

Precision Medicine How Sex and Gender Drive Innovation

A Report of the
Mary Horrigan Connors Center
for Women's Health
& Gender Biology
at Brigham and Women's Hospital



The Connors Center for Women’s Health and Gender Biology and the Division of Women’s Health at Brigham and Women’s Hospital, led by Paula A. Johnson, MD, MPH, are committed to improving the health of women and transforming their medical care through the discovery, dissemination, and integration of knowledge of women’s health and sex- and gender-based differences and the application of this knowledge to the delivery of care. We are committed to building awareness of issues related to women’s health and gender biology among clinicians, patients, and the general public; advocating for changes in public policy to improve the health of women; and advancing the field of women’s health globally by developing leaders with the experience and skills to have a major impact on improving the health of women. For more information, please see www.brighamandwomens.org/connorscenter.

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AUTHORS

Paula A. Johnson, MD, MPH

Chief, Division of Women's Health and Executive Director, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital; Grayce A. Young Family Professor of Medicine in the Field of Women's Health, Harvard Medical School

Therese Fitzgerald, PhD, MSW

Director, Women's Health Policy and Advocacy Program, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital

Amy Glynn, MBA, MPP

Senior Policy Analyst, Women's Health Policy and Advocacy Program, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital

Alina Salganicoff, PhD

Vice President and Director, Women's Health Policy, Kaiser Family Foundation

Susan F. Wood, PhD

Director, Jacobs Institute of Women's Health, Associate Professor of Health Policy, George Washington University, School of Public Health and Health Services

Jill M. Goldstein, PhD, MPH

Director of Research, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital;
Professor of Psychiatry and Medicine, Harvard Medical School



CONTRIBUTING AUTHORS

Andrea Camp

Senior Policy Advisor, Communications Consortium Media Center

Yolonda L. Colson, MD, PhD

Director, Women's Lung Cancer Program, Brigham and Women's Hospital;
Professor of Surgery, Harvard Medical School

Mary Angela O'Neal, MD

Director of the Women's Neurology Program, Brigham and Women's Hospital,
Instructor in Neurology, Harvard Medical School

Piper Starr Orton, MBA

Director of Women's Health Programs, Connors Center
for Women's Health and Gender Biology, Brigham and Women's Hospital

Gary Strichartz, PhD

Director of the Pain Research Center, Brigham and Women's Hospital;
Professor of Anaesthesia (Pharmacology), Harvard Medical School

Anem Waheed, MD, MPH

Harvard T.H. Chan School of Public Health

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EXECUTIVE SUMMARY

There is significant evidence that both sex and gender impact disease. Recent reports demonstrate that the death rates of middle-aged white Americans are climbing. However, stratifying the data by gender reveals that women are in fact the ones falling behind. In today's rapidly evolving healthcare landscape, it is vital to understand the complex biological and physiological aspects of sex, gender, gender identity, and race; how these factors intersect; and how they impact our health. Yet, a lack of adequate foundational information about males and females, and the most basic data on sex/gender, hinders innovation. We know that studying sex/gender not only benefits women's health, it is the key to improving men's health as well. By not examining health outcomes by sex/gender, we miss important findings that benefit both men and women.

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The White House and the National Institutes of Health (NIH) recently announced a "Precision Medicine Initiative" (PMI), a new approach to studying the differences in people's genes, environments, and lifestyle to develop targeted, more individualized treatments for a host of diseases. Against the backdrop of this landmark initiative, we can prioritize the inclusion of women and a focus on sex- and gender-specific medical research to drive innovation and ensure health equity in the new frontier of medicine by reimagining this framework with sex/gender at its center (See graphic on page 5).

Recent research highlighted below illustrates that, if we move toward a definition of precision medicine with sex/gender as a crucial sphere in the intersection of all aspects of disease, we will drive innovation and find the best health outcomes for all individuals, including both women and men.

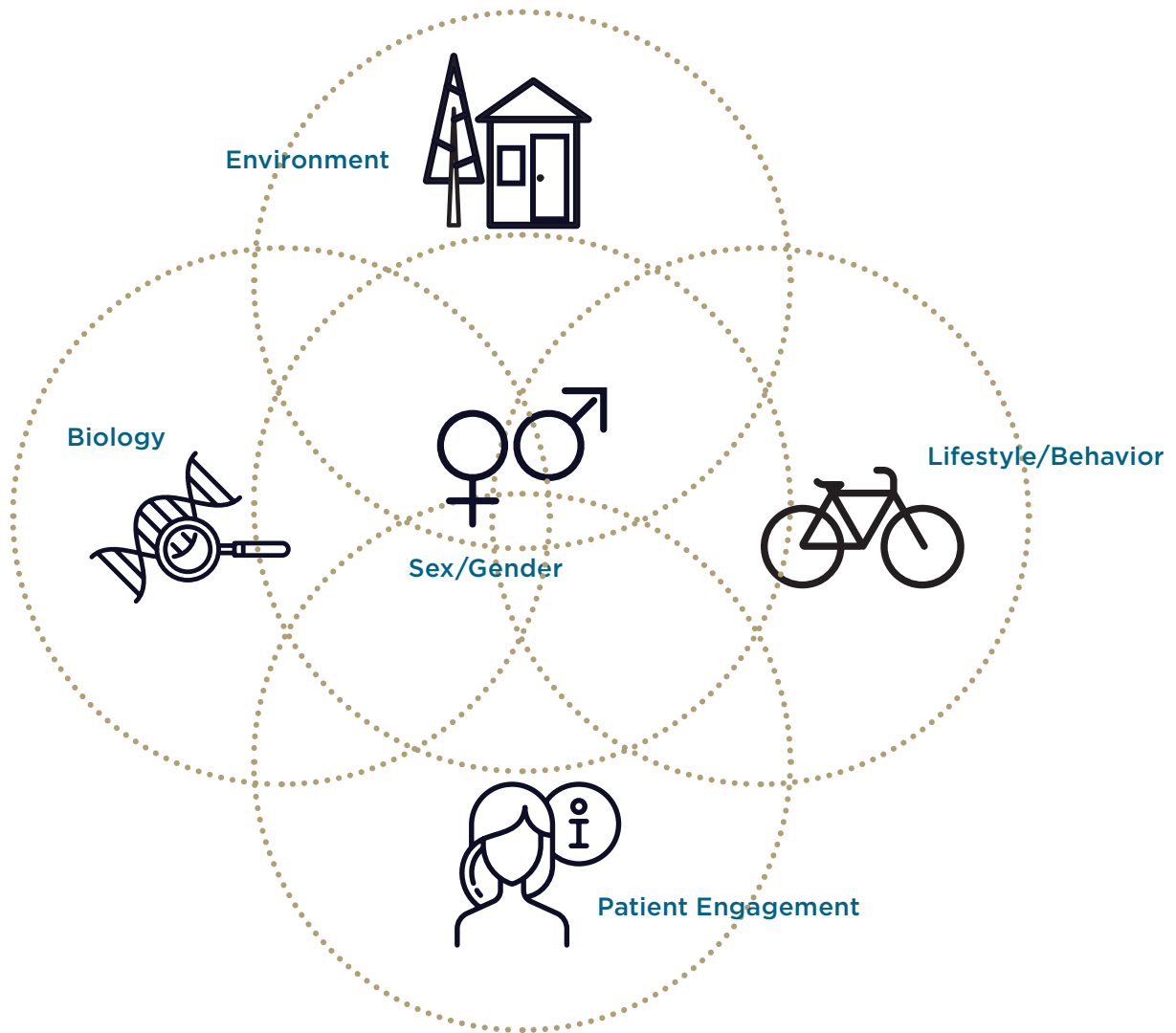
Heart disease is the number one killer of women in the United States, with more women than men dying each year from the disease.^{1,2,3} New research on the genetic causes of heart disease that included female subjects found that there is a female-specific genetic risk for heart disease.⁴ In another study, investigators stratified their findings by sex to examine a genetic risk that may be associated with higher premature risks for heart

