44.8
	Unknown	17,886	5.0	356,041	3.9

Table 4D: Minority Enrollment by Sex/Gender for Intramural NIH Clinical Research at U.S. Sites from FY2013 to 2018

Fiscal Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2013	Female	265,994	11.6	2,292,337	57.2
	Male	379,182	16.5	1,645,638	41.1
	Unknown	9,998	0.4	70,618	1.8
2014	Female	240,325	10.6	2,269,003	68.5
	Male	183,453	8.1	984,894	29.7
	Unknown	9,880	0.4	58,646	1.8
2015	Female	191,976	9.1	2,102,149	68.6
	Male	159,931	18.2	878,691	28.7
	Unknown	5,005	6.1	81,614	2.7
2016	Female	231,317	10.6	2,176,309	68.0
	Male	173,222	19.3	896,680	28.0
	Unknown	5,065	4.0	127,730	4.0
2017	Female	277,390	22.6	1,227,511	49.1
	Male	223,321	19.2	1,165,510	46.6
	Unknown	1,393	1.3	107,302	4.3
2018	Female	133,847	17.5	762,803	50.7
	Male	96,678	13.7	707,730	47.1
	Unknown	631	1.9	32,984	2.2

Table 4E: Minority Enrollment by Sex/Gender for All NIH-Defined Phase III Clinical Trials from FY2013 to 2018

Fiscal Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2013	Female	416,971	82.3	506,732	73.3
	Male	105,242	20.8	179,220	25.9
	Unknown	4,209	0.8	5,071	0.7
2014	Female	392,878	82.2	478,222	60.0
	Male	230,310	48.2	314,310	39.4
	Unknown	4,268	0.9	4,732	0.6
2015*	Female	1,030,479	94.4	1,091,910	67.4
	Male	442,084	87.1	507,561	31.3
	Unknown	19,685	98.2	20,037	1.2
2016*	Female	1,323,770	94.8	1,396,503	65.6
	Male	645,583	90.8	710,818	33.4
	Unknown	22,884	99.2	23,068	1.1
2017	Female	272,200	50.8	535,440	59.0
	Male	186,587	50.2	371,636	40.9
	Unknown	259	45.7	567	0.1
2018	Female	103,639	39.8	260,652	62.4
	Male	56,626	36.3	155,960	37.3
	Unknown	350	31.8	1,101	0.3

**FY2015 and FY2016 includes data from large foreign Phase III trials which tend to have larger numbers of participants than domestic Phase III trials.*

Table 4F: Minority Enrollment by Sex/Gender for All NIH-Defined Phase III Clinical Trials at U.S. Sites from FY2013 to 2018

Fiscal Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2013	Female	51,289	37.4	137,062	57.9
	Male	28,300	28.7	98,753	41.7
	Unknown	19	2.2	877	0.4
2014	Female	52,725	39.8	132,354	52.1
	Male	43,130	32.6	121,366	47.7
	Unknown	79	0.1	543	0.2
2015	Female	35,848	42.7	83,932	48.3
	Male	34,362	38.5	89,228	51.4
	Unknown	151	31.5	480	0.3
2016	Female	34,156	41.0	83,278	49.0
	Male	38,140	44.1	86,425	50.9
	Unknown	22	11.6	190	0.1
2017	Female	75,081	22.7	330,307	60.0
	Male	48,134	21.9	220,245	40.0
	Unknown	32	13.9	230	0.0
2018	Female	63,253	30.1	209,985	62.6
	Male	40,831	32.7	124,830	37.2
	Unknown	86	14.9	576	0.2

Table 4G: Minority Enrollment by Sex/Gender for Extramural NIH-Defined Phase III Clinical Trials at U.S. Sites from FY2013 to 2018

Fiscal Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2013	Female	48,209	37.3	129,126	57.1
	Male	27,802	21.5	96,201	42.5
	Unknown	19	0.0	877	0.4
2014	Female	49,653	39.7	125,118	50.9
	Male	42,725	34.1	119,950	48.8
	Unknown	79	0.1	543	0.2
2015	Female	32,534	43.5	74,759	46.4
	Male	33,493	39.0	85,794	53.3
	Unknown	149	31.2	477	0.3
2016	Female	30,878	41.2	74,969	47.2
	Male	37,279	44.6	83,586	52.7
	Unknown	19	10.2	186	0.1
2017	Female	72,140	22.4	322,436	59.6
	Male	47,601	21.8	217,976	40.3
	Unknown	31	13.6	228	0.0
2018	Female	62,460	30.2	206,817	63.1
	Male	39,757	33.1	120,274	36.7
	Unknown	68	12.5	542	0.2

