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Exploring the Impact of the 21st Century Cures Act

Understanding Sex- and Gender-Based
Differences in Disease and Participation
of Women in Clinical Research

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The Milken Institute recognizes the integral role of equality, diversity, and inclusion in driving shared prosperity. Our research and programmatic work reflect the value in all human talent and the right to build a meaningful life regardless of biological sex, gender, race, sexual orientation, or socioeconomic status. The Institute is committed to elevating these principles across industries, from finance and business to government and health care. Women are essential stakeholders in health care, serving as workers, caregivers, and consumers—yet they have not been afforded an equal voice in its leadership or research.

This inequality is why the nonprofit Society for Women's Health Research (SWHR) was founded in 1990 to ensure the appropriate inclusion of women in medical research at a time when they were intentionally excluded. Thanks in part to SWHR's advocacy efforts, women are now routinely included in most clinical trials, and offices dedicated to women's health exist across the federal government. SWHR has a long and successful history of encouraging investment in women's health and urging researchers to consider sex as a biological variable to uncover differences between women and men in the prevention, diagnosis, and treatment of disease.



SWHR and FasterCures, a Center of the Milken Institute, advocated for the 21st Century Cures Act, which resulted in positive changes for women's health research. The Cures Act, signed into law on December 13, 2016, aims to advance biomedical innovation, support research, and modernize medical product development to get treatments to patients more quickly. Through [FasterCures' 21st Century Cures tracker](#), FasterCures monitors the law's implementation.

In this brief report, FasterCures and SWHR explore how the Cures Act has affected the landscape for women in clinical research and understanding of sex- and gender-based differences in disease.

Sex and gender play critical roles in the risk, pathophysiology, presentation, diagnosis, treatment, and management of disease.

- *Sex* refers to the classification of living things according to reproductive organs and functions assigned by chromosomal complement.
- *Gender* refers to the social, cultural, and environmental influences on the biological factors of women or men. Gender is rooted in biology and shaped by environment and experience.¹



21st Century Cures Act: Key Impacts to Date

Consideration of Sex as a Biological Variable

- ✓ National Institutes of Health (NIH) formed the Advisory Committee to the Director (ACD) Peer Review Working Group—RIGOR, which first met in May 2017.
 - In April 2018, the working group presented its recommendations, including changing the NIH funding application and increasing training on reproducibility and rigor for applicants.
 - NIH is implementing these changes, including updating its [Rigor and Reproducibility webpage](#) and modifying the NIH funding application.

Increased Transparency on NIH-Funded Clinical Research Inclusion Data

- ✓ NIH created a research, condition, and disease classification ([RCDC Inclusion Statistics Report webpage](#)), which shows the percentage of female participants in trials for 269 diseases and conditions.

Reporting of Analyses by Sex/Gender in Phase III Clinical Trials

- ✓ NIH amended its [NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research](#) to require researchers conducting applicable phase III clinical trials to ensure that results of valid analyses by sex/gender, race, and/or ethnicity are submitted to [ClinicalTrials.gov](#).

Research on Pregnant Women and Lactating Women

- ✓ NIH established a Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) in March 2017.
 - In September 2018, PRGLAC submitted a [report](#) to the Secretary of Health and Human Services (HHS) and Congress with recommendations to improve the development of safe and effective therapies for pregnant and lactating women.
 - In March 2019, HHS extended the term of the PRGLAC Task Force for 2 additional years to provide advice and guidance to HHS on the implementation of its recommendations.



THE IMPORTANCE OF UNDERSTANDING SEX- AND GENDER-BASED DIFFERENCES IN DISEASE AND PARTICIPATION OF WOMEN IN CLINICAL RESEARCH

Until 1993, women of childbearing age were excluded from participation in most clinical trials to test new drugs (see Figure 1, below).² Because we did not study women in clinical research, we had no way of knowing whether new drugs would work for women until after the product entered the market. This bias put the health of women at risk, as evidenced by a government report³ that revealed that 8 of 10 drugs withdrawn from the market from 1997 to 2001 posed greater health risks for women than for men.