disease.⁵ What they found was significant. Women with certain gene mutations were two and a half times more likely to be at higher risk for heart disease, a finding that could not be replicated in men and, therefore, likely missed if the study had failed to examine sex differences.⁶

Lung cancer is the leading cause of cancer death for both men and women in the United States.⁷ More women die from lung cancer each year than from breast, ovarian, and uterine cancers combined, yet men have worse five-year survival rates than women.⁸ Mounting research suggests that genetic, hormonal, behavioral, and environmental factors influence different patterns of lung cancer.^{9,10,11} Research shows that some lung cancer targeted treatments work better for women than for men. Specifically, in the initial clinical trials of tyrosine kinase inhibitors (a targeted therapy), 82 percent of the patients who responded were women, making sex and smoking history the two most important factors in predicting therapeutic efficacy.¹² This targeted therapy has become one of the most effective drugs used to treat lung cancer, but its benefit would have been missed had the investigators not tracked sex-dependent data.

There are a number of **disorders of the brain** and conditions where biology, environment, lifestyle, behavior, and patient engagement intersect with sex/gender-related factors. For example, a woman's overall lifetime risk of developing Alzheimer's disease (AD) is almost twice that of a man, and not only because women live longer.¹³ Two-thirds of the 5.6 million people currently suffering from AD are women.^{14,15} Even when compared to men with similar genetic risk, women have a higher overall risk for the illness.¹⁶ Women who carry the APOE ε4 allele, the primary genetic risk factor for AD, are more likely to experience a faster decline in memory and physical functioning when they have AD than men who carry the same gene.¹⁷

PRECISION MEDICINE FRAMEWORK REIMAGINED



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Biology: Every cell has a sex. Therefore, every gene and molecule in our body is influenced by sex. For treatments to be individualized and tailored to a person's unique genetic and molecular makeup within precision medicine, the consideration of sex is essential.



Environment: Gender plays a role in individuals' susceptibility to environmental factors that consist of stressors, pollutants, and other exposures that can influence health.



Lifestyle/Behavior: Gender influences lifestyle and behavioral choices that impact one's health, from diet and exercise to smoking and drinking.



Patient Engagement: Women are often the healthcare decision makers for their families and communities. By engaging women you engage everyone.



Sex/Gender: Research on sex and gender differences (and similarities) have produced scientific advancements that promote health and help prevent, detect, and treat disease. Ignoring these differences will limit our understanding of both health and disease and lead to poorer outcomes for all.

For the Precision Medicine Initiative (PMI) to accomplish its goals of providing more individualized care, sex/gender must be incorporated throughout the process.

These examples underscore the fact that putting sex/gender at the forefront of medical research, leads to advancements that are better tailored to meet the needs of everyone. For the Precision Medicine Initiative (PMI) to accomplish its goals of providing more individualized care, sex/gender must be incorporated throughout the process. To accomplish this, the PMI will need to rely on NIH-funded research and U.S. Food and Drug Administration (FDA) oversight. However, NIH's current inclusion policies and guidelines on the analysis of sex differences do not go far enough to achieve health equity in preclinical and clinical research, which will negatively impact the PMI. Therefore, standards and guidelines for preclinical and clinical research, and strong oversight systems by government agencies are necessary to ensure that adequate numbers of women are included and that the study of sex/gender differences is integrated into every phase of the PMI. Toward that aim, we recommend the following health equity action plan.

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HEALTH EQUITY ACTION PLAN - POLICY RECOMMENDATIONS

1. Hold all NIH investigators accountable for achieving health equity and driving innovation in their research.

NIH should make reporting on the inclusion of women and racial/ethnic minorities in preclinical and clinical research one of the criteria of the NIH research review process and a stipulation of funding. Data on the inclusion of women and minorities must be made publicly available. And investigators should be required, in all published work, to disclose how their study addresses sex.

2. Reform the FDA preclinical and clinical research process.

FDA needs to ensure products are developed through research that includes women and diverse populations in all phases of study. To do this, medical device and pharmaceutical labels should include a warning label if testing did not include adequate numbers of female subjects. Additionally, an online gateway should be developed to provide public access to subpopulation data.

3. Develop a national strategy for achieving health equity in biomedical research.

The NIH and the Department of Health and Human Services (HHS) should develop a strategic plan to promote the inclusion of women and racial/ethnic minorities in all federally-funded preclinical and clinical research. The plan should ensure that research adequately represents characteristics of the entire population and reports these disaggregated data by research area, condition, and disease. Investments in all research must include all people, with a standardized focus on the routine examination of sex and gender.

