U.S. FOOD & DRUG ADMINISTRATION

Center for Devices and Radiological Health

Health of Women Program Strategic Plan

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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FOREWORD

MESSAGE FROM THE CENTER

Innovation | Safety | Effectiveness

These core principles of innovation, safety, and effectiveness are so integral to our mission that they shape how we protect and promote the public health. We protect the public health by using valid scientific evidence to determine whether there is a reasonable assurance that medical devices are safe and effective. We promote public health by facilitating device innovation. In the United States today, patients and their doctors have ready access to safe, effective medical devices that can save lives and improve health. Yet, to fully achieve our mission to improve the health and enhance the quality of life of all patients, it is essential that we recognize that for each of us, our sex and gender have considerable impact on our health and therefore on our interaction with medical devices.

Sex | Gender

Advances in science show that sex and gender differences may play significant roles in the course and outcome of conditions that affect all organ systems in the human body. Now more than ever, we need to understand the implication these attributes have for the performance of medical devices for both women and men, particularly as medical devices play an increasingly prominent role in providing health care to Americans.

The CDRH Health of Women Program | Strategic Plan

Because we recognize the importance of addressing sex- and gender-specific issues in medical technology design, development, and implementation, we have formally created the Health of Women Program in CDRH. We envision a groundbreaking, modern program to explore the unique issues related to the performance of medical devices in women, not only in the reproductive health space, but across a woman's lifetime. Health of Women encompasses health conditions that are specific to women, as well as conditions that are more common or more serious in women, have distinct causes or manifestations in women, have different outcomes or treatment options in women, or have higher morbidity or mortality in women.

This document describes the CDRH Health of Women Program's strategic priorities to continue our commitment to protect and promote public health. As we deepen our understanding of how medical devices work for women, we continue our efforts to help assure that medical devices – those developed specifically for women, and those developed for both men and women – optimally align with the considerations of usability and performance in women. In this way, we achieve the highest quality innovation, safety, and effectiveness for every patient.

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1| EXECUTIVE SUMMARY

The Center for Devices and Radiological Health (CDRH) has long been interested in a health of women framework to explore the unique issues related to the performance of medical devices in women. In 2016, CDRH formalized the creation of its Health of Women Program to address the steadily growing importance of sex- and gender-specific issues arising regarding medical technology design and development, clinical and non-clinical study design, and other medical device-related matters.

The CDRH Health of Women Program is charged to:

- Explore unique issues related to the performance of medical devices in women
- Improve analysis and communication of sex- and gender-specific data to better assure the safe and effective use of medical devices
- Develop and implement health science programs, strategies, and initiatives focused on women's health issues across CDRH

We seek to bring together industry, clinicians, researchers, patients, academia, government agencies, advocacy groups, and all customers[a] in an effort to encourage innovations in research study design, device development and appropriate ways to share information with women and their health care providers to help them make informed decisions about which device may best meet their needs.

Mission

The mission of the CDRH Health of Women Program is to protect and promote the health of all women.

Vision

Our vision is that customers, including patients, caregivers and providers, have timely access to high quality, safe and effective medical devices that perform optimally in women, as well as access to relevant and understandable sex- and gender-specific information about medical devices that can be used to make informed health care decisions.

Priorities

The CDRH Health of Women Program intends to focus its efforts on three priority areas:

[a] CDRH defines our customers as the members of the medical device ecosystem – including patients, industry, and health care professionals – and our colleagues. US FDA CDRH 2016-2017 Strategic Priorities.

Priority 1 – Sex- and Gender-Specific Analysis & Reporting

Improve availability, analysis, and communication of sex- and gender-specific information for the safe and effective use of medical devices to improve and better understand the performance of medical devices in women

- Optimize CDRH practices for consistent sex- and gender-specific data collection, analysis, and reporting
- Ensure CDRH's policies evolve with current science

Priority 2 – Integrated Approach for Current & Emerging Issues Related to the Health of Women

Strengthen internal health science programs and initiatives across CDRH, working together with CDRH offices and our customers, to create actions to improve the overall health and quality of life for women

- Coordinate and lead an integrated approach to analyze current and emerging issues related to the health of women
- Explore innovative strategies, technologies, and device-specific study paradigms
- Develop Center-wide policies and outreach activities related to the health of women

Priority 3 – Research Roadmap

Develop a research roadmap for the health of women device ecosystem

- Address identified gaps and unmet needs related to the health of women through targeted resources
- Promote advancement of regulatory science related to health of women



Through identification of these priorities and implementation of this strategic plan, along with insight obtained from public comments, we hope to further our mission of protecting and promoting the health of women, strengthen regulatory science, and more easily identify and address current and emerging issues for the health of women.

2| INTRODUCTION

Every cell has a sex that alters physiology at the molecular, cellular, and macro-organism level; affects behavior, perception, and health; and has implications for biomedical research, intervention, and all of health care.[1] There is a steadily growing body of evidence showing that sex and gender[b] differences may play significant roles in the course and outcome of conditions that affect all organ systems in the human body.[2] Current science indicates existence of both sex- and gender-based differences in numerous disorders including cardiovascular disease, pulmonary dysfunction, neurological debility, irritable bowel syndrome, endocrine and autoimmune disorders, and mental illness.[1-3] What implication does this have for the performance of every medical device in the health care for both women and for men, particularly as we move toward the goal of tailoring intervention to the individual or class of individuals?

Our Origin

CDRH has been working towards a better understanding of how medical devices perform in women and exploring unique issues in the regulation of medical devices related to the health of women.

In 2013, the FDA held a workshop entitled the "CDRH Health of Women (HoW) Program: Educate, Enable, Enlist and Explore – HoW to Improve the Health of Women."[4,5] This workshop sought public input on the priority activities for the CDRH Health of Women framework, and was a foundational step in launching the CDRH Health of Women Program. At the workshop, FDA discussed device-specific clinical study recruitment and retention strategies; analysis and communication of sex-specific findings to providers and patients; and a priority research road map for the health of women device ecosystem. Ideas generated at this workshop helped shape early programmatic goals that included:

- *Analysis & Communication*
  - Achieve consistent analysis, labeling, and reporting of inclusion and outcomes for women
  - Finalize the then draft Guidance on Sex-Specific Data in Medical Device Clinical Studies[c]
- *Recruitment & Retention*
  - Develop strategies for unique challenges of medical device trials
- *Research*
  - Perform gap analysis to identify priority research areas

[b] Sex is a classification derived from the chromosomal complement. Gender is a person's self-representation as male or female. Definitions derived from Institute of Medicine report entitled *Exploring the Biological Contributions to Human Health: Does Sex Matter?*, The National Academies Press, Washington, DC; 2001.
[c] US Food and Drug Administration, Center for Devices and Radiological Health. Guidance on Evaluation of Sex-Specific Data in Medical Device Clinical Studies for Industry and Food and Drug Administration Staff. Final document issued on August 22, 2014; https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf.

    - Explore patient-reported outcomes and preferences
- *Partnerships*
    - Forge and strengthen partnerships with industry, federal agencies, and professional societies
    - Develop communication strategies in partnership with stakeholder groups

In 2016, the FDA formalized the creation of the CDRH Health of Women Program to address the steadily growing importance of sex- and gender-specific issues arising in regard to medical technology design and development, clinical trial design, and other medical device-related matters. The terminology, "health of women" encompasses not only health conditions uniquely specific to women, but conditions that are more common or more serious in women, have distinct causes or manifestations, different outcomes or treatment options, or higher morbidity or mortality in women. Health of women extends far beyond reproductive, gynecologic, or breast health. It comprehensively includes the health of the entire female human being.

Our mission is to protect and promote the health of all women, both as a collective, and as individuals. We are guided by science to embrace all health of women subpopulations, including sexual and gender minorities[d].

Highlights of the Health of Women Regulatory Landscape

In section 907 of the Food and Drug Administration Safety and Innovation Act (FDASIA)[6] (2012), Congress directed the FDA to address the extent to which clinical trial participation and safety and effectiveness data stratified by demographic subgroups (sex, age, race, ethnicity) are included in applications submitted to the FDA. It also directed FDA to report on the extent to which subgroups participate in clinical trials, whether reports of subgroup safety and effectiveness are reported to FDA in a manner consistent with FDA requirements and guidance, and whether and how safety and effectiveness data by subgroups is eventually made public.

In 2013, the FDA published the FDASIA 907 Report.[7] In this document, FDA reported on the demographic subgroup analyses and public disclosure of information from sources including Premarket approval applications (PMA) for class III devices. The Report noted that 88 percent of approved PMA applications reviewed included sex-specific data analysis, and that 63 percent of the PMA applications reviewed publicly reported the sex subgroup analysis results.

[d] "Sexual and gender minority" is an umbrella term that encompasses lesbian, gay, two-spirit, bisexual, and transgender populations as well as those whose sexual orientation, gender identity and expressions, or reproductive development varies from traditional, societal, cultural, or physiological norms. This includes individuals with disorders or differences of sex development, sometimes known as intersex. Definition provided by the Sexual and Gender Minority Research Office, National Institutes of Health. https://dpcpsi.nih.gov/sgmro.

In 2014, the FDA issued the FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data[8] in response to section 907 of FDASIA, announcing the Agency's plan to improve the completeness and quality of demographic subgroup data collection, reporting, and analysis, and to make these data more available and transparent.

Also in 2014, the FDA issued a guidance titled Evaluation of Sex-Specific Data in Medical Device Clinical Studies,[9] outlining FDA's expectations regarding sex-specific patient enrollment, data analysis, and reporting of study information for medical device applications. The primary intent of the guidance is to improve the quality and consistency of available data regarding the performance of medical devices in both sexes by encouraging appropriate enrollment by sex in clinical studies of devices, and that data from such studies are appropriately analyzed by sex.