The 1990s brought about a shift in thinking as women’s health advocates such as SWHR decried the lack of research on women and sex-based biological differences in health and disease. [Resulting policy changes](#) at the NIH and Food and Drug Administration (FDA) sought to ensure women’s inclusion in research and began to change the culture of medical research.

Today, we continue to learn about how women react to drugs and experience disease differently from men, leading to sex-based clinical care paradigms replacing a “one-sex-fits-all” default. These sex-based differences are not rare occurrences; researchers have identified differences in many fields, including cardiovascular disease, pharmacology, oncology, liver disease, and osteoporosis.⁴

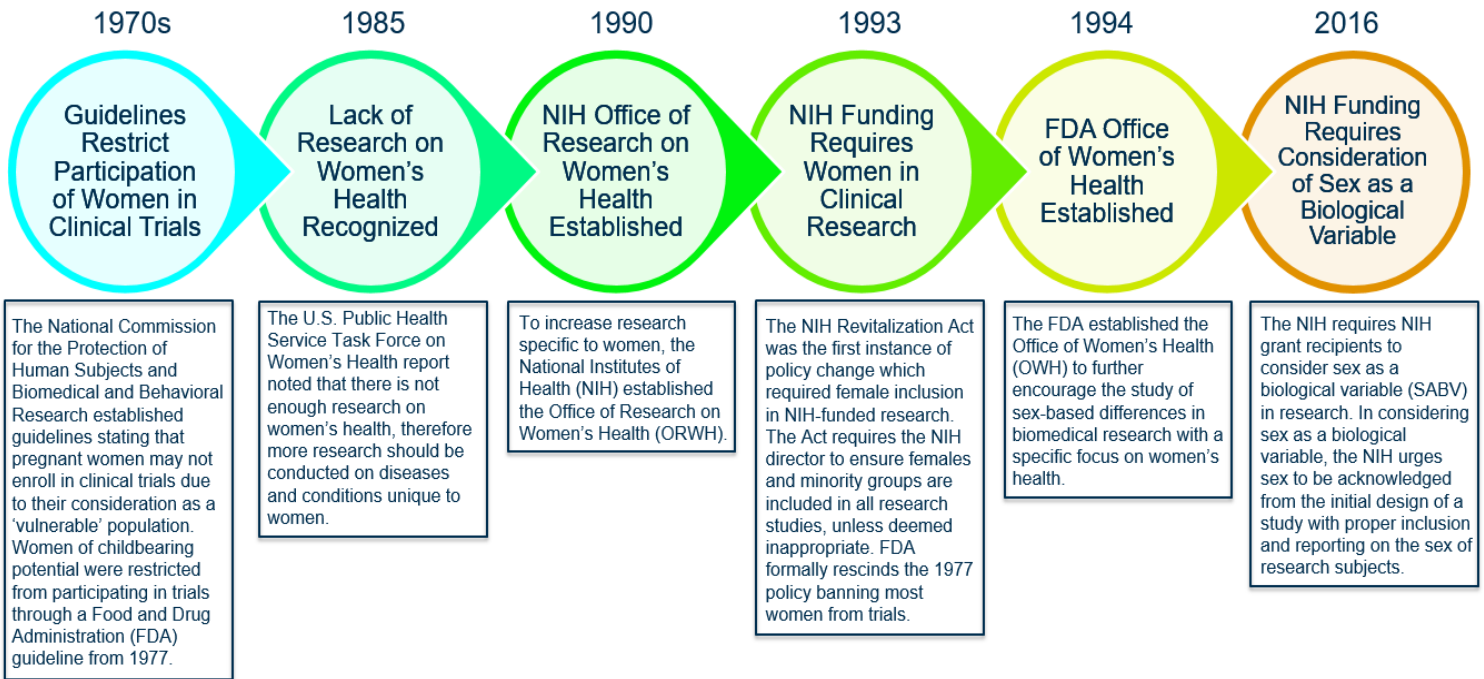
Understanding sex differences does not start with clinical trials; rather, it starts with basic cellular and animal model research and the importance of incorporating sex as a biological variable (SABV) in this work. Similar to clinical trials, basic research has typically been conducted using male cells, male animals, or a male model of disease. Overcoming this historical norm will require a concerted effort to change scientific culture in many research fields. Advancing research and health care requires action and transparency. If sex-based analyses are not conducted and reported, we cannot learn from them.