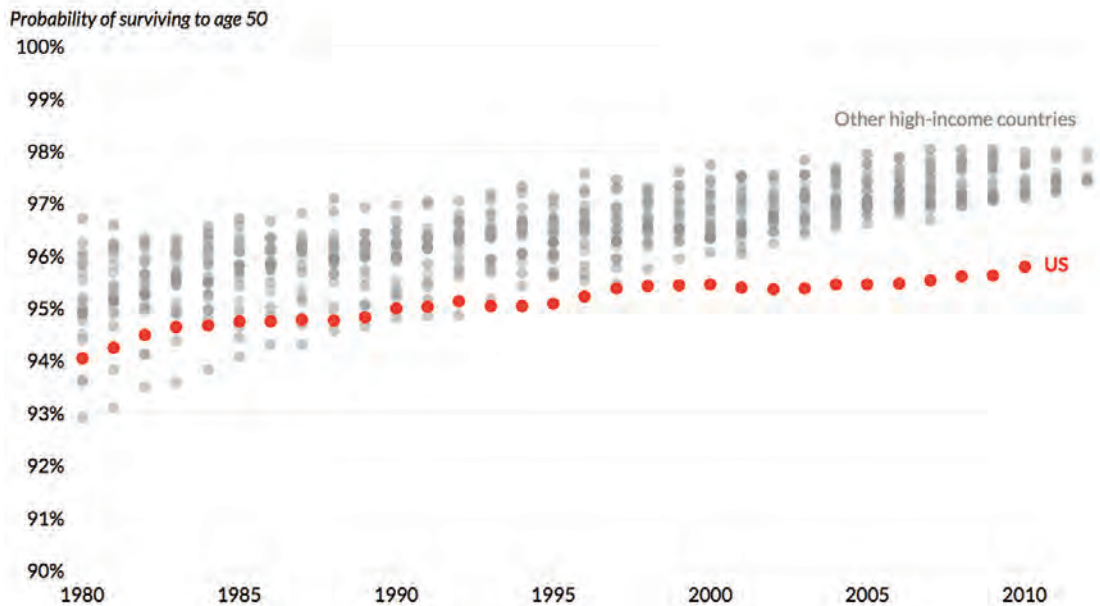
INTRODUCTION

More than 20 years ago, a bipartisan group of legislators worked with patients, providers, policy makers, and advocates to create and pass the 1993 National Institutes of Health (NIH) Revitalization Act, a law mandating that women and minorities be included in clinical trials funded by the NIH, the nation's medical research agency.¹ Women are now routinely included in clinical trials, and we have learned how certain diseases present differently in men and women. Yet, despite progress, medical research is too often flawed by its failure to examine sex/gender differences. For example, in 2015, the Government Accountability Office (GAO) reported that, although women's inclusion in clinical trials increased, we do not know if they are adequately represented in NIH-funded research for specific diseases

and conditions that have a major impact on the health of women and men, including cardiovascular disease, lung cancer, depression, and other diseases of the brain.² The report also stated that the NIH fails to effectively monitor the study of sex/gender differences in its funded research, a key requirement of its own inclusion policy.

There is significant evidence that both sex and gender impact disease. Recent reports demonstrate that the death rates of middle-aged white Americans are climbing. However, stratifying the data by gender reveals that women are in fact the ones falling behind (see Graph 1).

Graph 1:
**CHANCES OF WOMEN SURVIVING TO AGE 50:
US WOMEN ARE FALLING FAR BEHIND**



Source: Aron L. Dubay L. Waxman E. et al. To understand climbing death rates among white Americans, look to women. Urban Institute. 2015. Retrieved from <http://www.urban.org/urban-wire/understand-climbing-death-rates-among-white-americans-look-women>

SEX VS. GENDER

A note on our use of the terms *sex*, *gender*, and *sex/gender*: According to the World Health Organization (WHO), *sex* “refers to the biological and physiological characteristics that define men and women.” Thus, this report uses the term *sex* when discussing the implications of or need for scientific research and clinical trials that consider the “biological and physiological characteristics” of women as distinct from men. *Gender*, according to the WHO, “refers to the socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate for men and women.” This report will use the term *gender* when discussing how gender roles impact health outcomes. Finally, this report uses the term *sex/gender* in situations where both the biological characteristics of health and the societal roles, behaviors, and activities associated with lifestyle and healthcare are involved.

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Fortunately, we are not condemned to repeat the mistakes of the past. Instead we are at a unique point in our history, marked by unprecedented advancements in science and medicine, where the study of sex/gender is the catalyst for and foundation of lifesaving breakthroughs. In today’s rapidly evolving healthcare landscape, it is vital to understand the complex biological and physiological aspects of sex, gender, gender identity, and race; how these factors intersect; and how they impact our health. Yet, a lack of adequate foundational information about males and females, and the most basic data on sex/gender, hinders innovation. We know that studying sex/gender not only benefits women’s health, it is the key to improving men’s health as well. And by not examining health outcomes by sex/gender, we miss important findings that benefit both men and women.

The White House and NIH recently announced a “Precision Medicine Initiative” (PMI), a new approach to studying the differences in people’s genes, environments, and lifestyle to develop targeted, more individualized treatments for a host of diseases. Against the backdrop of this landmark initiative we can prioritize the inclusion of women and a focus on sex- and gender-specific medical research to drive innovation and ensure health equity in the new frontier of medicine.

Precision medicine provides an excellent opportunity to prioritize sex/gender to accelerate innovation to prevent and treat disease. This is evidenced by recent medical breakthroughs in the areas of heart disease, cancer, and brain disorders. The following report describes the key elements of the precision medicine model and how sex- and gender-specific medicine intersects with precision medicine to potentially drive breakthrough treatments for these diseases and conditions. The report also includes a health equity action plan to provide policymakers with recommendations to ensure that investments in precision medicine achieve the full benefit of innovation and health equity.

PRECISION MEDICINE

Precision medicine is an approach to disease treatment and prevention that:

- Considers “individual variability in genes, environment, and lifestyle;”
- Seeks to improve health with more precise measurement of molecular, environmental, and behavioral factors that contribute to health and disease; and
- Engages individuals as active partners—not just as patients or research subjects.

Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH. September 17, 2015

PRECISION MEDICINE

What Is Precision Medicine?

Rapid advancements in the field of molecular biology resulted in the availability of molecular data on humans.³ We now have vast databases (“big data”) that include biological data, including the human genome project. We have new technology and targeted drug treatments to individualize care, including the ability to study how a person’s genes and DNA impact disease. Further, the introduction of electronic medical records and social media applications give us the the ability to analyze and integrate large data sets with information about patients.⁴ In response to these rapid advancements, scientists and health experts worked to harness the power of the health data collected to advance medical research and improve health outcomes. The resulting framework is described as “precision medicine.”⁵ NIH defines precision medicine as the study of genes, environment, and lifestyle variables of subpopulations to provide more precise diagnosis, prevention, and treatment of disease.^{6,7}

The PMI’s near-term focus is to wage war on cancer in the United States by designing treatments for cancerous tumors based on an individual’s genetic abnormalities. The longer-term plan is to create a cohort of 1 million or more volunteer research participants “who will share their biological, environmental, lifestyle, and behavioral information and tissue samples with qualified researchers,” in order to better understand how our genes are related to other biologic and personal characteristics, such as sex.⁸ This coupling of genes with other characteristics will help to develop more individualized and thus more efficacious therapeutics.