Sex and gender data have also been key considerations for other divisions within the U.S. Department of Health and Human Services (HHS). In 2015, the NIH released its policy on sex as a biological variable stating that sex and gender play a role in how health and disease processes differ across individuals, and that consideration of these factors in research studies informs the development and testing of preventive and therapeutic interventions.[10,11] This policy specified that investigators must explain how relevant biologic variables, such as sex, are factored into research designs, analyses, and reporting of vertebrate animal and human studies; and in additional guidance, asked that investigators consider and describe how sex and gender may influence the research question(s) at hand.[10,12] Further, in 2016, section 2039 of the 21st Century Cures Act,[13] required the NIH to develop and issue recommendations for a formal policy to enhance rigor and reproducibility of scientific research funded by the NIH, and to consider a variety of factors that contribute to health disparities. Such factors include, but are not limited to, preclinical experimental design, including analysis of sex as a biological variable, and clinical experimental design, including the circumstances under which to conduct an analysis of the data collected during clinical studies on the basis of biological, social, and other factors that contribute to health disparities.

Sex- and Gender-Specific Data

"Every cell is sexed and every person is gendered."[14] *Sex* is a classification assigned by chromosomal complement.[11] It refers to an individual's biological characteristics, and is typically binary.[11,14] Genes on sex chromosomes are responsible for sex determination, sexual differentiation, and the orchestration of developmental programs that produce male and female anatomy and physiology.[15] Alternatively, *gender* refers to the social construct by which we define ourselves as man, woman, or other.[11,15] Our understanding of one's gender is highly influenced by our experiences, environment, and societal views of ourselves and others, as well as our socially-defined gender "roles".[15]

While sex and gender are distinct, they are interrelated and are not necessarily mutually exclusive.[3] Both sex and gender and their interactions may drive epigenetic influences and resultant physiologic reactions, influence etiology and presentation of disease, and affect treatment outcomes.[3,16]

Consideration of sex and gender is a critical component of the development and performance of medical devices. Based on initiatives taken and knowledge gained through actuation of the Strategic Plan, we aim to refine current, and develop new, policies and recommendations to help innovators and researchers consider the potential influence of sex- and gender-specific data and address these in the experimental design, analysis, and reporting of medical device biomedical research. Our hope is that this may lead to a stronger foundation upon which to develop devices and better inform the research community as to whether such influences need to be factored into the design and power calculations of future studies.

CDRH's vision is that with an integrated approach, innovators, researchers, and CDRH staff have the tools necessary to consider how sex and gender are factored into research designs, device development, and analyses of studies in humans, vertebrate animals[e], tissue culture and primary cell lines, when such are appropriate and/or necessary.

Our intent in structuring the Health of Women Strategic Plan is to embrace an approach that is both driven by science and based on least burdensome[17] principles. Since the Food and Drug Administration Modernization Act of 1997 (FDAMA), Congress has directed the FDA to take a least burdensome approach to medical device premarket evaluation in a manner that eliminates unnecessary burdens that may delay the marketing of beneficial new devices, while maintaining the statutory requirements for marketing authorization. In accord, the FDA defines "least burdensome" to be the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time.[17] Still, reasonable assurance of safety and effectiveness of a device is determined on the basis of valid scientific evidence (21 CFR § 860.7(c)(1)).

The principal objective is to spark innovation, never stifle it. Innovators and researchers are not being asked to generate more data, but to analyze and report on data already generated.

The CDRH Health of Women Program approach **begins with collecting, analyzing, and reporting data in a sex- and gender-disaggregated manner.** We recognize that the absence of scientific data does not mean there is an absence of knowledge, which may further support the need to report findings about sex and gender-based differences to help move the science forward.

[e] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage applicants to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method. Principles of 3Rs derived from Russell WMS, Burch RL. *The Principles of Humane Experimental Technique*. London, UK: Methuen; 1959.

Through the CDRH Health of Women Program, we plan to foster the development of tools to improve the completeness and quality of demographic subgroup data collection, analysis, and reporting to clarify expectations and update device submission recommendations, and refine policies and training to support more consistent and transparent collection, analysis, and communication of demographic subgroup data center-wide.

Collecting, analyzing, and reporting data disaggregated by demographic subgroups, including sex and gender, has a number of potential benefits, including:

- *Consistent and Efficient Processes* – provides a consistent approach for research considerations, study design, analysis, and reporting recommendations to support regulatory decisions; unencumbers innovators and researchers from seemingly disparate expectations or recommendations regarding scientific approach[18]
- *Save Resources* – prospectively considering the impact of sex and gender may result in saving resources in the long-term by revealing differences or similarities that need to be taken into consideration in subsequent phases of innovation and/or postmarket needs, which may be particularly crucial for small companies with only one device in development[18]
- *Improve Data Quality* – among other factors, well-characterized data help innovators and researchers develop safer, more effective, high-quality devices for their intended populations; help minimize disproportionate adverse events in women; help CDRH staff appropriately apply benefit-risk factors in the determination of reasonable assurance of safety and effectiveness; help CDRH achieve more efficient surveillance and signal detection[18]
- *Strengthen Science* – expands availability of sex- and gender-specific data; allows innovators and researchers to more readily build upon a stronger body of knowledge; enhances efficiency of future regulatory research[18]
- *Enrich Patient Information* – further enables women's access to relevant and understandable sex- and gender-specific information about medical devices that can be used to make health care decisions

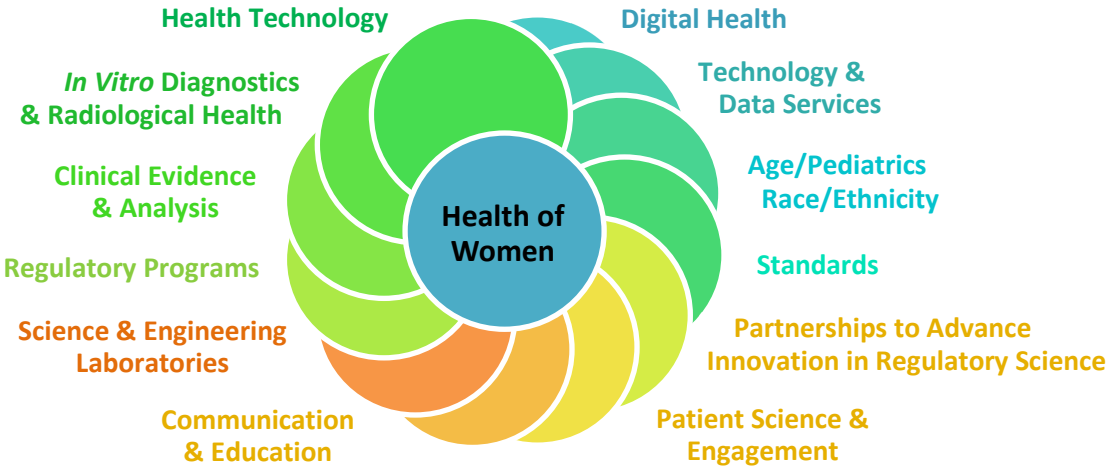
The Science is Ready and Scientists are Primed

The science has advanced. Developments in basic scientific and clinical data support the concept that sex is a basic biological variable and that every cell is sexed.[3] CDRH intends to explore modernizing our policies and to account for inclusion and evaluation of medical device data representing demographic subgroups, including sex- and gender-specific data. We also intend to develop an integrated approach for how CDRH can address current and emerging issues related to the health of women, and can strengthen the regulatory science for the health of women device ecosystem. In these ways, we will continue to work to assure that medical devices are innovated to perform safely, effectively, and optimally in all women.

3| THE PLAN

An Integrated Approach

The CDRH Health of Women Program provides the framework for an integrated approach that is intended to seamlessly interface with existing programs and offices across CDRH to address the steadily growing importance of the health of women to both internal and external customers. This approach will capitalize on common issues and goals across the Center.



The Health of Women Program shares these common goals with:

Technology & Data Services	• *Efficient streamlined data collection structures allowing for facile data extraction and analysis*
Age/Pediatrics – Race/Ethnicity	• *Subgroup data collection, analysis, reporting*
Partnerships to Advance Innovation in Regulatory Science **Patient Science & Engagement** **Communication & Education**	• *Engagement and education with external and internal customers* • *Patient perspectives to make informed and sound decisions*
Digital Health **Standards** **Health Technology** ***In Vitro* Diagnostics & Radiological Health** **Clinical Evidence & Analysis** **Regulatory Programs** **Science & Engineering Laboratories**	• *Safer, more effective, high-quality devices for their intended populations* • *Refined effectiveness and safety parameters* • *Better surveillance and signal detection* • *Inclusion of women in clinical trials*

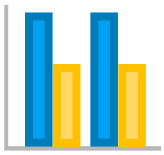
Priorities | Goals | Strategies | Outcomes

The CDRH Health of Women Strategic Plan described in this section outlines key strategies for the CDRH Health of Women Program to further its mission of protecting and promoting the health of all women through implementation of the following three programmatic priorities. Moreover, these collective strategies align with all priority areas of the FDASIA Section 907 Action Plan.

PRIORITY 1

Sex- and Gender-Specific Analysis & Reporting

Improve availability, analysis, and communication of sex and gender specific information for the safe and effective use of medical devices to improve and better understand performance of medical devices in women



Goal 1.A. Optimize CDRH for consistent sex- and gender-specific data collection, analysis, and reporting

Strategy 1.A.1.	**Assess current regulatory landscape regarding sex- and gender-specific data collection, analysis, and reporting**
Strategy 1.A.2.	**Evaluate internal workflow documents and update as needed for increased consistency related to sex- and gender-specific data collection, analysis, and reporting**

Strategy 1.A.3.	**Integrate sex- and gender-specific data collecting structure within CDRH's data collecting systems**
Strategy 1.A.4.	**Expand communication strategies regarding sex- and gender-specific data collection, analysis, and reporting**
Strategy 1.A.5.	**Further develop training/education plans for sex- and gender-specific data collection, analysis, and reporting**

Goal 1.B. Ensure CDRH's policies evolve with current science

Strategy 1.B.1.	**Update existing policies to align with the current scientific landscape**
Strategy 1.B.2.	**Develop recommendations related to non-clinical studies for sex and age sub-group analysis**

These strategies are intended to help us strengthen our processes for subgroup data collection, analysis, and reporting, and amplify capacity for continued innovation in this space. We intend to work closely with our offices and staff throughout CDRH to further ensure consistency in our systems, and coordinate the mapping of common data elements for sex and gender into established systems. We plan to explore enhancements in the use of data science technology to extract, manage, and analyze sex- and gender-specific data, and leverage data from digital technologies and electronic health information sources. We seek to ensure that our policies evolve with current science. And along with all of this, we strive to expand and further develop communication strategies and training/education plans for sex- and gender-specific data collection, analysis, and reporting. Our aim is to achieve improved understanding

and use of these data in submissions to CDRH, and to improve clarity and ease of access to the information that we provide about medical devices.