Despite the progress being made in women’s health research, pregnant and lactating women remain excluded from most medical research. As a result, little information exists on the impact of drugs on fetuses and breastfeeding babies—a potentially dangerous situation, because 90 percent of women take at least one medication during pregnancy, and more than 50 percent of women take one or more medications during the postpartum period.⁵ However, this topic has become an area of increased focus in recent years, with NIH evaluating the research gaps on safety of medications and biologic products used during pregnancy and lactation, and [FDA releasing several draft guidance for industry](#) in the past 2 years.^{6,7,8,9} SWHR considers research on pregnant and lactating women as the next frontier for the inclusion of women in medical research.

Advancing research and health care requires action and transparency. If sex-based analyses are not conducted and reported, we cannot learn from them.



Figure 1: A Brief History of Women in Clinical Trials and Research on Sex-based Differences



Source: Adapted from Liu, K., and N.A. Dipietro Mager. 2016. Women's involvement in clinical trials: historical perspective and future implications. *Pharm Pract (Granada)*, 14(1):708.

Consideration of sex may be critical to the interpretation, validation, and generalizability of research findings. – 2015 NIH notice

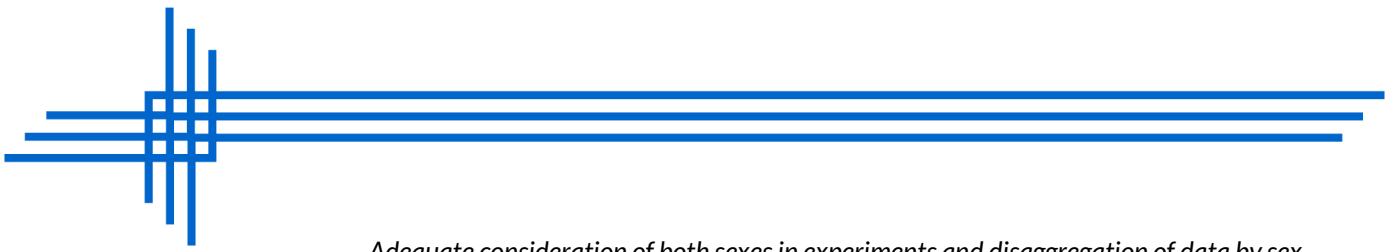
THE CURES ACT'S IMPACT ON BASIC RESEARCH

Consideration of Sex as a Biological Variable

The historical reliance on male cells, animals, and disease models in research originated as a result of the unfounded¹⁰ idea that females will demonstrate significant variability due to their estrous cycle¹¹ and the fear of causing harm to a potential pregnancy. Using only males in research misses an opportunity to observe any sex-based differences, distorts study conclusions, reduces the generalizability of the results, and impedes discoveries that could lead to new treatments for women.

In June 2015, NIH released a notice, [Consideration of Sex as a Biological Variable in NIH-funded Research](#), explaining that:

“Accounting for sex as a biological variable begins with the development of research questions and study design. It also includes data collection and analysis of results, as well as reporting of findings. Consideration of sex may be critical to the interpretation, validation, and generalizability of research findings.”