The NIH and the U.S. Centers for Disease Control and Prevention (CDC) have stressed the importance of including sex/gender in precision medicine. NIH experts, developing guidelines for the precision medicine cohort, specified that the cohort “be statistically powered to find factors contributing to differences in health and disease among major demographic groups in the U.S., including participants of diverse age, sex, as well as diverse racial/ethnic, socioeconomic, and geographic groups” in order “to ensure that the benefits of PMI cohort research will be

applicable to the broad population of the U.S.”⁹ The CDC emphasized the need for the precision medicine cohort to be “representative of the underlying population” rather than to rely on convenient samples that can be biased and unreliable because they fail to include such key variables as race/ethnicity, age, and sex/gender.¹⁰ Yet, the elements that should be included in the design of studies that are “representative of the underlying population” are still not clearly defined.

STRATIFYING BY SEX/GENDER IS A GOOD INVESTMENT

When conducting studies, investigators often assume that controlling for sex and gender is enough for their research to be considered “good science.” But we know from past research that stratifying by sex/gender allows scientists to more fully understand the differential impact an intervention has on the women AND men who participate in the study. We need to look at both groups or important findings may remain hidden and investments can be lost.

In addition to recruiting new participants, the PMI cohort will rely on data collected from previous clinical trials.^{11,12} Currently, clinical trials routinely fail to include adequate numbers of female subjects in clinical research and neglect to analyze and report on sex/gender differences in treatment outcomes.^{13,14,15,16,17} Fortunately, we have the time and opportunity to address these gaps to ensure that women and the study of sex/gender-dependent medical research are components of the design of the PMI and its cohort, and thus will be integrated into every aspect of this groundbreaking research.¹⁸ Without addressing these gaps, we run the risk of creating a new biomedical research environment under the PMI mired in the past and stunted in growth, the result of a persistent failure to encourage innovation by ignoring sex/gender. Thanks to rapid advancements over the past several decades, we now have the computer technology we need to translate vast quantities of “big data” into meaningful knowledge about our health. Big data have the ability to unlock hidden truths about human health but only if we include

SEX-SPECIFIC VS. SEX-DEPENDENT

“Sex-specific” research encompasses the study of diseases or conditions that occur in one sex but not the other. “Sex-dependent” research concerns the study of diseases or conditions that can occur in both sexes with potentially different effects in men and women.

the most fundamental health data of all, one’s sex/gender.

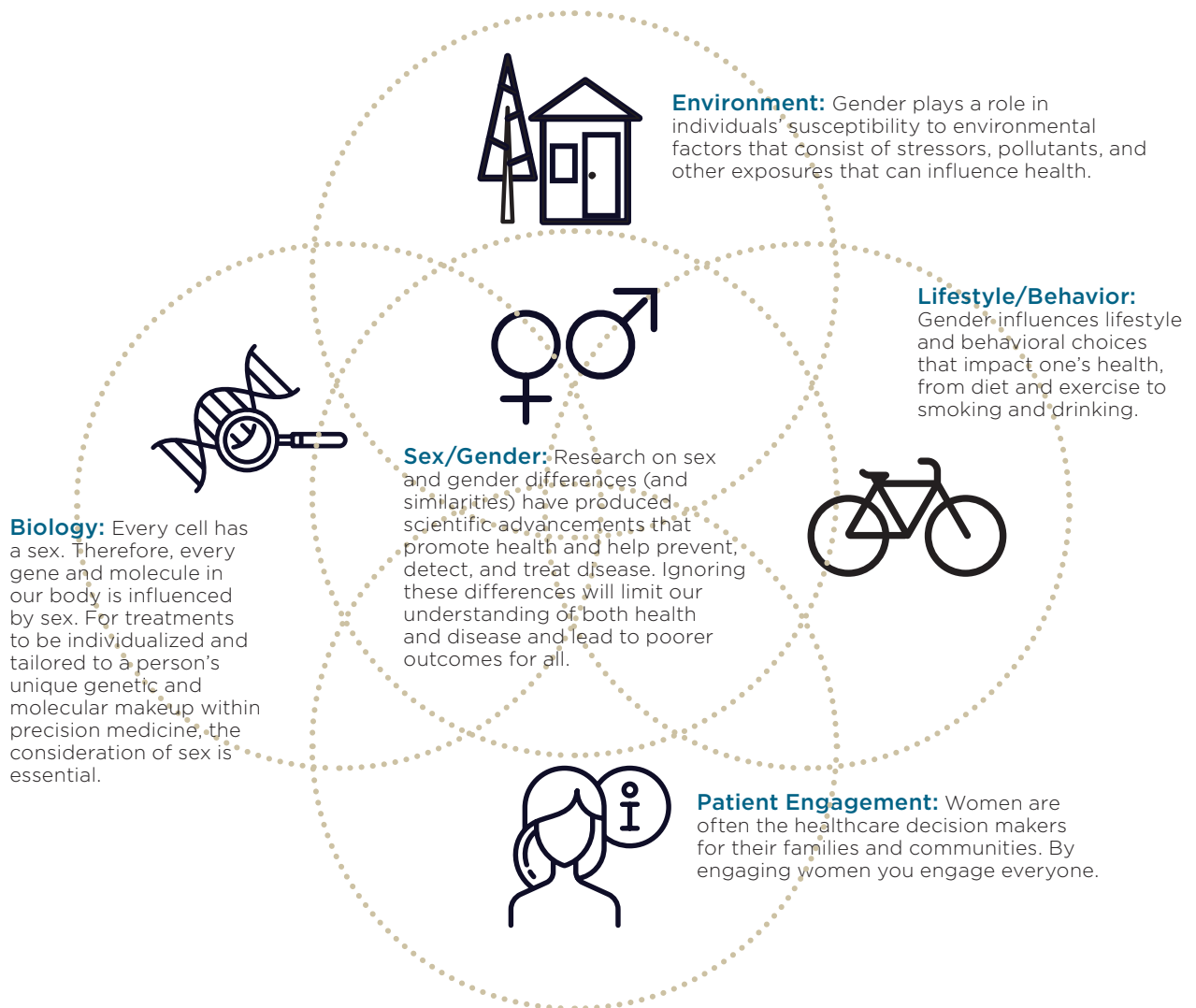
The precision medicine framework outlined in this report mirrors NIH’s definition and demonstrates how consideration of sex/gender is crucial to driving innovation in every aspect of the model.

Precision Medicine Framework

The precision medicine framework includes the *biological aspects* of the individual, including the person’s genetic and molecular makeup; *environmental factors* that can impact the biology and overall health of an individual; *individual lifestyle and behavioral factors* that also impact health; and *engagement* of precision medicine *participants as active agents in decisions* related to their disease or condition rather than passive recipients of the medical process. In the precision medicine framework, biology, environment, lifestyle, and patient engagement

PRECISION MEDICINE FRAMEWORK REIMAGINED

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In the precision medicine framework, biology, environment, lifestyle, and patient engagement all intersect to feed innovation emerging from cutting-edge research.

all intersect to feed innovation emerging from cutting-edge research.