PRIORITY

1

Intended Outcomes for Priority 1:

- **Improved understanding and use of sex- and gender-specific data for premarket submissions and post market surveillance**
- **Improved clarity and ease of access to the information that we provide about medical devices**

PRIORITY

2 Integrated Approach for Current & Emerging Issues Related to the Health of Women

Strengthen internal health science programs and initiatives across CDRH, working together with CDRH offices and our customers, to create actions to improve the overall health and quality of life for women

Goal 2.A. Coordinate and lead a center-wide integrated approach to analyze current and emerging issues related to the health of women

Strategy 2.A.1.	Create novel responsive and proactive approaches to identify issues and trends related to the health of women across the total product life cycle (development, evaluation, surveillance, real world evidence), incorporating both comprehensive and device-specific strategies
Strategy 2.A.2.	Leverage current and develop new systematic science-based approaches to address identified current and emerging issues related to the health of women

Strategy 2.A.3.	Develop an internal CDRH leadership Health of Women Steering Committee to provide recommendations to the Center
Strategy 2.A.4.	Form a CDRH Health of Women Core Community of Practice to coordinate existent subject matter expertise within the Center

Goal 2.B. Explore innovative strategies, technologies, and device-specific study paradigms

Strategy 2.B.1.	Expand existing and create new strategic alliances to maximize innovation in the health of women device ecosystem
Strategy 2.B.2.	Explore how to best incorporate findings of sex and gender differences in the design and application of new medical device technologies
Strategy 2.B.3.	Explore potential recommendations for encouraging innovation for novel device-specific study paradigms to address women-specific or sex- and gender-specific issues

Goal 2.C. Develop center-wide policies and outreach activities related to the health of women

Strategy 2.C.1.	Work in partnership with CDRH offices to develop initiatives to better incorporate women-specific issues and sex- and gender-based considerations in the regulatory framework

Strategy 2.C.2. Develop new communication and social networking strategies to increase understanding and appreciation of health of women device ecosystem and health of women issues for medical devices

To achieve these strategies, our outreach is both internal to our center and external to engage our customers. Internally, we plan to strengthen our approach in how we as a center survey, identify, scientifically evaluate, track, prioritize, address, and report current and emerging issues related to the health of women. We hope to harness the culture of continuous improvement throughout the Center and develop more creative and innovative approaches to better incorporate women-specific issues and sex- and gender-based considerations in our regulatory framework.

Reaching outward we aim to explore establishing new ventures and initiatives with a wide cross-section of partners to support research and innovation to improve the health of women device ecosystem throughout the world, including FDA, academia, other federal agencies, industry, private foundations, patient/advocacy groups, and international organizations. We hope to help foster innovative technologies that may address sex- and gender-based differences via alternative means, including novel animal[f], *in vitro*, and computational models to study sex differences; information systems used for collecting, sharing, and comparing clinical data; and sex- and gender-conscious engineering design and development of medical devices. We will continue to encourage innovative clinical trial designs and data analysis approaches to address women-specific or sex- and gender-specific issues. And we intend to expand our outreach activities related to the health of women and medical devices and serve as a key informational resource for the public by developing new communication and social networking strategies and better messaging to increase understanding and appreciation of the health of women across the medical device ecosystem.

[f] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage applicants to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method. Principles of 3Rs derived from Russell WMS, Burch RL. *The Principles of Humane Experimental Technique*. London, UK: Methuen; 1959.

PRIORITY

2

Intended Outcomes for Priority 2:

- **Developed processes for early identification and communication of adverse effects of medical devices on women**
- **Facilitated establishment of new strategic alliances to maximize innovation and safety in the health of women device ecosystem**

PRIORITY

3 Research Roadmap

Develop a research roadmap for the health of women device ecosystem

Goal 3.A. Address identified gaps and unmet needs related to health of women through targeted resources

Strategy 3.A.1.	Leverage intramural and extramural regulatory research programs and projects to address identified gaps and unmet needs related to the health of women
Strategy 3.A.2.	Develop peer-reviewed reports and other tools that can be referenced and accounted for in regulatory submissions

Goal 3.B. Promote advancement of regulatory science related to health of women

Strategy 3.B.1.	Establish portfolio of women-specific device efforts
Strategy 3.B.2.	Build upon the sex- and gender-specific analysis and reporting of available data within the Center

Strategy 3.B.3. **Establish a Health of Women initiative on the science of patient input**

Strategy 3.B.4. **Work with customers to build registries of women's devices and facilitate sex and gender analyses in registries of devices developed for use in both men and women**

Strategy 3.B.5. **Enhance recommendations on clinical trial device design**

Our goal in pursuing these strategies is to advance regulatory science for the health of women and improve evidence generation for women about the safety and effectiveness of health technologies. We want to discover and improve our understanding of the clinically-meaningful sex and gender-based difference outcomes that are best to incorporate into clinical trial designs that are looking specifically for sex- and gender-specific outcomes. And we will constantly seek to identify areas where clinical trial enrollment can be better balanced for women.

We aim to establish a portfolio of women-specific device efforts and strategize around gap areas to inform our research roadmap development. We hope to explore regulatory research programs to address identified gaps and unmet needs for the health of women device ecosystem. We plan to establish a science of patient input initiative to better understand women's experience with devices and to incorporate this into our decision making. We plan to continue to work with customers to build a coordinated registry network for women's health technologies. And, we intend to leverage existing registry networks for devices used in both men and women to evaluate for sex- and gender-specific differences.

PRIORITY

3

Intended Outcomes for Priority 3:

- **Established portfolio of Health of Women devices and gaps identified to inform research roadmap**
- **Established Health of Women initiative on the science of patient input**
- **Established appropriate relationships to foster developing and supporting women's device registries**

4| SUMMATION

Over recent decades, the scientific knowledge about the health of women has evolved alongside advancements in medical technology, and this ecosystem will continue to evolve. The scientific community is learning how to integrate biological sex and current gender identity into understanding of the presentation of disease, risk assessment, proper testing, effective treatment; and incorporate this gained knowledge into communication strategies.[19] CDRH is committed to identifying and acting on opportunities to improve the lives of those relying on our expertise and to address the complex and rapidly changing regulatory challenges related to health of women.

The CDRH Health of Women Program welcomes comments and feedback on the outlined Strategic Plan and encourages other ideas and suggestions on how we can strengthen our collection and dissemination of information associated with sex and gender related devices.

Comments and feedback can be sent to docket number FDA-2019-N-3804 in the Federal Register.

5| APPENDICES: SCIENTIFIC RATIONALE

Sex and gender are dynamic modulators of human development and have impact on disease epidemiology, etiology, presentation, diagnosis, treatment, response to therapy, safety, and outcomes.[20] Attention to these distinctions has evolved as a standard of scientific design of research and evidence-based medicine.[21] Advances in science show that sex and gender influence all aspects of human health, and that considerations of both sex and gender are important in the development and performance of medical devices.[22] "We have learned that it is necessary to examine variables of sex and gender across the spectrum of research, from basic molecular and cellular studies to clinical investigation, and ultimately to clinical application – providing personalized sex- and gender-appropriate health care to the individual."[21]

At present, most data are sex-based as this research includes non-clinical studies, which can be accomplished in less time than gender-based clinical trials. As the science continues to grow, more gender-based studies will emerge. Below we offer a review of some significant findings in sex- and gender-based research; some with known impact on medical device performance as outlined; others with promising significance to medical device design and development, diagnostics, and ionizing radiation; and all with discernible contribution to the understanding of sex- and gender-based differences in the performance of medical devices.

A. History of Male Predominance in Research

Historically, biomedical research has been conducted predominantly in males. However, sex is a principal biological variable with immense consequence.[23] Insufficient representation of female cells and animals in non-clinical research, and females in clinical research, has resulted in limited understanding of the biological, physiological, and patho-physiological mechanisms in the female versus the male.[23] Without data from females, it is not feasible to resolve whether results from male cells and animals also apply to female cells and animals.[23] Traditional reliance on male vertebrate animals in non-clinical research has generated incomplete data to inform translation to clinical trials that enroll both males and females.[24] And these issues extend beyond the basic biological research fields.[3] In the surgical literature, for female-prevalent diseases, only 12 percent of studies that indicated sex of the animals, studied female animals.[25]

Data from females are prerequisite for our better understanding of health of women in general, and the health of women device ecosystem more specifically.

B. Sex is a Basic Biological Variable

Since the *landmark* Institute of Medicine report titled *Exploring the Biological Contributions to Human Health: Does Sex Matter?*[11], there has been deliberate escalation in basic science research and the development of clinical data to affirm the premise that sex is a basic biological variable and that every cell has a sex.[3] Risks for cardiovascular disease and responses to biomedical intervention vary between women and men.[3] Aspirin has a different preventive result in women versus men.[3] In women, aspirin decreases risk of ischemic stroke, whereas in men, aspirin therapy decreases risk of heart attack.[26-30] Cholesterol plaque in women may not develop into major arterial blockages, but alternatively spreads more uniformly throughout the artery wall, making arterial compromise more challenging to diagnose in women, and is indicative of an entirely different underlying microvascular physiology and pathology.[31-33] Women more often require permanent pacing for sick sinus syndrome than men, and appear to have a higher incidence of complications with pacemaker implantation.[34] The majority of reported adverse drug events occur in women.[35-37] And while women are more prone to multiple sclerosis than men, they manifest more moderate forms of the disease.[38]

There are clear distinctions in global gene expression patterns between male and female animals.[3] In mice, 50 to 75 percent of genes displayed sexually dimorphic expression in tissues such as liver, fat, and muscle.[39] Seventy-two percent of active genes in the liver were sex-biased (expressed differently in the two sexes), 68 percent in adipose tissue, 55 percent in muscle, and 14 percent in the brain. While mean difference in sexually dimorphic gene expression level was only eight to nine percent between males and females, this sex difference in a majority of genes may indicate existence of fundamental sex differences in physiology.[40]