Table 4H: Minority Enrollment by Sex/Gender for Intramural NIH-Defined Phase III Clinical Trials at U.S. Sites from FY2013 to 2018

Fiscal Year	Sex	Total Minority Enrollees	% of Minority Enrollees	Total Enrollees	% Total
2013	Female	3,080	38.8	7,936	75.7
	Male	498	19.5	2,552	24.3
	Unknown	0	0.0	0	0.0
2014	Female	3,072	42.5	7,236	83.6
	Male	405	28.6	1,416	16.4
	Unknown	0	0.0	0	0.0
2015	Female	3,314	36.1	9,173	72.7
	Male	869	25.3	3,434	27.2
	Unknown	2	66.7	3	0.0
2016	Female	3,278	39.5	8,309	74.5
	Male	861	30.3	2,839	25.5
	Unknown	3	75.0	4	0.0
2017	Female	2,941	37.4	7,871	77.6
	Male	533	23.5	2,269	22.4
	Unknown	1	50.0	2	0.0
2018	Female	793	25.0	3,168	40.8
	Male	1,074	23.6	4,556	58.7
	Unknown	18	52.9	34	0.4

Table 4I: Enrollment for All NIH-Defined Clinical Research, Sex/Gender by Race and Ethnicity for FY 2017 and 2018

Fiscal Year	Sex/ Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2017	Female	69,566	0.7	2,479,094	26.2	1,273,628	13.4	15,936	0.2	4,784,118	50.5	222,888	2.4	625,034	6.6	8,040,269	84.9	743,453	7.9	686,542	7.2
	Male	59,547	0.6	3,546,916	35.0	1,037,346	10.2	11,592	0.1	4,569,107	45.1	213,224	2.1	689,423	6.8	8,755,704	86.5	622,140	6.1	749,311	7.4
	Unknown	1,495	0.3	15,525	3.3	14,435	3.1	335	0.1	45,789	9.7	1,947	0.4	391,844	83.1	124,896	26.5	13,038	2.8	333,436	70.7
2018	Female	68,459	1.0	659,027	9.8	1,159,229	17.3	18,814	0.3	3,990,907	59.5	198,427	3.0	616,701	9.2	5,429,923	80.9	665,003	9.9	616,638	9.2
	Male	54,612	1.0	475,745	8.4	877,026	15.5	11,971	0.2	3,476,108	61.3	158,620	2.8	614,393	10.8	4,549,129	80.3	519,087	9.2	600,259	10.6
	Unknown	1,376	0.3	23,931	5.5	9,701	2.2	269	0.1	33,212	7.7	3,859	0.9	361,775	83.3	54,912	12.6	6,759	1.6	372,452	85.8

Table 4J: US Site Enrollment for All NIH-Defined Clinical Research, Sex/Gender by Race and Ethnicity for FY 2017 and 2018

Fiscal Year	Sex/ Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2017	Female	62,535	1.0	221,182	3.4	965,314	14.9	15,813	0.2	4,460,475	68.7	198,198	3.1	568,122	8.8	5,294,546	81.6	616,218	9.5	580,875	8.9
	Male	53,243	0.8	197,644	3.1	833,463	13.2	11,454	0.2	4,355,444	69.1	190,815	3.0	660,280	10.5	5,016,896	79.6	571,462	9.1	713,985	11.3
	Unknown	1,492	0.3	3,377	0.8	10,172	2.3	334	0.1	43,852	10.0	1,886	0.4	376,071	86.0	105,094	24.0	12,031	2.8	320,059	73.2
2018	Female	55,126	1.0	254,694	4.7	807,630	14.9	18,566	0.3	3,560,776	65.8	163,400	3.0	553,213	10.2	4,385,098	81.0	540,467	10.0	487,840	9.0
	Male	41,266	0.9	165,749	3.5	673,825	14.1	11,738	0.2	3,199,798	67.0	130,252	2.7	553,228	11.6	3,794,068	79.4	437,610	9.2	544,178	11.4
	Unknown	865	0.2	2,979	0.8	6,568	1.7	269	0.1	31,502	8.1	3,784	1.0	343,058	88.2	28,723	7.4	5,071	1.3	355,231	91.3