We know from decades of research that sex and gender are the keys to unlocking the potential of precision medicine and accelerating innovation in the decades to come. The graphic on page 10 demonstrates a paradigm shift in the framework for precision medicine and presents an illustration of how all aspects of precision medicine intersect with and are influenced by sex/gender.



Biology: Both sex-specific and sex-dependent research demonstrate that genetic susceptibility and hormones have an impact on each individual's health. We know that sex-specific cellular building

blocks are the foundation for every gene and molecule in our body. In fact, every cell in our body has a sex.¹⁹ Therefore, innovative treatments developed and designed to be individualized, precise, and tailored to a person's unique genetic and molecular makeup within precision medicine must include consideration of sex as an essential aspect of the process.



Environment: Each individual has a unique environmental background that consists of environmental exposures and other factors that can influence health, such as exposure to stress or pollutants.²⁰

Research demonstrates that sex and gender intersect with environmental factors in unique ways to influence our health.²¹ Consequently, the field of epigenetics, which examines how our environment can influence biological processes, is a crucial element of precision medicine.



Lifestyle and Behavior: Diet, physical activity, alternative therapies, and risk factors such as smoking and illicit drug use are examples of lifestyle and behavior choices that factor into the framework

of precision medicine. Research demonstrates that sex/gender have important influences on lifestyle and behavior.²²



Patient Engagement: Engaging patients as key partners in the process of healthcare decision making is a key tenet of the PMI's framework. It is crucial for providers to know the impact sex/gender can have on various aspects of a patient's health if they want to provide patients with the individualized care promised by precision medicine. A gendered lens is particularly important given that women are often the healthcare decision makers for their families and communities. By engaging women you engage everyone.



Sex/Gender: Research on sex/gender differences (and similarities) has already produced scientific advancements that promote health and help prevent, detect, and treat disease in both women and men. Ignoring these differences will limit our understanding of health as well as disease, and lead to poorer outcomes for all. But even as the evidence is mounting on sex/gender differences in major causes of disease and disability, so is our awareness of the gaps in knowledge that remain, particularly in regard to women's health. It is also important to note that the study of sex/gender differences benefits men as much as it benefits women. Therefore, when we fail to routinely consider the impact of sex/gender in research, we are leaving everyone's health to chance.

PRECISION MEDICINE REIMAGINED: EXAMPLES OF SEX- AND GENDER-SPECIFIC INNOVATION

The following examples outline how the various aspects of the precision medicine framework intersect with and are impacted by sex/gender to drive innovation. Examples include medical conditions that have a devastating impact on women's health—heart disease, lung cancer, and disorders of the brain—and illustrate that, if we move toward having sex/gender as a crucial sphere in the intersectionality of all aspects of disease, we will drive innovation and find the best health outcomes for all individuals, whatever their sex or gender.

Heart Disease

Heart disease is the number one killer of women in the United States. Half of all American women will develop heart disease in their lifetime.^{23,24} More women than men die each year of heart disease.^{25,26,27} Although progress has been made in identifying sex differences in heart disease, much remains unknown.²⁸ We know that heart disease affects women and men differently at every level, including prevalence, underlying physiology, risk factors, presenting symptoms, and outcomes. Racial and ethnic disparities also exist in heart disease, with black women experiencing both higher prevalence and higher mortality than white women.²⁹

The underlying causes for these many sex differences still elude us, and yet only 35 percent of clinical trial subjects in heart disease research are women, and just 31 percent of those studies report outcomes by sex.³⁰ Fortunately, there are aspects of the precision medicine framework that show great promise in accelerating advances in heart disease in women when sex and gender are taken into consideration.



Over the years, substantial research on heart disease has identified sex differences in the underlying biology of the disease. More recent

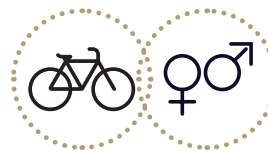
research on the genetic causes of heart disease that included female subjects found that there is a female-specific genetic risk for heart disease.³¹ In another study, investigators stratified their findings by sex to examine a genetic risk that may be associated with higher risk

for heart disease.³² What they found was significant. Women with certain gene mutations were two and a half times more likely to be at higher risk for heart disease, a finding that could not be replicated in men and, therefore, likely missed if the study had failed to examine sex differences.³³



Some social and environmental influences on heart disease, such as stress and poverty, differ for women and cause differences in the expression, diagnosis, treatment, and outcomes of the disease.^{34,35,36}

For example, researchers were aware that mental stress is associated with heart disease. However, in 2014, researchers decided to stratify their findings by sex to examine whether mental stress might impact men's and women's heart disease differently. The answer is yes. In fact, women in the study experienced a type of heart disease called ischemia (i.e., a reduction in blood flow to the heart that can lead to stroke and death) when exposed to mental stress at significantly higher rates than men (57 percent of women vs. 41 percent of men).³⁷ The research also demonstrates that women's blood pressure and platelets react differently under stress than men's.³⁸ Stressed women are more likely than stressed men to experience a reduction in blood flow, putting them at increased risk for heart disease. Stressed women are more likely to experience a build-up of blood platelets, putting them at higher risk for blockages and heart attacks compared to men under stress.



Lifestyle and behaviors can positively and negatively impact one's risk for heart disease. For example, research shows our risk for many types

of heart disease decreases when we engage in regular exercise. However, researchers were unable to detect an association between exercise and the risk for one type of heart condition, atrial fibrillation (AFib), a condition marked by an irregular heart beat that can lead to stroke, blood clots, heart failure, and other heart complications if not diagnosed and treated appropriately.³⁹ In 2014,

Heart disease kills more women in the U.S. than any other disease and more women than men die each year from the disease.

investigators examining the link between AFib and exercise stratified their findings by sex. The authors reported that, while exercise reduced the risk of AFib in women, it was associated with a small *increased* risk of AFib in men.⁴⁰