There are sex-based differences in metabolism and related conditions.[41] In humans, DNA methylation patterns differ between men and women for genes involved in metabolic and cardiovascular disease.[42] There are sex-based differences in gene expression of P450 cytochromes (CYP), responsible for metabolizing agents, toxins and hormones.[43] In women, higher levels of CYP1A1, prominent in the metabolism of aromatic hydrocarbons, results in increased levels of carcinogenic DNA segments in some tissues.[44] Human female liver cells contain more of the cytochrome (CYP3A) that accounts for metabolism of half of medical substances, which may have implications for sex-specific response to agents in combination devices.[45-48]

Sex Chromosomes and Gonadal Hormones

All biological sex differences are initiated at the genetic level by the genes of the sex chromosomes.[49] Dissimilarity between XY and XX cells may be imputed to: (a) Y genes only in male cells, (b) a higher dose of X genes in female compared to male cells with inactivation of one X chromosome in female cells, (c) mixed maternal and paternal genomic imprint on X genes in female cells, and (d) only maternal imprinting on X genes in male cells.[50] The SRY gene on the Y chromosome, which initiates a

testis-determining cascade and resultant secretion of testosterone, also affects expression of other genes on the autosomal chromosomes.[49] The X chromosome, exceedingly complex, manifests effects across the entire organism with genes involved in cellular function, metabolism, development; and growth of neurologic, cardiovascular, endocrine, hematologic, and immunologic systems; oncogenic processes; and of course reproductive physiology.[51,52]

Though sex differences originate from a differential of X and Y genes, sex hormones cause sex-based distinctions in gene expression by acting directly on genes *throughout* the genome.[3,40] Gonadal hormones regulate gene expression through hormone receptors and cause both long-term (activational and organizational) and short-term effects.[40] As evidenced in the heart, estrogen functions via the estrogen receptor and directly initiates the transcription of genes containing an estrogen-responsive element in the nucleus of cardiac myocytes.[53,54] Furthermore, estrogen affects other signaling pathways in the heart including calcium influx, nitric oxide production, and growth factor receptor signaling.[54] What is observed clinically is that sex and gender differences affect heart rhythms. For instance, women have higher resting heart rates, longer QT intervals, and increased risk for agent induced fatal heart arrhythmia (torsades de pointes) than men.[55-57]

Physiologic Systems and Medical Device Technologies

In the cardiovascular system, sex-based differences are observed in clinical outcomes with several medical device types. With left ventricular assist devices, women have a higher risk for right ventricular failure, stroke, other neurologic complications, arrhythmias, bleeding and thrombosis.[58-64] It is important to know more about sex-based differences in the thrombosis cascade. Women are more likely than men to have complications from implantable cardioverter-type defibrillators.[65] Although earlier trials suggested a less vigorous response in women from implantable cardioverter defibrillators, this was likely the result of the few women enrolled in these studies.[55] More recent reports, with more equal sex distributions, demonstrated comparable outcome gains to men.[55,66] With cardiac resynchronization defibrillators, women demonstrate greater benefit than men overall (cardiac left ventricular function, and survival), particularly with left bundle-branch-block; but also at different thresholds compared to clinical guidelines.[67-69] Women benefited even at a shorter QRS interval, which may have implications for targeting a shorter QRS duration as the treatment criterion in women.[69] Women undergoing percutaneous coronary intervention with drug-eluting coronary stents are at increased risk for both antithrombotic drug-related bleeding and vascular complications from both femoral and radial artery access compared with men.[70-72] Female sex independently predicts bleeding and death after percutaneous intervention.[73,74] For endovascular grafts, while abdominal aortic aneurysm (AAA) occurs predominantly in men (only 21 percent of AAA occur in women), women have up to a four-fold higher risk of AAA rupture, and have higher perioperative morbidity and mortality from endovascular aneurysm repair.[75-77] Based solely on anatomy (neck length, neck diameter, angulation, landing zone diameter, and access diameter), significantly more women were ineligible for endovascular aneurysm repair than men.[78]

There are other cardiovascular sex-based differences that may influence device performance. In Takotsubo (stress-induced) cardiomyopathy, women seem more susceptible to catecholamine-induced myocardial dysmotility due to their small left ventricular size.[79-82] Estrogen modulation of endothelial vasoreactivity, adrenal glands, and the central nervous system can counteract the sympathetic nervous system.[83] And, although men are more likely than women to experience atrial flutter, surgical treatment (ablation) of this arrhythmia affects women and men differently.[84] After ablation, women are more likely to experience surgical complications and have persistent atrial flutter.[84]

In the brain, testosterone can cause significant anatomic sexual dimorphism,[53] with sex differences in every lobe of the brain, including many cognitive loci such as the amygdala, hippocampus and neocortex;[85,86] affecting brain morphology and neurocognitive function.[87] Moreover, sex differences can be relatively widespread.[85] Broad regions of the cerebral cortex are thicker in women than in men and ratios of grey to white matter also differ.[88,89] Some structures (such as hippocampus) are larger in the female brain, others (such as amygdala, hypothalamus) are larger in the male brain relative to cerebral size.[90] When the structural connectome was examined, males were found to have stronger front-to back circuits (links between perception and action), and females were found to have stronger left-to right circuits (links between reasoning and intuition).[91]

Male and female neurons respond uniquely to numerous stimuli.[3] Male neurons are more prone to oxidative stress and excitotoxicity, and lack the capacity to maintain intracellular levels of reduced glutathione.[92] These observations are pertinent to many central nervous system conditions where nitrosative stress is thought to be a contributing factor, such as cerebral ischemia and traumatic brain injury.[93] Variations in how male and female neurons respond to oxidative stress and ischemia may partially explain the observation that boys have a poorer outcome following traumatic brain injury than girls.[93] In contrast, female neurons are more sensitive to apoptosis-inducing etoposide and staurosporine.[92] Moreover, other investigators have shown that the apoptosis pathways are different in males and females.[94] After cytologic challenge in male neurons, programmed cell death predominantly follows a caspase-independent (poly-ADP-ribose polymerase/nitric-oxide-mediated) pathway; whereas in female neurons, this process follows a caspase-dependent (cytochrome C) pathway. In addition, there is an incapacity of male neurons to preserve intracellular levels of reduced glutathione, a major protector from oxidative insult.[92] The Y chromosome predisposes mice to greater central nervous system neurodegeneration than the X chromosome.[95]

In humans, the sex of the patient can have significant effects on enzyme activity, protein binding, receptor density, pharmacokinetics, and outcomes of the brain injury cascade.[96] These data have implicit indications for diagnosis and treatment of stroke, cerebral ischemia, traumatic brain injury, neurodegenerative debilities and other neurologic conditions with sex-specific characteristics such as schizophrenia and Parkinson's disease.[85,92,97] And neuroscience researchers have recognized and

identified sexual dimorphism in these clinical disorders as well as intracranial aneurysms, Tourette syndrome and obsessive compulsive disorder.[97-99]

In orthopedics, implanted devices are affected by sex. Women have an increased risk of knee osteoarthritis than men, and greater severity at presentation.[100,101] More women have total knee replacement surgery than men in the United States, and are three times more likely than men to undergo total knee replacement at a more advanced stage.[100-105] Women undergoing primary total knee replacement surgery for end-stage osteoarthritis experience worse pre- and post-operative pain and pre-operative functional scores than men.[100,106-108] However, even though women achieve greater improvement in outcome, women do not reach the benefit levels of men in final outcome.[100,109] While it is known that there are anatomical differences between the male and female knee, the literature has not supported the clinical need for sex-specific total knee prostheses, and anatomical differences may be generally addressed through implant size rather than implant design considerations.[110] Retrospective analysis of total knee replacement with a high-flex knee showed no sex-based difference in postoperative motion gains.[110]

In regards to hip fractures, older women who fall have twice the fracture incidence of older men.[111-113] More women undergo total hip replacements than men in the United States, and are at higher risk for surgical revision [odds ratio (OR) 2.5] than men when undergoing primary metal-on-metal hip resurfacing arthroplasty.[105,114,115] Female patients are also at higher risk for adverse local tissue reaction [OR 5.7], dislocation [OR 3.04] and aseptic loosening [OR 3.18] when compared to men.[114] Smaller femoral head size, acetabular geometry, metal allergy, and component malpositioning may be contributing factors.[114]

Sex-specific disease prevalence may suggest underlying sex-based influences,[116] and this may have impact on medical devices. For spinal fusion devices for adolescent idiopathic scoliosis (AIS), there is a 1.5- to three-fold higher prevalence of AIS in girls than in boys.[117,118] And for fracture fixation devices, bone growth stimulators, and stereotaxic devices, trauma fractures are more common in men in youth and women in old age.[119,120] Current treatment recommendations are the same, but will this be the case in the future?

Disease Processes and Diagnostics

For some disease processes, there is a sex-based divergence in gene association. This may have several implications for sex-based diagnosis and treatment strategies for these clinical conditions, as well as sex-based performance of medical devices for these clinical indications. For Alzheimer's, the presence of apolipoprotein E (ApoE)-4 has been associated with an increased risk of Alzheimer's disease.[121] This was later found true for women, but not as true for men.[121] In post-traumatic stress disorder, studies have found an association for pituitary adenylate cyclase – activating polypeptide

(PACAP) and PACAP selective (PAC1) receptor – in women, but not in men; and for the glucocorticoid receptor gene – in men, but not in women.[122,123]

Mental health studies have shown that there is a sex-based difference in cellular reaction to chemical and microbial stressors.[124] Substance abuse is affected by sex.[125] Female rats present a greater stress-induced norepinephrine response than male rats.[126,127] In humans, transient reduction of stress related cocaine and alcohol craving, anxiety and negative emotion has been shown in females, but not in males when using the alpha2 adrenergic agonist guanfacine, which attenuates the body's neurologic reaction to stress.[128] Sex-based differences in substance abuse and stress response may have implications for both sex- and gender-based differences in performance of devices for pain management.

Estrogen effects on immune response and inflammatory reaction may affect performance of implantable and endovascular devices. Estrogen increases the immune response while testosterone hinders it as supported by the greater incidence of posttraumatic pneumonia and multisystem organ failure in men versus women.[129,130] Estrogen influences the brain's response to acute stroke by acting on endothelial cells, microglia, astrocytes and neurons.[97,131,132] Explicitly, estrogen is vasodilatory and antiadhesive in endothelial cell models, and suppresses inflammatory pathways in neural cells.[97,131,132] This may have implications for endovascular catheters, coronary stents, and neurologic and spinal implants.