Table 4K: US Site Enrollment for NIH-Defined Extramural Clinical Research, Sex/Gender by Race and Ethnicity for FY 2017 and 2018

Fiscal Year	Sex/ Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2017	Female	46,420	0.9	191,624	3.6	807,200	15.3	12,921	0.2	3,532,457	67.1	190,368	3.6	483,138	9.2	4,322,302	82.1	549,398	10.4	392,428	7.5
	Male	39,098	0.8	166,928	3.2	726,767	14.1	8,869	0.2	3,422,215	66.6	185,020	3.6	587,936	11.4	4,096,355	79.7	505,440	9.8	535,038	10.4
	Unknown	1,478	0.4	3,321	1.0	9,765	3.0	325	0.1	43,009	13.0	1,847	0.6	270,137	81.9	100,696	30.5	11,141	3.4	218,045	66.1
2018	Female	40,583	0.9	242,342	5.2	729,388	15.7	16,450	0.4	2,968,034	63.8	157,837	3.4	495,968	10.7	3,695,395	79.5	516,880	11.1	438,327	9.4
	Male	28,828	0.7	153,018	3.8	627,259	15.4	9,904	0.2	2,612,309	64.2	126,228	3.1	510,580	12.6	3,145,977	77.3	416,898	10.2	505,251	12.4
	Unknown	863	0.2	2,975	0.8	6,494	1.8	268	0.1	31,362	8.8	3,776	1.1	310,303	87.2	25,610	7.2	4,528	1.3	325,903	91.5

Table 4L: US Site Enrollment for NIH-Defined Intramural Clinical Research, Sex/Gender by Race for FY 2017 and 2018

Fiscal Year	Sex/ Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2017	Female	16,115	1.3	29,558	2.4	158,114	12.9	2,892	0.2	928,018	75.6	7,830	0.6	84,984	6.9	972,244	79.2	66,820	5.4	188,447	15.4
	Male	14,145	1.2	30,716	2.6	106,696	9.2	2,585	0.2	933,229	80.1	5,795	0.5	72,344	6.2	920,541	79.0	66,022	5.7	178,947	15.4
	Unknown	14	0.0	56	0.1	407	0.4	9	0.0	843	0.8	39	0.0	105,934	98.7	4,398	4.1	890	0.8	102,014	95.1
2018	Female	14,543	1.9	12,352	1.6	78,242	10.3	2,116	0.3	592,742	77.7	5,563	0.7	57,245	7.5	689,703	90.4	23,587	3.1	49,513	6.5
	Male	12,438	1.8	12,731	1.8	46,566	6.6	1,834	0.3	587,489	83.0	4,024	0.6	42,648	6.0	648,091	91.6	20,712	2.9	38,927	5.5
	Unknown	2	0.0	4	0.0	74	0.2	1	0.0	140	0.4	8	0.0	32,755	99.3	3,113	9.4	543	1.6	29,328	88.9

Table 4M: Enrollment of All NIH-Defined Phase III Trials, Sex/Gender by Race and Ethnicity for FY 2017 and 2018

Fiscal Year	Sex/ Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2017	Female	1,513	0.3	157,501	29.4	82,261	15.4	378	0.1	266,794	49.8	3,088	0.6	23,905	4.5	470,908	87.9	31,773	5.9	32,759	6.1
	Male	895	0.2	116,709	31.4	51,355	13.8	239	0.1	184,369	49.6	1,244	0.3	16,825	4.5	318,850	85.8	18,208	4.9	34,578	9.3
	Unknown	2	0.4	8	1.4	226	39.9	1	0.2	10	1.8	9	1.6	311	54.9	334	58.9	18	3.2	215	37.9
2018	Female	1,413	0.5	9,625	3.7	53,136	20.4	499	0.2	166,346	63.8	10,538	4.0	19,095	7.3	221,270	84.9	32,015	12.3	7,367	2.8
	Male	976	0.6	9,328	6.0	26,195	16.8	347	0.2	103,532	66.4	4,754	3.0	10,828	6.9	132,944	85.2	17,361	11.1	5,655	3.6
	Unknown	1	0.1	8	0.7	273	24.8	1	0.1	65	5.9	6	0.5	747	67.8	538	48.9	70	6.4	493	44.8