Adequate consideration of both sexes in experiments and disaggregation of data by sex allows for sex-based comparisons and may inform clinical interventions. Appropriate analysis and transparent reporting of data by sex may therefore enhance the rigor and applicability of preclinical biomedical research.”¹²

Since January 2016, NIH has required researchers to explain in their grant applications how they factor SABV into their research designs, analyses, and reporting (or justify why single-sex studies are appropriate), and NIH grant reviewers evaluate the adequacy of their research plan concerning SABV.¹³

The Cures Act supported NIH’s existing policies on SABV by directing NIH to “develop policies for projects of basic research funded by [NIH] to assess (a) relevant biological variables including sex, as appropriate; and (b) how differences between male and female cells, tissues, or animals may be examined and analyzed.”¹⁴

In developing, updating, or revising SABV policies, NIH must consult with the Office of Research on Women’s Health (ORWH), the Office of Laboratory Animal Welfare, and appropriate members of the scientific and academic communities. In addition, the Cures Act required NIH to ensure that NIH-funded basic research complies with these policies and to encourage that the results of such research be reported disaggregated by sex, as appropriate.¹⁵

Another provision of the Cures Act required NIH to convene a working group to issue recommendations for a formal policy on rigor and reproducibility of scientific research funded by NIH, including consideration of SABV (and other relevant biological variables) in preclinical experiment design.¹⁶ The NIH director is required to consider the recommendations and develop or update policies as appropriate, and NIH is directed to issue a report to Congress regarding the recommendations and any subsequent policy changes implemented.¹⁷

To meet this requirement and to build on its notice, [Implementing Rigor and Transparency in NIH & AHRQ Research Grant Applications](#),¹⁸ NIH formed the Advisory Committee to the Director Peer Review Working Group—RIGOR, which first met in May 2017.¹⁹ In April 2018, the working group presented its recommendations, which include changing the NIH funding application to add resources (e.g., linked to the application instructions), increasing training on reproducibility and rigor for applicants, and assessing applicants’ and reviewers’ adherence to the policy through continued outcomes evaluation.²⁰

NIH is implementing changes, including updating its [Rigor and Reproducibility webpage](#) and modifying the NIH funding application (e.g., clarify “scientific premise”²¹).



THE CURES ACT'S IMPACT ON WOMEN IN CLINICAL RESEARCH

Increased Transparency of NIH-Funded Clinical Research Inclusion Data

NIH has reported aggregate enrollment information for historically underrepresented populations for NIH-funded clinical research since 1994.²² Building on that, the Cures Act directed NIH to make publicly available on its website information on study populations of NIH-funded clinical research, including women, disaggregated by research area, condition, and disease categories.²³ This information can be found on the NIH research, condition, and disease classification [Inclusion Statistics Report webpage](#), which shows the percentage of female participants in trials for 269 diseases and conditions.²⁴ According to the report, “in Fiscal Year (FY) 2018 over 52% of participants in NIH-supported clinical research were women, while about 29% of participants were members of racial minority groups, and 9% were ethnic minorities.”²⁵

According to NIH, disaggregating and disclosing the number of women in clinical trials by disease or condition is a key development:

“As part of overall RCDC reporting, the availability of inclusion data on research participants is another important step in increasing transparency of NIH-supported clinical research. It also helps us understand the generalizability of NIH research across populations. In future years, NIH plans to add data on age at enrollment of participants and allow users to view trends over time. We look forward to increased understanding of the distribution of participants in our research to ensure the knowledge gained from NIH research is applicable to those populations with the condition or disease under study.”²⁶

REPORTING OF ANALYSES BY SEX AND GENDER IN PHASE III CLINICAL TRIALS

The Cures Act also required NIH to update its guidelines on the inclusion of women and minorities in clinical research to “reflect the science regarding sex differences”²⁷ and improve adherence to reporting requirements by having “entities conducting applicable clinical trials submit results of valid analyses by sex/gender, race and ethnicity in ClinicalTrials.gov.”²⁸ As a way to encourage compliance, the Cures Act directed NIH to consider whether researchers have previously complied with this requirement when making new grant funding decisions, in addition to encouraging compliance by other means, as appropriate.²⁹

In response, in November 2017, NIH amended its [NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research](#) to require researchers conducting applicable phase III clinical trials to “ensure results of valid analyses by sex/gender, race, and/or ethnicity are submitted to [ClinicalTrials.gov](#).”³⁰



RESEARCH ON PREGNANT AND LACTATING WOMEN

The Cures Act sought to address the significant gap in research on safe and effective therapies for pregnant and lactating women by requiring NIH to establish a Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) within 90 days of enactment for an initial 2-year term.³¹

To date, insufficient attention has been paid to pregnant and lactating women, and the dearth of research means that these women and their health care providers lack the information needed to make knowledgeable decisions about medication use.