In multiple sclerosis, a disease characterized by neurodegeneration, inflammation and autoimmunity, sexual dimorphism is exhibited in both the reproductive and non-reproductive states.[133] Sex-based differences for multiple sclerosis in the animal model (rodent experimental autoimmune encephalomyelitis) and in the human are now correlated with genetic factors.[95] Some Y chromosomal genes in male mice are protective against the disease, and some X chromosomal genes have a disease-causing effect, and this may have implications for multiple sclerosis diagnosis and intervention.[95]

There are sex-based differences in diagnostic testing patterns. For women, the focus of imaging is changing from an anatomy-based coronary artery disease assessment to a more physiologic-based ischemic heart disease analysis.[79,134] The reason for this shift is that women suffer more often than men from microvascular cardiac disease, primarily in the precapillary coronary arterioles.[135] As a result, imaging limited to epicardial artery anatomy may be less useful in women than in men.[136] In contrast, diagnostic measurements of cardiac perfusion, microcirculatory resistance, and coronary flow reserve may be more beneficial in women.[137-140] This shift in diagnostic testing patterns is also evident in neurology where studies from the National Inpatient Sample showed that women with acute ischemic stroke were less likely to undergo cerebral angiography.[141]

Women are more prone to the hazards associated with ionizing radiation from computed tomography, and undergo diagnostic testing with computed tomography more frequently than men.[129,142-144] Women having computed tomography, especially if under the age of 30 years, are projected to be at greater risk for developing cancer compared to males, with an estimated 66 percent of radiation-induced malignancies in women.[142,145,146] Also, contrast-induced nephropathy and anaphylactoid reactions to radiographic contrast media are more common in females.[143,147,148]

The diagnostic yield of computed tomography imaging of the pulmonary arteries (CTPA) to diagnose pulmonary embolism was considerably lower in women than in men.[149] While use of validated screening tools for pulmonary embolism, particularly D-dimer measurement, may avert up to 30 percent of CTPA imaging studies, this is an incomplete solution for women.[143,150,151] Female sex is an independent predictor for a positive D-dimer, with a false-positive-to-true-positive ratio of 9.5 in women.[151]

There are sex differences in results of the urea breath test, a commonly used test for the diagnosis of Helicobacter pylori infection, with the adjusted mean urea breath test value higher in women than in men (33.8 versus 24.9 percent).[152]

All of these observations – in humans and animals – at both non-clinical and clinical research levels – are evidence of sex-specific data. These observations indicate that innovative study designs and analytic approaches to enhance sex-specific data reporting from non-clinical studies, and sex- and gender-specific reporting from clinical studies, may be valuable.

C. Gender is a Clinical Variable

The evolution of science continues to reveal that both sex and gender are key considerations in the development and performance of medical devices.[22] Gender refers to the social construct by which we define ourselves as man, woman or other.[11] Gender plays an important role in human health and disease, and as such, is a clinical variable. There are gender-based differences in mental health, pain assessment and management, psychiatric stressors, patient-centered outcomes, patient preferences for devices, substance abuse, risk behavior, and healthcare utilization.[129,153-155] While sex and gender are distinct terms, it is important to recognize that sex and gender are interrelated and not always mutually exclusive.[3] For instance, both sex and gender and their interactions may induce epigenetic events as in stress response and resultant physiological cascades.[3]

Extensive literature outlines gender-based differences in the prevalence of mental health illnesses such as unipolar and bipolar depression, anxiety, schizophrenia, and suicide.[154] Women are twice as likely as men to develop unipolar depressive disorders and present with different symptomatology.[156] Patient-reported stress and anxiety is more frequent among women than men.[157] Women are more apt

to develop posttraumatic stress.[156,158-160] In contrast, schizophrenia, antisocial personality disorder, and alcohol use disorder are diagnosed more often in men.[87,156] And, although the suicide rate is four times higher in men,[161] and men represent a four-fold higher rate of completed suicide,[154] women have more suicidal ideation, recurrent deliberate self-harm, repeated suicide attempts, and use less lethal suicide methods.[162-166]

Mental health disorders have been linked to multiple chronic conditions and correlate with an elevated risk of developing ischemic heart disease in both men and women.[154,167] When epidemiologic data were pooled for depression, anxiety or panic disorder, social support, hostility, anger, personality (type D), type A behavior pattern, posttraumatic stress, and psychological distress, no gender differences were found for the pooled effect of mental health disorders and increased incident ischemic heart disease.[167] Both men and women with mental health disorders have an equally elevated risk for developing ischemic heart disease.[167]

There are gender-based differences in delays in seeking care for cardiac and cerebral episodes.[79] Women with acute ischemia tend to delay going to a health care facility by up to two to three hours compared to men.[168] These longer prehospital delays have been shown to correspond with circumstances more attributable to women, such as living alone and having unwitnessed strokes.[97,169] Women have a lower probability of being admitted to intensive care units and are three-times more likely to receive a “do not attempt resuscitation” order within 24 hours of an intracerebral hemorrhage compared to men.[170,171] And, after suffering a cardiac arrest, women have a higher tendency of life-sustaining therapy withdrawal.[172]

Over the years, there has been much research about gender-based differences related to pain experiences and analgesic effects.[173,174] Wide variation in individual responses to opioid medications, due to underlying physiologic, genetic, and hormonal determinants of the response, has made it difficult to detect gender differences in clinical response.[155] Nevertheless, it has been shown that there are gender-based differences in pain severity perceptions.[155] In population-based research, women consistently experience more severe acute and chronic pain across a range of conditions than men.[175-177]

Many biopsychosocial mechanisms are theorized to contribute to sex-based and gender-based differences related to the effects of acute and chronic pain, including variability in how sex hormones have impact on the functioning of central and peripheral nervous systems[155,175,178,179]; and gender based differentiations in stress-induced hyperalgesia and analgesia,[179-181] psychological responses to stress and pain,[178,179,182] endogenous opioid function,[183,184] and pain reporting.[175,178]

As the science progresses and more sex- and gender-specific data are accessible, innovators and researchers will better comprehend how to study the interaction of sex with gender,[3] and will continue to identify possible sex- and gender-specific differences throughout the total product life cycle.

REFERENCES

1. Plank-Bazinet JL, Sampson A, Kornstein SG, et al. A Report of the 24th Annual Congress on Women's Health-Workshop on Transforming Women's Health: From Research to Practice. *J Womens Health (Larchmt).* 2018;27(1):115-120.
2. Plank-Bazinet JL, Sampson A, Miller LR, et al. The science of sex and gender in human health: online courses to create a foundation for sex and gender accountability in biomedical research and treatment. *Biology of sex differences.* 2016;7(Suppl 1):47.
3. Cornelison TL, Clayton JA. Considering Sex as a Biological Variable in Biomedical Research. *Gender and the Genome.* 2017;1(2):89-93.
4. US Food and Drug Administration. Center for Devices and Radiological Health: Health of Women Program; Public Workshop; Request for Comments [Docket No. FDA-2013-N-0329]. *Federal Register* 2013; 20928. Available at: https://www.gpo.gov/fdsys/pkg/FR-2013-04-08/pdf/2013-08015.pdf. Accessed September 16, 2019.
5. US Food and Drug Administration Center for Devices and Radiological Health. Public Workshop: The Center for Devices and Radiological Health (CDRH) Health of Women (HoW) Program Launch: Educate, Enable, Enlist and Explore - HoW to Improve the Health of Women, June 24-25, 2013. 2013; http://wayback.archive-it.org/7993/20170112091045/http:/www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346073.htm. Accessed September 16, 2019.
6. US Government. Food and Drug Administration Safety and Innovation Act of 2012, Public Law 112-144. July 9, 2012; https://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf. Accessed September 16, 2019.
7. US Food and Drug Administration. Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products. 2013; https://www.fda.gov/media/86561/download. Accessed September 16, 2019.
8. US Food and Drug Administration. FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data. 2014; https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf. Accessed September 16, 2019.
9. US Food and Drug Administration, Center for Devices and Radiological Health. Guidance on Evaluation of Sex-Specific Data in Medical Device Clinical Studies for Industry and Food and Drug Administration Staff. 2014; https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf. Accessed September 16, 2019.
10. National Institutes of Health. Consideration of Sex as a Biological Variable in NIH-Funded Research. 2015; http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html. Accessed September 16, 2019.
11. Institute of Medicine. Exploring the Biological Contributions to Human Health: Does Sex Matter? In: Wizemann TM, Pardue M-L, eds. Washington, DC: The National Academies Press; 2001: http://www.nationalacademies.org/hmd/Reports/2001/Exploring-the-Biological-Contributions-to-Human-Health-Does-Sex-Matter.aspx. Accessed September 16, 2019.
12. National Institutes of Health. Consideration of Sex as a Biological Variable in NIH-Funded Research (Additional Guidance for NOT-OD-15-102, NIH Office of Extramural Research link-out from Guide Notice). 2015; https://orwh.od.nih.gov/resources/pdf/NOT-OD-15-102_Guidance.pdf. Accessed September 16, 2019.