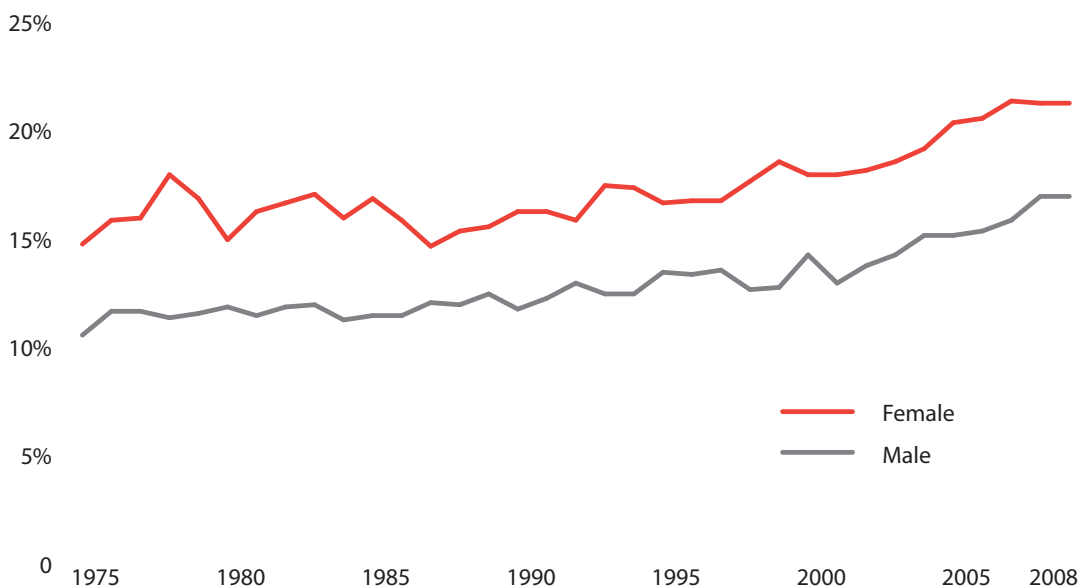
Lung Cancer

Lung cancer is the leading cause of cancer death for both men and women in the United States.⁴¹ Once rare among women, lung cancer surpassed breast cancer in 1987 to become the leading cause of cancer death among women, with more women dying from lung cancer each year than from breast, ovarian, and uterine cancers combined.⁴² Despite substantial improvements in the overall survival rates for many cancers, including prostate (99.3 percent), breast (90.8 percent), and colon (66.2 percent), lung cancer

survival rates have only risen to 18.8 percent over the past three decades, up from 13.2 percent.⁴³ Women with lung cancer actually have higher five-year survival rates than men across all ages with comparable stages of lung cancer (Graph 2).

Accumulating research findings suggest that genetic, hormonal, behavioral, and environmental factors influence different patterns of lung cancer.^{44,45,46} Nonsmoking women are three times more likely than nonsmoking men to get lung cancer.^{47,48,49} These findings underscore the need to better understand sex/gender differences in lung cancer, including risk factors, clinical characteristics, cancer progression, and survival. A better understanding of these factors can advance preventive, diagnostic, and therapeutic practice and improve outcomes for this disease in both men and women.

Graph 2:
LUNG CANCER* 5-YEAR RELATIVE SURVIVAL BY SEX, 1975-2012



*Includes lung and bronchus cancer

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Age-adjusted 5-year survival data. <http://seer.cancer.gov/faststats/selections.php?#Output>

Lung cancer is the leading cause of cancer death for both men and women in the United States.



Women are at higher risk for lung cancer due to such factors as genetic susceptibility and hormonal impact.^{50,51,52} Research shows

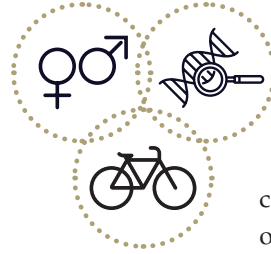
that sex correlates with the incidence of gene mutations associated with lung cancer. For example, women with adenocarcinoma, a subtype of non-small cell lung cancer (the most common type of lung cancer) are much more likely than men to express specific genetic mutations in proteins found on the surface of their cells.^{53,54} Research also demonstrates that hormones, particularly estrogen, also influence lung cancer risk (as well as development and mortality).^{55,56} Estrogen receptors, a group of proteins found in and on cells, are found in 45 percent to 70 percent of non-small cell lung cancer tumors for both sexes, and may play a significant role in stimulating lung cancer cell growth.⁵⁷ Women who have never smoked are much more likely than men who have never smoked to get lung cancer,^{58,59,60} with the incidence and mortality particularly striking among young women.^{61,62}

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One of the most significant advancements in lung cancer therapy in the last several decades is targeted therapies that allow doctors to consider

the specific characteristics of a patient's tumor, including the gene mutations or proteins found in his or her cancer cells, to determine the best possible course of treatment.^{63,64,65} Clinical trials that track data by sex have shown that some targeted treatments for lung cancer work better for women than for men. In the initial clinical trials of tyrosine kinase inhibitors (a targeted therapy), 82 percent of the patients who responded were women, making sex and smoking history the two most important factors in predicting therapeutic efficacy.⁶⁶ This targeted therapy has become one of the most effective drugs used to treat lung cancer, but its benefit would have been missed had the investigators not tracked and analyzed sex-dependent data.



The intersection between biology and sex in lifestyle choices is particularly evident in smoking. Smoking is the largest risk factor for lung cancer, contributing to 80 percent of lung cancer deaths in women and 90 percent in men.^{67,68} However,

controversy persists on whether women who smoke are more likely to develop lung cancer than men who smoke due to biological differences between the sexes, and the fact that women metabolize nicotine faster than men.^{69,70,71,72} It is well established that women who are nonsmokers are diagnosed with lung cancer more often than non-smoking men, but even more research is needed on these sex differences to determine if, in fact, women who smoke are at even greater risk for lung cancer than men with similar smoking exposure. New guidelines for lung cancer screening may be needed based on findings from sex-dependent research given that current screenings do not take sex into account. The ability to stop smoking also differs between women and men. Ovarian hormones that fluctuate during a woman's menstrual cycle and mood changes caused by oral contraceptives may stymie attempts to stop smoking.⁷³ And the faster metabolism of nicotine mentioned above may also get in the way of smoking cessation efforts if nicotine replacement medications have inadequate dosages.

Brain Diseases and Conditions

There are a number of disorders of the brain and conditions where biology, environment, lifestyle, behavior, and patient engagement intersect with sex/gender-related factors. Important sex/gender differences exist in Alzheimer's disease (AD), depression, pain, and sport-related concussions.