Only in 2019 were pregnant women no longer presented as an example of a “vulnerable” population,³² having been labeled as such and restricted from participating in clinical trials since 1975 due to concerns about potential teratogenic effects and adverse pregnancy outcomes. In addition, it wasn't until 2017 that NIH began to track research funding for pregnancy, breastfeeding, and maternal health in its Research, Condition and Disease Categorization (RCDC) database. These category additions are thanks to the PRGLAC task force.

The task force aims to guide the Department of Health and Human Services (HHS) on how to identify and address the gaps in knowledge that exist regarding drug safety and efficacy in pregnant and lactating women. Task force membership consists of the heads of NIH and other national research agencies and institutes, the FDA commissioner, and representatives from medical societies, nonprofit organizations, industry, and others with expertise on pregnant women, lactating women, or children.³³

The Cures Act directed the PRGLAC Task Force to meet at least twice a year, convene public meetings, and send a report to Congress within 18 months of task force establishment.³⁴ The Cures Act also charged HHS to review the PRGLAC report and, if needed, update regulations and guidance regarding the inclusion of pregnant and lactating women in clinical research.³⁵

Officially established in March 2017, the PRGLAC Task Force has held six public meetings as of the date of this publication^{36, 37} and in September 2018 submitted a [report](#) to the secretary of HHS and Congress that addressed the five topics required by the Cures Act:

1. A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies
2. Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research



3. Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women
4. Identification of federal activities
5. Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women

The 15 recommendations to improve the development of safe and effective therapies for pregnant and lactating women (see Appendix A) include expanding the workforce of clinicians and researchers with expertise in obstetric and lactation pharmacology and therapeutics, removing regulatory barriers to research in pregnant women, and creating a public awareness campaign around research on pregnant and lactating women. Importantly, the report highlighted:

“...the need to alter cultural assumptions that have significantly limited scientific knowledge of therapeutic product safety, effectiveness, and dosing for pregnant and lactating women. This cultural shift is necessary to emphasize the importance and public health significance of building a knowledge base to inform medical decision-making for these populations.”³⁸

In March 2019, HHS extended the term of the PRGLAC Task Force for 2 years to guide HHS on the implementation of its recommendations.³⁹ Six working groups across agencies have been created to address the recommendations, and the task force’s meeting schedule is available on its [webpage](#).⁴⁰

CONCLUSION AND FUTURE DIRECTIONS

The 21st Century Cures Act has advanced the field of women’s health in significant ways and has emphasized the critical importance of women’s participation in clinical trials and the study and reporting of sex- and gender-based differences in disease.

The Cures Act achieved this by the following:

- **Bolstering NIH’s stance on the importance of incorporating sex as a biological variable** and instructing the agency to develop new policies for basic research to assess biological variables (including sex) and how differences between male and female cells, tissues, or animals may be examined
- **Forming an NIH working group to develop recommendations to increase rigor and transparency in research** through changes to NIH’s grant application and increased training for researchers, including on SABV



- **Accelerating existing NIH initiatives on women’s health research**, such as directing the agency to amend its policies to ensure that the results of sex/gender analyses in clinical trials are submitted to [ClinicalTrials.gov](https://clinicaltrials.gov) and providing provisions that encourage researcher compliance
- **Creating the RCDC Inclusion Statistics Report webpage** to publicly disclose the number of women in NIH-funded clinical trials by disease or condition
- **Establishing the PRGLAC Task Force** to give much-needed attention to increasing research on pregnant and lactating women
- **Increasing collaboration and engagement across the NIH Institutes and Centers**, resulting in more coordinated efforts to advance women’s health research, as illustrated by the [2019-2023 Trans-NIH Strategic Plan for Women’s Health Research](#)

Scientific culture will change to serve women’s health better as more researchers report the sex of the cells, tissues, and animal models they use, consider SABV in study design, and conduct and report the results of sex-based analyses. As sex differences are observed in preclinical studies, these learnings will influence clinical trial design and produce important hypotheses to test, ushering in a new era of research norms.