13. US Government. 21st Century Cures Act, Public Law 114-255. *P.L. 114-255* 2016; https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf. Accessed September 16, 2019.
14. Canadian Institutes of Health Research. Shaping Science for a Healthier World Strategy. 2017; http://www.cihr-irsc.gc.ca/e/48633.html. Accessed June 11, 2019.
15. US Food and Drug Administration. 2018; https://www.fda.gov/consumers/women/scientific-conference-opioid-and-nicotine-use-dependence-and-recovery-influences-sex-and-gender. Accessed September 16, 2019.
16. Miller VM. Why are sex and gender important to basic physiology and translational and individualized medicine? *Am J Physiol Heart Circ Physiol.* 2014;306(6):H781-788.
17. US Food and Drug Administration, Center for Devices and Radiological Health. The Least Burdensome Provisions: Concept and Principles, Guidance for Industry and Food and Drug Administration Staff. 2019; https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085999.pdf. Accessed September 16, 2019.
18. National Institutes of Health. Frequently Asked Questions for Applicants: Rigor and Transparency. 2015; http://grants.nih.gov/reproducibility/faqs.htm. Accessed September 16, 2019.
19. McGregor AJ. Sex and gender in emergency medicine: advancing care through person-specific research, education, and advocacy. In: Legato MJ, Glezerman M, eds. *The International Society for Gender Medicine: History and Highlights.* London, United Kingdom: Elsevier, Inc.; 2017:125-131.
20. McGregor AJ, Barr H, Greenberg MR, et al. Gender-specific Regulatory Challenges to Product Approval: a panel discussion. *Acad Emerg Med.* 2014;21(12):1334-1338.
21. Pinn VW. A view of the history of sex/gender medicine in the United States. In: Legato MJ, Glezerman M, eds. *The International Society for Gender Medicine: History and Highlights.* London, United Kingdom: Elsevier, Inc.; 2017:17-21.
22. Miller VM, Rice M, Schiebinger L, et al. Embedding concepts of sex and gender health differences into medical curricula. *J Womens Health (Larchmt).* 2013;22(3):194-202.
23. Sandberg K, Umans JG, Georgetown Consensus Conference Work G. Recommendations concerning the new U.S. National Institutes of Health initiative to balance the sex of cells and animals in preclinical research. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology.* 2015;29(5):1646-1652.
24. Zucker I, Beery AK. Males still dominate animal studies. *Nature.* 2010;465(7299):690.
25. Yoon DY, Mansukhani NA, Stubbs VC, Helenowski IB, Woodruff TK, Kibbe MR. Sex bias exists in basic science and translational surgical research. *Surgery.* 2014;156(3):508-516.
26. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;352(13):1293-1304.
27. Becker DM, Segal J, Vaidya D, et al. Sex differences in platelet reactivity and response to low-dose aspirin therapy. *Jama.* 2006;295(12):1420-1427.
28. Gum PA, Kottke-Marchant K, Poggio ED, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol.* 2001;88(3):230-235.
29. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. *Pharmacological research.* 2007;55(2):81-95.
30. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *Jama.* 2006;295(3):306-313.
31. Kavousi M, Bielak LF, Peyser PA. Genetic Research and Women's Heart Disease: a Primer. *Current atherosclerosis reports.* 2016;18(11):67.
32. Tobin JN, Wassertheil-Smoller S, Wexler JP, et al. Sex bias in considering coronary bypass surgery. *Annals of internal medicine.* 1987;107(1):19-25.

33. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *Journal of the American College of Cardiology.* 2009;54(17):1561-1575.
34. Elango K, Curtis AB. Cardiac implantable electrical devices in women. *Clin Cardiol.* 2018;41(2):232-238.
35. Tharpe N. Adverse drug reactions in women's health care. *Journal of midwifery & women's health.* 2011;56(3):205-213.
36. American Association for Justice. Unequal harm: The Disproportionate Damage to Women from Dangerous Drugs and Medical Devices. 2013; https://www.justice.org/sites/default/files/file-uploads/AAJ_Unequal_Harm_0.pdf. Accessed September 16, 2019.
37. Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. *Arch Intern Med.* 2005;165(12):1363-1369.
38. Voskuhl RR, Gold SM. Sex-related factors in multiple sclerosis susceptibility and progression. *Nature reviews Neurology.* 2012;8(5):255-263.
39. Yang X, Schadt EE, Wang S, et al. Tissue-specific expression and regulation of sexually dimorphic genes in mice. *Genome research.* 2006;16(8):995-1004.
40. Arnold AP, van Nas A, Lusis AJ. Systems biology asks new questions about sex differences. *Trends in endocrinology and metabolism: TEM.* 2009;20(10):471-476.
41. Link JC, Reue K. Genetic Basis for Sex Differences in Obesity and Lipid Metabolism. *Annu Rev Nutr.* 2017;37:225-245.
42. Tobi EW, Lumey LH, Talens RP, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Human molecular genetics.* 2009;18(21):4046-4053.
43. Penaloza CG, Estevez B, Han DM, Norouzi M, Lockshin RA, Zakeri Z. Sex-dependent regulation of cytochrome P450 family members Cyp1a1, Cyp2e1, and Cyp7b1 by methylation of DNA. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology.* 2014;28(2):966-977.
44. Mollerup S, Ryberg D, Hewer A, Phillips DH, Haugen A. Sex differences in lung CYP1A1 expression and DNA adduct levels among lung cancer patients. *Cancer research.* 1999;59(14):3317-3320.
45. Engeland A. Trends in the incidence of smoking-associated cancers in Norway, 1954-93. *International journal of cancer.* 1996;68(1):39-46.
46. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. *Journal of the National Cancer Institute.* 1996;88(3-4):183-192.
47. Prescott E, Osler M, Hein HO, et al. Gender and smoking-related risk of lung cancer. The Copenhagen Center for Prospective Population Studies. *Epidemiology (Cambridge, Mass).* 1998;9(1):79-83.
48. Paine MF, Ludington SS, Chen ML, Stewart PW, Huang SM, Watkins PB. Do men and women differ in proximal small intestinal CYP3A or P-glycoprotein expression? *Drug metabolism and disposition: the biological fate of chemicals.* 2005;33(3):426-433.
49. Miller VM, Kaplan JR, Schork NJ, et al. Strategies and methods to study sex differences in cardiovascular structure and function: a guide for basic scientists. *Biology of sex differences.* 2011;2:14.
50. Becker JB, Arnold AP, Berkley KJ, et al. Strategies and methods for research on sex differences in brain and behavior. *Endocrinology.* 2005;146(4):1650-1673.
51. Spatz A, Borg C, Feunteun J. X-chromosome genetics and human cancer. *Nature reviews Cancer.* 2004;4(8):617-629.
52. Gene Gateway: Human Chromosomes from "Human Genome Landmarks: Selected Genes, Traits, and Disorders" Poster. 2006; https://public.ornl.gov/site/gallery/highres/GenomePoster2009.pdf. Accessed June 11, 2019.

53. Jazin E, Cahill L. Sex differences in molecular neuroscience: from fruit flies to humans. *Nature reviews Neuroscience.* 2010;11(1):9-17.
54. Luczak ED, Leinwand LA. Sex-based cardiac physiology. *Annual review of physiology.* 2009;71:1-18.
55. McGregor AJ, Frank Peacock W, Marie Chang A, Safdar B, Diercks D. Sex- and gender-specific research priorities for the emergency management of heart failure and acute arrhythmia: proceedings from the 2014 Academic Emergency Medicine Consensus Conference Cardiovascular Research Workgroup. *Acad Emerg Med.* 2014;21(12):1361-1369.
56. Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. *Journal of women's health.* 1998;7(5):547-557.
57. Wolbrette DL. Risk of proarrhythmia with class III antiarrhythmic agents: sex-based differences and other issues. *Am J Cardiol.* 2003;91(6A):39D-44D.
58. Birks EJ, McGee EC, Jr., Aaronson KD, et al. An examination of survival by sex and race in the HeartWare Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) Bridge to Transplant (BTT) and continued access protocol trials. *J Heart Lung Transplant.* 2015;34(6):815-824.
59. Weymann A, Patil NP, Sabashnikov A, et al. Gender differences in continuous-flow left ventricular assist device therapy as a bridge to transplantation: a risk-adjusted comparison using a propensity score-matching analysis. *Artif Organs.* 2015;39(3):212-219.
60. Morris AA, Pekarek A, Wittersheim K, et al. Gender differences in the risk of stroke during support with continuous-flow left ventricular assist device. *J Heart Lung Transplant.* 2015;34(12):1570-1577.
61. Sherazi S, Kutyifa V, McNitt S, et al. Effect of Gender on the Risk of Neurologic Events and Subsequent Outcomes in Patients With Left Ventricular Assist Devices. *Am J Cardiol.* 2017;119(2):297-301.
62. Hsich EM, Naftel DC, Myers SL, et al. Should women receive left ventricular assist device support?: findings from INTERMACS. *Circ Heart Fail.* 2012;5(2):234-240.
63. Magnussen C, Bernhardt AM, Ojeda FM, et al. Gender differences and outcomes in left ventricular assist device support: The European Registry for Patients with Mechanical Circulatory Support. *J Heart Lung Transplant.* 2018;37(1):61-70.
64. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). *Journal of the American College of Cardiology.* 2011;57(19):1890-1898.
65. Peterson PN, Daugherty SL, Wang Y, et al. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. *Circulation.* 2009;119(8):1078-1084.
66. Zareba W, Moss AJ, Jackson Hall W, et al. Clinical course and implantable cardioverter defibrillator therapy in postinfarction women with severe left ventricular dysfunction. *J Cardiovasc Electrophysiol.* 2005;16(12):1265-1270.
67. Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. *JAMA Intern Med.* 2014;174(8):1340-1348.
68. Zusterzeel R, Spatz ES, Curtis JP, et al. Cardiac resynchronization therapy in women versus men: observational comparative effectiveness study from the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes.* 2015;8(2 Suppl 1):S4-11.
69. Zusterzeel R, Curtis JP, Canos DA, et al. Sex-specific mortality risk by QRS morphology and duration in patients receiving CRT: results from the NCDR. *Journal of the American College of Cardiology.* 2014;64(9):887-894.