ALZHEIMER'S DISEASE (AD)

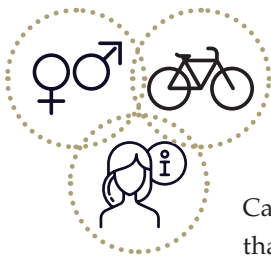
A woman's overall lifetime risk of developing Alzheimer's disease (AD) is almost twice that of a man's, and not only because women live longer.⁷⁴ Even when compared

to men with similar genetic risk, women have a higher overall risk for the illness.⁷⁵ To complicate matters, other chronic diseases with known sex differences, such as depression and cardiovascular disease, are themselves risk factors for AD. In fact, two-thirds of the 5.6 million people currently suffering from AD are women.^{76,77} AD costs society (families, businesses, and government) \$300 billion per year, a number that may triple in the coming years as Baby Boomers age.⁷⁸



New evidence sheds light on potential biological factors contributing to the disproportionate impact of AD on women. For example,

women who carry the APOE ε4 allele, the primary genetic risk factor for AD, are more likely to experience a faster decline in memory and physical functioning when they have AD than men who carry the same gene.⁷⁹ Although we do not fully understand why, this may be related to the fact that estradiol has been found to impact the expression of the APOE ε4 allele, which may also be associated with the finding that, controlled for age and severity of AD, women often have a greater accumulation of amyloid (proteins that can cause plaques when overproduced) than men.⁸⁰ Sex-dependent research on the genetic and hormonal regulation of AD and associated pathology will allow scientists to determine which factors present the highest risk for AD in early midlife for women and for men in order to intervene early in the process to slow the progression of the disease and, ultimately, prevent AD.



In addition to sex differences in the risk and prevalence of AD, women are disproportionately the primary caregivers of adult loved ones with AD.

Caregiving is a lifestyle factor that can negatively impact health.

Almost two-thirds of caregivers are women, and of these, 25 percent report health problems as a result of caregiving activities.⁸¹ Female caregivers are more likely than female non-caregivers to not fill a prescription due to cost (40 percent vs. 27 percent)⁸² and

they experience higher levels of depression and impaired health due to their caregiving activities.^{83,84,85,86,87} As AD continues to impact the lives of many Americans, it is essential to consider the impact on female caregivers and for providers and insurers to support their therapeutic role in the disease course.

DEPRESSION

Depression is the world's leading cause of disease burden, affecting 350 million people (16 million in the United States) with women disproportionately affected.⁸⁸ Twice as many women as men suffer from depression, and women are 70 percent more likely than men to suffer from it over their lifespan.^{89,90} Causes for these sex/gender differences remain elusive. However, biological and environmental factors contribute to these disparities.



Research now demonstrates that sex hormones play a significant role in the development of brain regions that regulate mood and response to stress. Major hormonal changes throughout a woman's

life including fetal development, puberty, pregnancy, postpartum, and menopause have been directly linked to increased risk of depression.⁹¹ Sex hormones interact with stress hormones to regulate brain activity in environments where stress is abundant, which can further pose risks for women of other chronic diseases, including heart disease.⁹² A better understanding of how sex hormones change the way our brain copes with stressful challenges will elucidate sex-dependent pathways that contribute to depression.



Environmental risk factors that contribute to depression among women may, in some cases, differ from men. For example, higher rates of

intimate partner violence, socioeconomic disadvantage, caregiving status, and differential responses to stress may all contribute to women's higher rates of depression.⁹³

...one review of basic science of pain literature from 1996 to 2005 found that 79 percent of all published papers tested male subjects exclusively...

The epidemic of violence against women is a particularly striking factor associated with depression. Women who experience intimate partner violence are at a twofold risk of depression and those who are depressed are at twofold risk of intimate partner violence compared to primarily other women.⁹⁴ In addition, one in ten women in the United States have been raped by an intimate partner and one in three women experienced physical violence by an intimate partner in her lifetime.⁹⁵ Understanding environmental risk factors through a gendered lens is essential to addressing disparities associated with depression.



Research shows there can be gender biases in the treatment of depression and other psychological disorders. For example, providers are more

likely to diagnose depression in women than in men, even when they present similar scores on standardized measures.⁹⁶ In fact, this may lead to poorer identification of major depression in men. Despite evidence of sex differences in responses to drug treatment, sex-dependent research on how the body metabolizes drugs is rare.⁹⁷ In fact, the only medication for which the FDA requires sex-dependent drug dosages is Ambien, with lower doses for women than men.⁹⁸ Ambien is a sleep medication that involves a neurotransmitter, gamma amino butyric acid, whose regulation is associated with gonadal hormones. In addition, research on drug interactions during pregnancy and for those taking oral contraceptives or hormone replacement therapy is limited. These factors contribute to a lack of sex-dependent efficacious therapeutic responses, higher rates of side effects, and compliance.⁹⁹

PAIN

As with other brain disorders and conditions, it is important that both sexes be included in all biomedical research on pain, even on the basic science level, to ensure that appropriate diagnosis and treatments are being used. Indeed, a growing body of basic research has found that female rodents used to test pain responses to different noxious conditions are more responsive than their male counterparts, although almost all such research in the

past had been conducted exclusively on males.^{100,101}

Unfortunately, we know women also are not adequately represented in pain clinical trial research.¹⁰² In fact, one review of basic science of pain literature from 1996 to 2005 found that 79 percent of all published papers tested male subjects exclusively, and 5 percent of papers tested both sexes yet did not report any analysis of potential sex differences.^{103,104}



The intersection of biology, environment, and sex/gender come together in the study of sex differences and pain. Pain is influenced by sex/gender, inasmuch as female neuroanatomy and neurochemistry differ from

that of males. Pain is also influenced by exposure to environmental stressors, such as socioeconomic status, social-familial role, and a history of trauma. Researchers examining the association between trauma history and pain stratified their findings by gender and demonstrated that childhood abuse is associated with decreased tolerance for pain in women that is not observed in men.¹⁰⁵ It is therefore important for providers to ask patients about trauma history and to factor this into their work to engage patients in treating their pain effectively.



Women consistently have higher rates of chronic pain than men and are at greater risk for many pain conditions, yet they are more likely to be undertreated.^{106,107,108} Multiple reasons have been proposed to explain these sex/gender differences

in pain including: It may be more socially acceptable for women to report pain than men; women may be exposed to more pain risk factors throughout their lives (such as exposure to stress); and biological factors, including the role of hormones, may make women more vulnerable to developing pain.^{109,110} Furthermore, when women are treated for pain, they experience more adverse drug effects and complications.¹¹¹

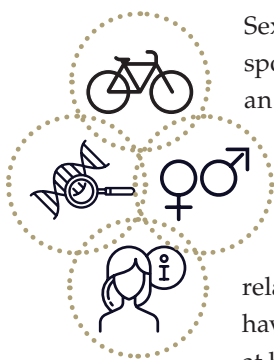


Not only do societal, environmental, and biological factors impact women's pain sensitivity and treatments, they can interfere with patient

provider relationships. For example, female patients may face added burdens when discussing pain with their providers, including gender bias.^{112,113} Women are also less likely to receive aggressive treatment than men when diagnosed, and although more women report pain to their providers, they are more likely to have their pain discounted as "emotional."¹¹⁴ This puts women at risk and impedes provider-patient engagement and communication.