Even with recent progress, women’s health research is still considered by many to be a relatively young and niche area, despite serving half of the world’s population. To make women’s health mainstream, policy makers should create incentives to encourage financial investment in women’s health research across public and private sectors.

The study of SABV and research on conditions and diseases that are specific to women’s health, or that present differently in women than men, must be a priority for federally funded research. Continuation of work led by NIH’s PRGLAC Task Force is also essential to advancing the participation of pregnant and lactating women in clinical trials to shrink research and knowledge gaps on safe and effective therapies for these women.

In addition, a deeper analysis of NIH’s RCDC database will help uncover where investment gaps persist so we can optimize the identification of research, condition, and disease categories that need more attention in order to improve the health of women across the lifespan.

NIH should also consider expanding initiatives such as the Sex & Gender Administrative Supplement Program, which grants supplemental funding as an incentive to add a sex component to an existing research program. ORWH has invested almost \$33 million in the program since fiscal year 2013 to “support research



highlighting the impact of sex/gender influences in human health and illness, including basic, preclinical, clinical, translational, and behavioral studies.”⁴¹

To achieve optimal health outcomes for women, the scientific community must engage in an open discussion about the opportunities and challenges around women’s health research so that we can advance biomedical innovation in ways that speed the development of new therapies for women and optimize the delivery of care for women.



APPENDIX A: PRGLAC REPORT RECOMMENDATIONS

Task Force on Research Specific to Pregnant Women and Lactating Women Recommendations

1. Include and integrate pregnant women and lactating women in the clinical research agenda
2. Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women
3. Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics
4. Remove regulatory barriers to research in pregnant women
5. Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women
6. Develop and implement evidence-based communication strategies with healthcare providers on information relevant to research on pregnant women and lactating women
7. Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the NIH Best Pharmaceuticals for Children Act (BPCA) as a model
8. Reduce liability to facilitate an evidence base for new therapeutic products that may be used by women who are or may become pregnant and by lactating women
9. Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research
10. Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women
11. Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women
12. Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women
13. Optimize registries for pregnancy and lactation
14. The HHS Secretary should consider exercising the authority provided in law to extend the PRGLAC Task Force when its charter expires in March 2019
15. Establish an Advisory Committee to monitor and report on implementation of recommendations, updating regulations, and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research



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Dr. Michael Lauer, deputy director for extramural research at NIH and his team

Dr. Sabra Klein, associate professor at the Johns Hopkins University Bloomberg School of Public Health

ABOUT THE AUTHORS

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Emily Ortman is director of communications at the Society for Women’s Health Research, where she leads development of strategic communications efforts to maximize the reach and impact of SWHR’s scientific programs and policy activities. Before joining SWHR, Ortman worked at the Society for Neuroscience (SfN), where she coordinated press activities for hundreds of reporters at SfN’s annual meeting, oversaw production of member communications, and crafted advocacy communications on biomedical research funding, animals in research, and more. Prior to entering the nonprofit sector, Ortman worked as an editor and web producer at a daily newspaper in Indiana and at *Roll Call*, a newspaper covering Capitol Hill and the White House.



Anna DeGarmo is an associate at FasterCures, a Center of the Milken Institute, supporting the organization's programs and external relations initiatives. Her primary responsibilities include research on the science of patient input in medical device and drug development, tracking and analyzing the progress and impact of the 21st Century Cures Act, and partnering externally to assess the breadth of FasterCures' network and identifying opportunities for growth. Before joining FasterCures, DeGarmo was a research intern at the Riverside Center for Excellence in Aging and Lifelong Health, where she aided studies focused on reducing caregiver burden and providing effective training for nursing home staff. She did further aging-related work assisting ChooseHome, a program dedicated to providing support and resources for older adults to comfortably age in place.