70. Lansky AJ, Hochman JS, Ward PA, et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. *Circulation.* 2005;111(7):940-953.
71. Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. *Circulation.* 2006;114(13):1380-1387.
72. Rao SV, Ou FS, Wang TY, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. *JACC Cardiovasc Interv.* 2008;1(4):379-386.
73. Duvernoy CS, Smith DE, Manohar P, et al. Gender differences in adverse outcomes after contemporary percutaneous coronary intervention: an analysis from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) percutaneous coronary intervention registry. *Am Heart J.* 2010;159(4):677-683 e671.
74. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *Journal of the American College of Cardiology.* 2010;55(23):2556-2566.
75. Kent KC, Zwolak RM, Egorova NN, et al. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. *J Vasc Surg.* 2010;52(3):539-548.
76. Lo RC, Lu B, Fokkema MT, et al. Relative importance of aneurysm diameter and body size for predicting abdominal aortic aneurysm rupture in men and women. *J Vasc Surg.* 2014;59(5):1209-1216.
77. Abedi NN, Davenport DL, Xenos E, Sorial E, Minion DJ, Endean ED. Gender and 30-day outcome in patients undergoing endovascular aneurysm repair (EVAR): an analysis using the ACS NSQIP dataset. *J Vasc Surg.* 2009;50(3):486-491, 491 e481-484.
78. Sweet MP, Fillinger MF, Morrison TM, Abel D. The influence of gender and aortic aneurysm size on eligibility for endovascular abdominal aortic aneurysm repair. *J Vasc Surg.* 2011;54(4):931-937.
79. Safdar B, Nagurney JT, Anise A, et al. Gender-specific research for emergency diagnosis and management of ischemic heart disease: proceedings from the 2014 Academic Emergency Medicine Consensus Conference Cardiovascular Research Workgroup. *Acad Emerg Med.* 2014;21(12):1350-1360.
80. Nef HM, Mollmann H, Kostin S, et al. Tako-Tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery. *Eur Heart J.* 2007;28(20):2456-2464.
81. Kurisu S, Inoue I, Kawagoe T, et al. Presentation of Tako-tsubo cardiomyopathy in men and women. *Clin Cardiol.* 2010;33(1):42-45.
82. Schneider B, Athanasiadis A, Sechtem U. Gender-related differences in takotsubo cardiomyopathy. *Heart Fail Clin.* 2013;9(2):137-146, vii.
83. Maturana MA, Irigoyen MC, Spritzer PM. Menopause, estrogens, and endothelial dysfunction: current concepts. *Clinics (Sao Paulo).* 2007;62(1):77-86.
84. Brembilla-Perrot B, Huttin O, Manenti V, et al. Sex-related differences in peri- and post-ablation clinical data for patients with atrial flutter. *Int J Cardiol.* 2013;168(3):1951-1954.
85. Cahill L. Why sex matters for neuroscience. *Nature reviews Neuroscience.* 2006;7(6):477-484.
86. Juraska JM. Sex differences in "cognitive" regions of the rat brain. *Psychoneuroendocrinology.* 1991;16(1-3):105-109.
87. Mendrek A, Mancini-Marie A. Sex/gender differences in the brain and cognition in schizophrenia. *Neurosci Biobehav Rev.* 2016;67:57-78.
88. Luders E, Narr KL, Thompson PM, et al. Gender effects on cortical thickness and the influence of scaling. *Human brain mapping.* 2006;27(4):314-324.
89. Allen JS, Damasio H, Grabowski TJ, Bruss J, Zhang W. Sexual dimorphism and asymmetries in the gray-white composition of the human cerebrum. *NeuroImage.* 2003;18(4):880-894.

90. Goldstein JM, Seidman LJ, Horton NJ, et al. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cereb Cortex.* 2001;11(6):490-497.
91. Ingalhalikar M, Smith A, Parker D, et al. Sex differences in the structural connectome of the human brain. *Proceedings of the National Academy of Sciences of the United States of America.* 2014;111(2):823-828.
92. Du L, Bayir H, Lai Y, et al. Innate gender-based proclivity in response to cytotoxicity and programmed cell death pathway. *The Journal of biological chemistry.* 2004;279(37):38563-38570.
93. Shah K, McCormack CE, Bradbury NA. Do you know the sex of your cells? *Am J Physiol Cell Physiol.* 2014;306(1):C3-18.
94. Manwani B, McCullough LD. Sexual dimorphism in ischemic stroke: lessons from the laboratory. *Women's health (London, England).* 2011;7(3):319-339.
95. Du S, Itoh N, Askarinam S, Hill H, Arnold AP, Voskuhl RR. XY sex chromosome complement, compared with XX, in the CNS confers greater neurodegeneration during experimental autoimmune encephalomyelitis. *Proceedings of the National Academy of Sciences of the United States of America.* 2014;111(7):2806-2811.
96. Wright DW, Espinoza TR, Merck LH, Ratcliff JJ, Backster A, Stein DG. Gender differences in neurological emergencies part II: a consensus summary and research agenda on traumatic brain injury. *Acad Emerg Med.* 2014;21(12):1414-1420.
97. Madsen TE, Seigel TA, Mackenzie RS, et al. Gender differences in neurologic emergencies part I: a consensus summary and research agenda on cerebrovascular disease. *Acad Emerg Med.* 2014;21(12):1403-1413.
98. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol.* 2011;10(7):626-636.
99. Nordstrom EJ, Burton FH. A transgenic model of comorbid Tourette's syndrome and obsessive-compulsive disorder circuitry. *Mol Psychiatry.* 2002;7(6):617-625, 524.
100. Lim JB, Chi CH, Lo LE, et al. Gender difference in outcome after total knee replacement. *J Orthop Surg (Hong Kong).* 2015;23(2):194-197.
101. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage.* 2005;13(9):769-781.
102. Hawker GA, Wright JG, Coyte PC, et al. Differences between men and women in the rate of use of hip and knee arthroplasty. *N Engl J Med.* 2000;342(14):1016-1022.
103. Katz JN, Wright EA, Guadagnoli E, Liang MH, Karlson EW, Cleary PD. Differences between men and women undergoing major orthopedic surgery for degenerative arthritis. *Arthritis Rheum.* 1994;37(5):687-694.
104. Petterson SC, Raisis L, Bodenstab A, Snyder-Mackler L. Disease-specific gender differences among total knee arthroplasty candidates. *J Bone Joint Surg Am.* 2007;89(11):2327-2333.
105. Maradit Kremers H, Larson DR, Crowson CS, et al. Prevalence of Total Hip and Knee Replacement in the United States. *J Bone Joint Surg Am.* 2015;97(17):1386-1397.
106. Dalury DF, Mason JB, Murphy JA, Adams MJ. Analysis of the outcome in male and female patients using a unisex total knee replacement system. *J Bone Joint Surg Br.* 2009;91(3):357-360.
107. Ritter MA, Wing JT, Berend ME, Davis KE, Meding JB. The clinical effect of gender on outcome of total knee arthroplasty. *J Arthroplasty.* 2008;23(3):331-336.
108. MacDonald SJ, Charron KD, Bourne RB, Naudie DD, McCalden RW, Rorabeck CH. The John Insall Award: gender-specific total knee replacement: prospectively collected clinical outcomes. *Clin Orthop Relat Res.* 2008;466(11):2612-2616.
109. Lavernia C, D'Apuzzo M, Rossi MD, Lee D. Is postoperative function after hip or knee arthroplasty influenced by preoperative functional levels? *J Arthroplasty.* 2009;24(7):1033-1043.

110. Nassif JM, Pietrzak WS. Clinical Outcomes in Men and Women following Total Knee Arthroplasty with a High-Flex Knee: No Clinical Effect of Gender. *ScientificWorldJournal.* 2015;2015:285919.
111. Greenberg MR, Kane BG, Totten VY, et al. Injury due to mechanical falls: future directions in gender-specific surveillance, screening, and interventions in emergency department patients. *Acad Emerg Med.* 2014;21(12):1380-1385.
112. Stevens JA, Sogolow ED. Gender differences for non-fatal unintentional fall related injuries among older adults. *Inj Prev.* 2005;11(2):115-119.
113. Donald IP, Bulpitt CJ. The prognosis of falls in elderly people living at home. *Age Ageing.* 1999;28(2):121-125.
114. Haughom BD, Erickson BJ, Hellman MD, Jacobs JJ. Do Complication Rates Differ by Gender After Metal-on-metal Hip Resurfacing Arthroplasty? A Systematic Review. *Clin Orthop Relat Res.* 2015;473(8):2521-2529.
115. Ford MC, Hellman MD, Kazarian GS, Clohisy JC, Nunley RM, Barrack RL. Five to Ten-Year Results of the Birmingham Hip Resurfacing Implant in the U.S.: A Single Institution's Experience. *J Bone Joint Surg Am.* 2018;100(21):1879-1887.
116. Ritz SA, Antle DM, Cote J, et al. First steps for integrating sex and gender considerations into basic experimental biomedical research. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology.* 2014;28(1):4-13.
117. Cheng JC, Castelein RM, Chu WC, et al. Adolescent idiopathic scoliosis. *Nat Rev Dis Primers.* 2015;1:15030.
118. Konieczny MR, Senyurt H, Krauspe R. Epidemiology of adolescent idiopathic scoliosis. *J Child Orthop.* 2013;7(1):3-9.
119. Farr JN, Melton LJ, 3rd, Achenbach SJ, Atkinson EJ, Khosla S, Amin S. Fracture Incidence and Characteristics in Young Adults Aged 18 to 49 Years: A Population-Based Study. *J Bone Miner Res.* 2017;32(12):2347-2354.
120. Liang W, Chikritzhs T. The Effect of Age on Fracture Risk: A Population-Based Cohort Study. *J Aging Res.* 2016;2016:5071438.
121. Altmann A, Tian L, Henderson VW, Greicius MD, Alzheimer's Disease Neuroimaging Initiative I. Sex modifies the APOE-related risk of developing Alzheimer disease. *Annals of neurology.* 2014;75(4):563-573.
122. Ressler KJ, Mercer KB, Bradley B, et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature.* 2011;470(7335):492-497.
123. Vukojevic V, Kolassa IT, Fastenrath M, et al. Epigenetic modification of the glucocorticoid receptor gene is linked to traumatic memory and post-traumatic stress disorder risk in genocide survivors. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2014;34(31):10274-10284.
124. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature.* 2014;509(7500):282-283.
125. Becker JB, Hu M. Sex differences in drug abuse. *Front Neuroendocrinol.* 2008;29(1):36-47.
126. Heinsbroek RP, van Haaren F, Feenstra MG, van Galen H, Boer G, van de Poll NE. Sex differences in the effects of inescapable footshock on central catecholaminergic and serotonergic activity. *Pharmacol Biochem Behav.* 1990;37(3):539-550.
127. Heinsbroek RP, Van Haaren F, Van de Poll NE, Steenbergen HL. Sex differences in the behavioral consequences of inescapable footshocks depend on time since shock. *Physiol Behav.* 1991;49(6):1257-1263.
128. Fox HC, Morgan PT, Sinha R. Sex differences in guanfacine effects on drug craving and stress arousal in cocaine-dependent individuals. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2014;39(6):1527-1537.