SPORT-RELATED CONCUSSIONS

There has been a dramatic increase in the number of girls and women participating in competitive sports since the passage of Title IX, the federal law designed to provide women with equitable opportunities to play sports.¹¹⁵ Along with an increase in youth sports participation, researchers report a significant increase in the number of sport-related concussions, with higher rates among young women and girls.^{115,117,118}



Sex and gender differences in sport-related concussion rates are an example of how lifestyle, biology, and patient engagement factors interact to influence health. There are important sex/gender differences in sport-related concussions where studies have shown that female athletes are at higher risk for concussion and

take longer to recover from these injuries compared to male athletes.^{119,120}

The science behind sex differences in sport-related concussions is lacking, but some scientists believe that females' smaller, weaker neck muscles may make their heads more susceptible to trauma, while others point to the role hormones might play in the duration of

symptoms.^{121,122} A second theory is that female athletes may be more open about their symptoms than male athletes.¹²³ This theory points to the important role gender plays in engaging patients to be forthcoming about symptoms and recovery. Some research suggests that male athletes may be more likely to underreport their concussion symptoms and to be cleared by their provider to return to sports earlier than they should.¹²⁴ Another theory is that there are psychiatric underpinnings to explain why there may be gender-specific responses after concussion.¹²⁵ In general, studies point to sex/gender differences in concussion symptoms and recovery time. Only further research on sex/gender differences will allow scientists to fully understand whether the differences are related to hormones, anatomy, brain functioning, and/or gendered social norms.¹²⁶

HEALTH EQUITY ACTION PLAN — POLICY RECOMMENDATIONS

Our 2014 report, *Sex-Specific Medical Research: Why Women’s Health Can’t Wait*, included a Health Equity Action Plan to hold federal agencies accountable in addressing the issue of gender inequity in biomedical research and the status of women’s health research conducted under the NIH Revitalization Act. After the release of the report at a summit in 2014, several members of Congress requested that the Government Accountability Office (GAO) report on the status of the NIH Revitalization Act. The GAO report, titled *Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research*, released on October 23, 2015, found that more women than men were enrolled in NIH-funded clinical research. However:

- Enrollment data were not readily available at the institute or center level.
- Detailed enrollment data were not readily available and were not disaggregated by specific research and disease/condition area, making it difficult to examine whether women were adequately represented in clinical research for specific diseases.
- NIH did not maintain, analyze, or report summary data by sex thus compromising NIH’s oversight of implementation of its own inclusion policy.
- NIH did not have a reporting system in place to monitor grant awardees’ analysis plans and compliance with its own inclusion policy.

The Precision Medicine Initiative (PMI) will need to rely on NIH-funded research and the Food and Drug Administration (FDA) oversight to accomplish its goals. NIH’s current inclusion policies and guidelines on the analysis of sex differences do not go far enough to achieve sex/gender equity in preclinical and clinical research, which will negatively impact the PMI. Given the issues detailed in the GAO report findings, we now know that federal legislation alone is not enough to achieve the goals of health equity that will drive innovation in biomedical research. FDA regulations and guidelines also need to be strengthened to ensure that new targeted medicines or medical devices benefit all segments of our population. We will not realize the full value of the vast amount of public and private sector investment in pioneering this new venture if we cannot evaluate its impact on both women and men, of all races and ethnicities. Therefore, standards and guidelines for preclinical and clinical research, and strong oversight systems by government agencies are necessary to ensure that adequate numbers of women are included and the study of sex/gender differences are integrated into every phase of the PMI. Toward that aim, we recommend the following health equity action plan:

1. Hold all NIH investigators accountable for achieving health equity and driving innovation in their research.

- NIH should make reporting on the inclusion of women and racial/ethnic minorities in preclinical and clinical research a criteria of the NIH research review process and a stipulation of funding. Investigators funded by the NIH to conduct preclinical or clinical research must report on the number of women and racial/ethnic minority women. Data on subpopulations should be reported to the registry data bank and the Director of NIH. Submission of these data should be a condition of continued funding.
- Analysis of data on the inclusion of women and minority women in NIH-funded preclinical and clinical research should be made publicly available through the National Institutes of Health and the National Library of Medicine websites.

Investigators funded by the NIH to conduct preclinical or clinical research must report on the number of women and racial/ethnic minority women.

- Investigators should be required, in all published work, to disclose in a standardized format (similar to a nutritional label seen here) how their study addresses sex and whether the data are analyzed by sex/gender.

Research Facts	
Sex-specific breakdown for medical research	
Total number of study	Subjects 100
% Study Subjects	
50%	Women 50 participants
30%	Minorities 30 participants
10%	African American
8%	Latino/Hispanic
5%	Asian
4%	American Indian/Alaska Native
3%	Pacific Islander
<input checked="" type="checkbox"/>	Stratified Analysis by sex conducted
<input checked="" type="checkbox"/>	Stratified Analysis by minority status conducted
<input checked="" type="checkbox"/>	Findings by sex/minority status presented

2. Reform the FDA preclinical and clinical research process.

- FDA policies will govern the development of new drugs and devices produced as a result of the PMI. Therefore, FDA needs to ensure products are developed through research that includes women and diverse populations in all phases of study. The success of the PMI will depend on the promotion of transparency and disclosure to ensure that all medical products are developed using sex-specific and sex-dependent research and that outcomes research includes the routine analysis and reporting of sex differences.

- Medical device and pharmaceutical labels should include a warning label if preclinical and clinical research and testing did not include adequate numbers of female subjects.



- An online gateway should be developed to provide public access to subpopulation data on drugs and devices approved by the FDA for every phase of research and development.

3. Develop a national strategy for achieving health equity in biomedical research.

- The NIH and the Department of Health and Human Services (HHS) should develop a strategic plan to promote the inclusion of women and racial/ethnic minorities in all federally-funded preclinical and clinical research. The plan should be developed by leadership from across the agencies of HHS including all NIH research institutes and centers including the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, and the Food and Drug Administration. Outside reviewers and expertise not affiliated with the government, including researchers and advocacy groups, should be included in the creation of this strategic plan. There must be:

- A plan to ensure that NIH-funded research adequately represents the characteristics of the entire population being studied and includes subpopulation analysis.
- A plan for investing in biomedical research that includes women and racial/ethnic minority women in adequate numbers and the analysis and reporting on subpopulations of women in research outcomes.
- A plan for reporting on the number and proportion of women and racial/ethnic minority women included as subjects in federally-funded research disaggregated by research area, condition, and disease. All research agencies should also report on any single-sex studies with a rationale for why study designs only include one sex.
- A plan that looks to the future of research and innovation in health care, whether in precision medicine, the cancer “moonshot,” or any new research initiative, must include sex and gender. Publicly funded research and the development of new medical products must take advantage of the opportunity to gain knowledge on both sex differences and similarities, and to develop approaches to prevention and treatments that benefit both men and women.

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