Sarah Wells Kocsis is vice president of public policy at the Society for Women's Health Research, where she leads policy development, government relations, and stakeholder engagement activities on behalf of SWHR. Wells Kocsis brings more than 20 years of expertise in driving public policy solutions aimed at improving patient access to care. She has held diverse public policy and government affairs leadership roles at Hologic, Amgen, and Boston Scientific. Wells Kocsis received a BS in biology from Tulane University and an MBA from the University of Virginia Darden School of Business.

Dr. Tanisha Carino is the executive director of FasterCures, a Center of the Milken Institute that is devoted to saving lives and improving the medical research system. Throughout her distinguished career, Carino has been at the forefront of collaborative efforts to promote policies, research, and business practices that support the fight against disease and improve the lives of patients. She most recently led the US policy function for GlaxoSmithKline, a UK-based science-led global health care company. Prior to her role at GlaxoSmithKline, she spent more than a decade with Avalere Health, where, among other responsibilities, she founded the Center on Evidence Based Medicine and worked with patients, government, and senior leaders at Fortune 500 companies to maximize opportunities and mitigate challenges related to biomedical research and patient access. Prior to Avalere, Carino worked in the Medicare program to improve access for its beneficiaries and support the development of real-world evidence.



Dr. Amy Miller is president and CEO of the Society for Women’s Health Research, a national nonprofit organization dedicated to promoting research on biological differences in disease and improving the health of all women through science, policy, and education. Miller previously worked at the Personalized Medicine Coalition (PMC), where she served as executive vice president, working with innovators, scientists, providers, and payers on scientific policy and business challenges impacting personalized medicine. Before joining PMC, Miller worked in the office of the director of the National Institute of Mental Health. A former American Association for the Advancement of Science fellow, Miller also served as a domestic policy advisor to Senator Jay Rockefeller.



ABOUT US

About the Milken Institute

The Milken Institute is a nonprofit, nonpartisan think tank that helps people build meaningful lives, in which they can experience health and well-being, pursue effective education and gainful employment, and access the resources required to create ever-expanding opportunities for themselves and their broader communities.

About FasterCures

FasterCures, a Center of the Milken Institute, is working to build a system that is effective, efficient, and driven by a clear vision: patient needs above all else. We believe that transformative and life-saving science should be fully realized and deliver better treatments to the people who need them.

About the Society for Women's Health Research

The Society for Women's Health Research (SWHR) is a national nonprofit dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. Founded in 1990 by a group of physicians, medical researchers, and health advocates, SWHR aims to bring attention to the variety of diseases and conditions that disproportionately, differently, or exclusively affect women and to eliminate imbalances in health care for women. Thanks to SWHR's efforts, women are now routinely included in most major medical research studies, and more scientists are considering sex as a biological variable in their work. To learn more, visit swhr.org.



ENDNOTES

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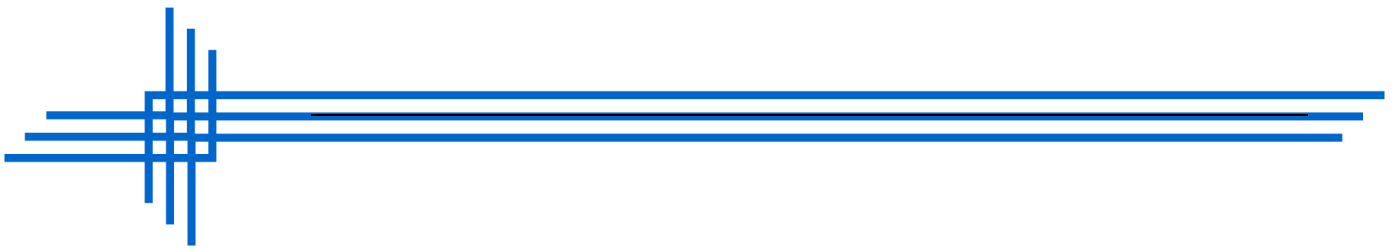
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