129. Safdar B, Greenberg MR. Applying the gender lens to emergency care: from bench to bedside. *Acad Emerg Med.* 2014;21(12):1325-1328.
130. Sperry JL, Minei JP. Gender dimorphism following injury: making the connection from bench to bedside. *J Leukoc Biol.* 2008;83(3):499-506.
131. Bushnell CD, Hurn P, Colton C, et al. Advancing the study of stroke in women: summary and recommendations for future research from an NINDS-Sponsored Multidisciplinary Working Group. *Stroke.* 2006;37(9):2387-2399.
132. Mendelsohn ME. Genomic and nongenomic effects of estrogen in the vasculature. *Am J Cardiol.* 2002;90(1A):3F-6F.
133. Voskuhl RR, Palaszynski K. Sex hormones in experimental autoimmune encephalomyelitis: implications for multiple sclerosis. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry.* 2001;7(3):258-270.
134. Mieres JH SL, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK; Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation.* 2005;111(5):682-696.
135. von Mering GO, Arant CB, Wessel TR, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation.* 2004;109(6):722-725.
136. Yiu KH, de Graaf FR, Schuijf JD, et al. Age- and gender-specific differences in the prognostic value of CT coronary angiography. *Heart.* 2012;98(3):232-237.
137. Kern MJ, Lerman A, Bech JW, et al. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation.* 2006;114(12):1321-1341.
138. Ng MK, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. *Circulation.* 2006;113(17):2054-2061.
139. Gulati M, Shaw LJ, Bairey Merz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. *Clin Cardiol.* 2012;35(3):141-148.
140. Safdar B, Lichtman JH, D'Onofrio G. Sex and the CT: an evolving story of the heart. *Acad Emerg Med.* 2012;19(2):197-200.
141. Towfighi A, Markovic D, Ovbiagele B. Sex differences in revascularization interventions after acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 2013;22(8):e347-353.
142. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med.* 2009;169(22):2078-2086.
143. Ashurst JV, Cherney AR, Evans EM, et al. Research priorities for the influence of gender on diagnostic imaging choices in the emergency department setting. *Acad Emerg Med.* 2014;21(12):1431-1437.
144. Barrett TW, Schriger DL. Annals of Emergency Medicine Journal Club. Computed tomography imaging in the emergency department: benefits, risks and risk ratios. *Ann Emerg Med.* 2011;58(5):463-464.

145. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med.* 2009;361(9):849-857.
146. Berrington de Gonzalez A, Mahesh M, Kim KP, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med.* 2009;169(22):2071-2077.
147. Iakovou I, Dangas G, Mehran R, et al. Impact of gender on the incidence and outcome of contrast-induced nephropathy after percutaneous coronary intervention. *J Invasive Cardiol.* 2003;15(1):18-22.
148. Lang DM, Alpern MB, Visintainer PF, Smith ST. Gender risk for anaphylactoid reaction to radiographic contrast media. *J Allergy Clin Immunol.* 1995;95(4):813-817.
149. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost.* 2008;6(5):772-780.
150. Venkatesh AK, Kline JA, Courtney DM, et al. Evaluation of pulmonary embolism in the emergency department and consistency with a national quality measure: quantifying the opportunity for improvement. *Arch Intern Med.* 2012;172(13):1028-1032.
151. Kabrhel C, Mark Courtney D, Camargo CA, Jr., et al. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. *Acad Emerg Med.* 2010;17(6):589-597.
152. Eisdorfer I, Shalev V, Goren S, Chodick G, Muhsen K. Sex differences in urea breath test results for the diagnosis of Helicobacter pylori infection: a large cross-sectional study. *Biology of sex differences.* 2018;9(1):1.
153. Greenberg MR, Safdar B, Choo EK, McGregor AJ, Becker LB, Cone DC. Future directions in sex- and Gender-specific Emergency Medicine. *Acad Emerg Med.* 2014;21(12):1339-1342.
154. Ranney ML, Locci N, Adams EJ, et al. Gender-specific research on mental illness in the emergency department: current knowledge and future directions. *Acad Emerg Med.* 2014;21(12):1395-1402.
155. Musey PI, Jr., Linnstaedt SD, Platts-Mills TF, et al. Gender differences in acute and chronic pain in the emergency department: results of the 2014 Academic Emergency Medicine consensus conference pain section. *Acad Emerg Med.* 2014;21(12):1421-1430.
156. Afifi M. Gender differences in mental health. *Singapore Med J.* 2007;48(5):385-391.
157. Patel R, Biros MH, Moore J, Miner JR. Gender differences in patient-described pain, stress, and anxiety among patients undergoing treatment for painful conditions in the emergency department. *Acad Emerg Med.* 2014;21(12):1478-1484.
158. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *J Psychiatr Res.* 2011;45(8):1027-1035.
159. Russo J, Katon W, Zatzick D. The development of a population-based automated screening procedure for PTSD in acutely injured hospitalized trauma survivors. *Gen Hosp Psychiatry.* 2013;35(5):485-491.
160. Zona K, Milan S. Gender differences in the longitudinal impact of exposure to violence on mental health in urban youth. *J Youth Adolesc.* 2011;40(12):1674-1690.
161. National Institute of Mental Health, Information Resource Center. Mental Health Information, Statistics, Suicide, Suicide Rates, Trends over Time. 2017; https://www.nimh.nih.gov/health/statistics/suicide.shtml#part_154969. Accessed September 19, 2019.
162. Elisei S, Verdolini N, Anastasi S. Suicidal attempts among Emergency Department patients: one-year of clinical experience. *Psychiatr Danub.* 2012;24 Suppl 1:S140-142.
163. Bi B, Tong J, Liu L, et al. Comparison of patients with and without mental disorders treated for suicide attempts in the emergency departments of four general hospitals in Shenyang, China. *Gen Hosp Psychiatry.* 2010;32(5):549-555.

164. Bilen K, Ottosson C, Castren M, et al. Deliberate self-harm patients in the emergency department: factors associated with repeated self-harm among 1524 patients. *Emerg Med J.* 2011;28(12):1019-1025.
165. Bramness JG, Walby FA, Hjellvik V, Selmer R, Tverdal A. Self-reported mental health and its gender differences as a predictor of suicide in the middle-aged. *Am J Epidemiol.* 2010;172(2):160-166.
166. Beautrais AL. Gender issues in youth suicidal behaviour. *Emerg Med (Fremantle).* 2002;14(1):35-42.
167. Smaardijk VR, Lodder P, Kop WJ, van Gennep B, Maas A, Mommersteeg PMC. Sex- and Gender-Stratified Risks of Psychological Factors for Incident Ischemic Heart Disease: Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2019;8(9):e010859.
168. Nguyen HL, Gore JM, Saczynski JS, et al. Age and sex differences and 20-year trends (1986 to 2005) in prehospital delay in patients hospitalized with acute myocardial infarction. *Circ Cardiovasc Qual Outcomes.* 2010;3(6):590-598.
169. Di Carlo A, Lamassa M, Baldereschi M, et al. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. *Stroke.* 2003;34(5):1114-1119.
170. Ganti L, Jain A, Yerragondu N, et al. Female gender remains an independent risk factor for poor outcome after acute nontraumatic intracerebral hemorrhage. *Neurol Res Int.* 2013;2013:219097.
171. Nakagawa K, Vento MA, Seto TB, et al. Sex differences in the use of early do-not-resuscitate orders after intracerebral hemorrhage. *Stroke.* 2013;44(11):3229-3231.
172. Wigginton JG PS, Barr GC, McGregor AJ, Miller AC, Napoli AM, Safdar B, Weaver KR, Deutsch S, Kayea T, Becker L. Sex- and gender-specific research priorities in cardiovascular resuscitation: proceedings from the 2014 Academic Emergency Medicine Consensus Conference Cardiovascular Resuscitation Research Workgroup. *Acad Emerg Med.* 2014;21(12):1343-1349.
173. Fillingim RB, Gear RW. Sex differences in opioid analgesia: clinical and experimental findings. *Eur J Pain.* 2004;8(5):413-425.
174. Fillingim RB, Ness TJ, Glover TL, et al. Morphine responses and experimental pain: sex differences in side effects and cardiovascular responses but not analgesia. *J Pain.* 2005;6(2):116-124.
175. Leresche L. Defining gender disparities in pain management. *Clin Orthop Relat Res.* 2011;469(7):1871-1877.
176. Riley JL, 3rd, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain.* 1998;74(2-3):181-187.
177. Bingefors K, Isacson D. Epidemiology, co-morbidity, and impact on health-related quality of life of self-reported headache and musculoskeletal pain--a gender perspective. *Eur J Pain.* 2004;8(5):435-450.
178. International Association for the Study of Pain. Global Year Against Pain in Women: Real Women, Real Pain. Differences in Pain between Women and Men. 2007; https://s3.amazonaws.com/rdcms-iasp/files/production/public/Content/ContentFolders/GlobalYearAgainstPain2/RealWomenRealPainFactSheets/All_English.pdf. Accessed September 16, 2019.
179. Greenspan JD, Craft RM, LeResche L, et al. Studying sex and gender differences in pain and analgesia: a consensus report. *Pain.* 2007;132 Suppl 1:S26-45.
180. Barrett AC, Smith ES, Picker MJ. Capsaicin-induced hyperalgesia and mu-opioid-induced antihyperalgesia in male and female Fischer 344 rats. *The Journal of pharmacology and experimental therapeutics.* 2003;307(1):237-245.
181. Donello JE, Guan Y, Tian M, et al. A peripheral adrenoceptor-mediated sympathetic mechanism can transform stress-induced analgesia into hyperalgesia. *Anesthesiology.* 2011;114(6):1403-1416.

182. Wuest J, Merritt-Gray M, Ford-Gilboe M, Lent B, Varcoe C, Campbell JC. Chronic pain in women survivors of intimate partner violence. *J Pain.* 2008;9(11):1049-1057.
183. Frew AK, Drummond PD. Negative affect, pain and sex: the role of endogenous opioids. *Pain.* 2007;132 Suppl 1:S77-85.
184. Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppe RA, Zubieta JK. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2006;26(21):5777-5785.