Table 4N: US Site Enrollment for NIH-Defined Phase III Trials, Sex/Gender by Race and Ethnicity for FY 2017 and 2018

Fiscal Year	Sex/ Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2017	Female	1,465	0.4	7,123	2.2	44,715	13.5	346	0.1	258,888	78.4	3,041	0.9	14,729	4.5	278,035	84.2	22,256	6.7	30,016	9.1
	Male	839	0.4	4,918	2.2	26,665	12.1	204	0.1	172,691	78.4	1,173	0.5	13,755	6.2	171,817	78.0	16,209	7.4	32,219	14.6
	Unknown	1	0.4	1	0.4	7	3.0	1	0.4	8	3.5	9	3.9	203	88.3	27	11.7	15	6.5	188	81.7
2018	Female	1,352	0.6	5,230	2.5	30,730	14.6	466	0.2	157,357	74.9	7,628	3.6	7,222	3.4	186,030	88.6	20,606	9.8	3,349	1.6
	Male	896	0.7	3,761	3.0	18,598	14.9	302	0.2	91,689	73.5	4,271	3.4	5,313	4.3	107,031	85.7	15,071	12.1	2,728	2.2
	Unknown	1	0.2	1	0.2	18	3.1	1	0.2	64	11.1	6	1.0	485	84.2	70	12.2	64	11.1	442	76.7

Table 4O: Enrollment for NIH-Defined US Site Extramural Phase III Trials for FY 2017 and 2018

Fiscal Year	Sex/ Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2017	Female	1,118	0.3	6,882	2.1	42,740	13.3	341	0.1	253,815	78.7	3,006	0.9	14,534	4.5	270,690	84.0	21,824	6.8	29,922	9.3
	Male	723	0.3	4,843	2.2	26,418	12.1	203	0.1	170,935	78.4	1,159	0.5	13,695	6.3	169,654	77.8	16,109	7.4	32,213	14.8
	Unknown	1	0.4	1	0.4	6	2.6	1	0.4	8	3.5	9	3.9	202	88.6	26	11.4	15	6.6	187	82.0
2018	Female	1,189	0.6	5,126	2.5	30,377	14.7	466	0.2	154,974	74.9	7,523	3.6	7,162	3.5	182,963	88.5	20,512	9.9	3,342	1.6
	Male	785	0.7	3,584	3.0	18,041	15.0	301	0.3	88,189	73.3	4,152	3.5	5,222	4.3	102,609	85.3	14,944	12.4	2,721	2.3
	Unknown	1	0.2	1	0.2	18	3.3	1	0.2	64	11.8	6	1.1	451	83.2	70	12.9	46	8.5	426	78.6

Table 4P: US Site Enrollment for NIH-Defined Intramural Phase III Trials, Sex/Gender by Race and Ethnicity for FY 2017 and 2018

Fiscal Year	Sex/ Gender	American Indian/ Alaska Native	%	Asian	%	Black/ African American	%	Native Hawaiian/ Pacific Islander	%	White	%	More Than One Race	%	Unknown/ Not Reported	%	Not Hispanic	%	Hispanic	%	Unknown/ Not Reported	%
2017	Female	347	4.4	241	3.1	1,975	25.1	5	0.1	5,073	64.5	35	0.4	195	2.5	7,345	93.3	432	5.5	94	1.2
	Male	116	5.1	75	3.3	247	10.9	1	0.0	1,756	77.4	14	0.6	60	2.6	2,163	95.3	100	4.4	6	0.3
	Unknown	0	0.0	0	0.0	1	50.0	0	0.0	0	0.0	0	0.0	1	50.0	1	50.0	0	0.0	1	50.0
2018	Female	163	5.1	104	3.3	353	11.1	0	0.0	2,383	75.2	105	3.3	60	1.9	3,067	96.8	94	3.0	7	0.2
	Male	111	2.4	177	3.9	557	12.2	1	0.0	3,500	76.8	119	2.6	91	2.0	4,422	97.1	127	2.8	7	0.2
	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	34	100.0	0	0.0	18	52.9	16	47.1

Appendix E. 2019 Biennial Advisory Council Reports Certifying Compliance With NIH Policy on Inclusion Guidelines

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

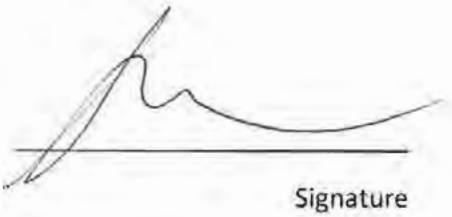
National Institutes of Health

Office of the Director

FY 2017-2018 Biennial Advisory Council Reports

Certifying Compliance with

NIH Policy on Inclusion Guidelines



Signature

Eric Dishman
Director
All of Us Research Program

3-22-19

Date

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of the Director

FY 2017-2018 Biennial Advisory Council Reports

Certifying Compliance with

NIH Policy on Inclusion Guidelines

Signature

Matthew W. Gillman, M.D.
Director
The Environmental influences on Child Health Outcomes Program

02-08-2019

Date

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Signature

Roger I. Glass, M.D., Ph.D.
Director of the Fogarty International Center
and Associate Director for International Research

1/31/2019

Date

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Signature

Christopher P. Austin, M.D.
Director
National Center for Advancing Translational Sciences

March 20, 2019

Date

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Signature

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

2/13/19.

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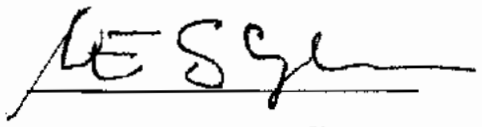

Signature

Norman E. Sharpless, M.D.
Director
National Cancer Institute

2-11-19

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Paul A. Sieving, M.D., Ph.D.
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National Eye Institute

Jan 15, 2019

Date

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Eric D. Green, M.D., Ph.D.
Director
National Human Genome Research Institute

2/21/2019

Date

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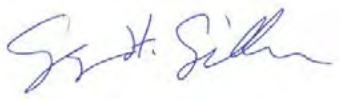

Signature

Gary H. Gibbons, M.D.
Director
National Heart, Lung, and Blood Institute

02/11/2019

Date

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Richard J. Hodes, M.D.
Director
National Institute on Aging

2/28/19

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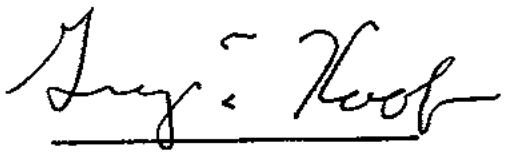

Signature

George F. Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism

2-12-2019

Date

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Anthony S. Fauci, M.D.
Director

National Institute of Allergy and Infectious Diseases

02/15/2019

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Signature

Robert H. Carter, M.D.
Acting Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases

2-11-19

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Signature

Jill Heemskerk, Ph.D.
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National Institute of Biomedical Imaging and Bioengineering

1/4/19

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Diana W. Bianchi MD

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Diana W. Bianchi, M.D.
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Eunice Kennedy Shriver
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02-19-2019

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Nora D. Volkow, M.D.
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02/08/2019

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Judith A Cooper

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Judith Cooper, Ph.D.
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National Institute on Deafness and Other Communication Disorders

2.4.19

Date

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Signature

Martha J. Somerman, D.D.S., Ph.D.
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National Institute of Dental and Craniofacial Research

2/6/2019

Date

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Griffin P. Rogers, M.D., M.A.C.P.
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2/19/2019.

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Linda S. Birnbaum

Signature

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director
National Institute of Environmental Health Sciences
and National Toxicology Program

2/8/2019

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National Institute of General Medical Sciences

2/19/2019

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Joshua A. Gordon, M.D., Ph.D.
Director
National Institute of Mental Health

2/11/19

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Signature

Eliseo J. Pérez-Stable, M.D.
Director
National Institute on Minority Health and Health Disparities

02/26/2019

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Signature

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

2/8/2019

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Ann Cashion, Ph.D., R.N., F.A.A.N.
Acting Director
National Institute of Nursing Research

2/11/19

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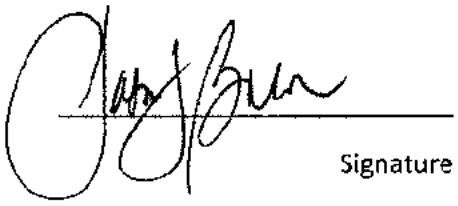

Signature

Patricia F. Brennan, Ph.D., R.N.
Director
National Library of Medicine

2/7/19

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Signature

Franziska Grieder, D.V.M., Ph.D.
Director of Office of Research Infrastructure Programs
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Office of the Director

1·28·2019

Date

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