

The Science of Sex and Gender

FDA Small Business Regulatory Education for Industry (REdI)

June 8, 2022

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Health of Women

Office of Strategic Partnerships and Technology Innovation

Center for Devices and Radiological Health

U.S. Food and Drug Administration

Learning Objectives

Define

Sex and Gender

Describe

Personalized Medicine

Identify

Sex/Gender-Specific Differences

Show

Move Science Forward

1

2

Foreword

Every day, we help develop innovative technologies to improve the lives of those counting on our expertise — technologies that specifically target women and technologies that target men and women.

Driven by science, dedicated to quality, we are duty-bound to consider the potential influence of sex and/or gender in device development.

Through this discovery, we will improve the performance of medical devices for everyone, strengthen the science, and more easily unravel current and emerging issues for the health of women.

CDRH Health of Women Program

This is a comprehensive, collaborative, landmark program built on the premise that both sex and gender have a considerable impact on a woman's overall health, not just reproductive or sexual health.

With patients at the heart of this initiative,
Health of Women intends to ensure all women have
access to innovative, safe and effective medical devices.

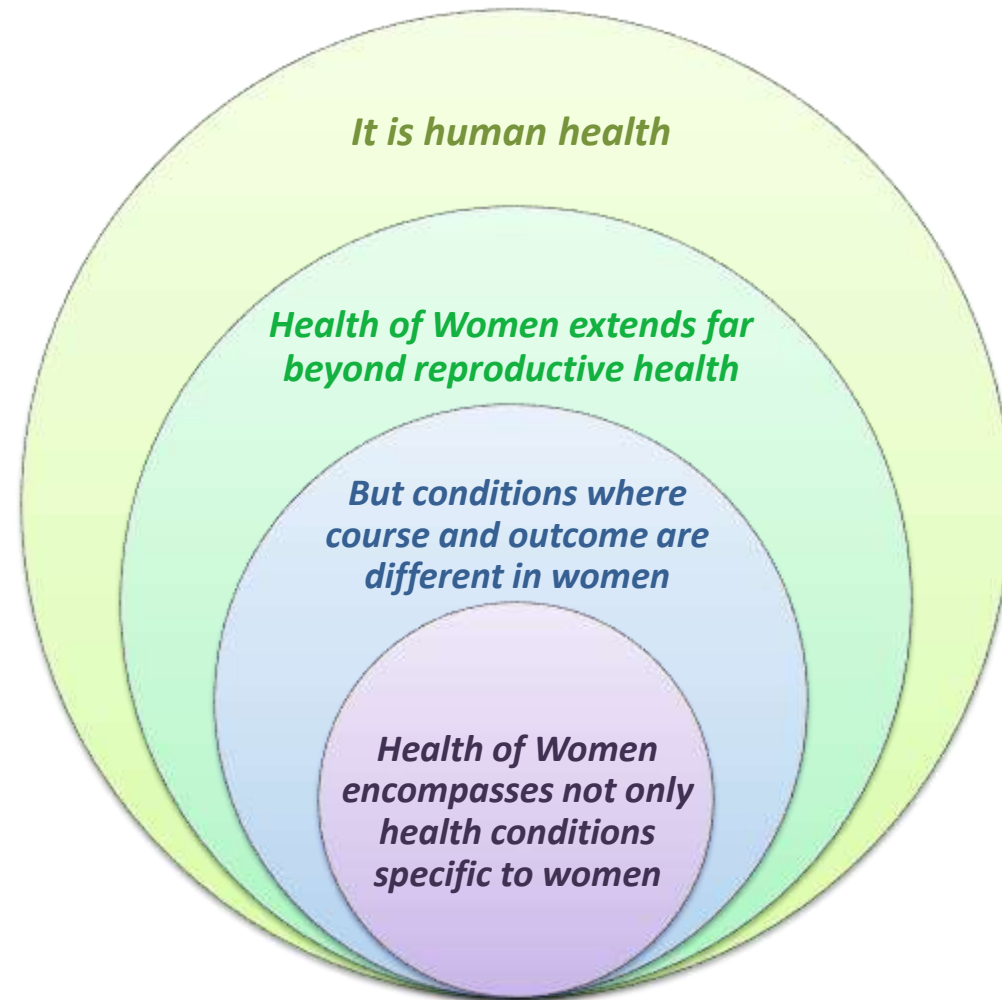
Twitter--@DrWoodcockFDA



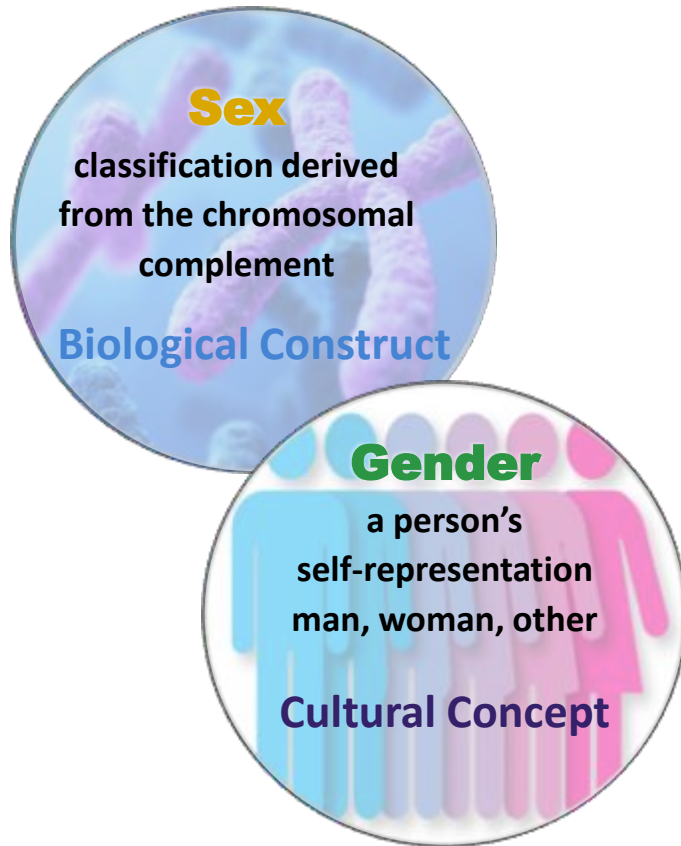
CDRH Health of Women Program

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

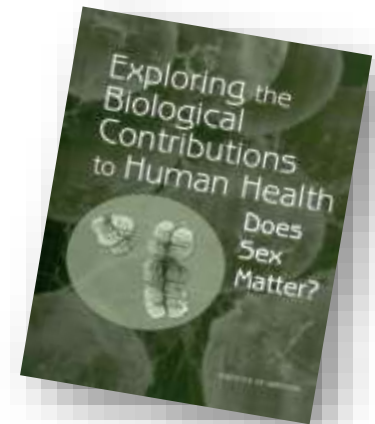
Visionary



Science increasingly reveals that sex and gender differences may play significant roles in the course and outcome of conditions that affect all human organ systems



- Sex hormones cause sexual bias in gene expression by acting directly on genes throughout the genome
- Both sex and gender and their interactions may drive epigenetic influences
- For each of us, sex and gender are valid clinical variables



IOM Report , 2001

Every Cell is Sexed, and Many People are Gendered

What implication does this have for the performance of every medical device in the health care for everyone?

Canadian Institutes of Health Research, Institute of Gender and Health, 2016
Institute of Medicine Report, 2001

FDA

Physical Medicine





FDA Center for Devices and Radiologic Health



Radiology

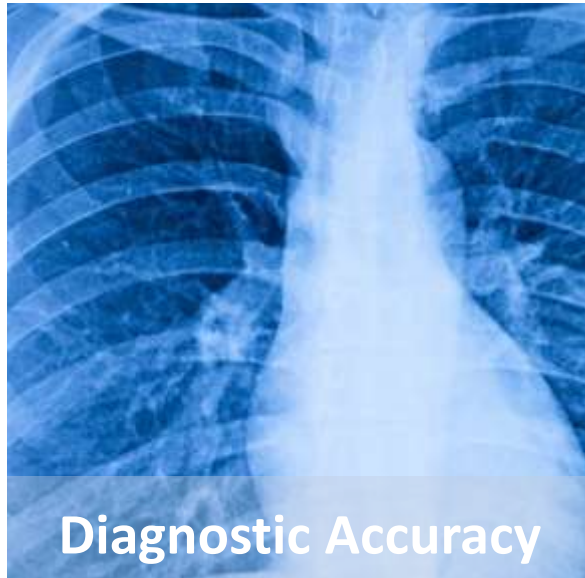
Diagnostics

Biomarkers

Digital Health

Artificial Intelligence

Machine Learning

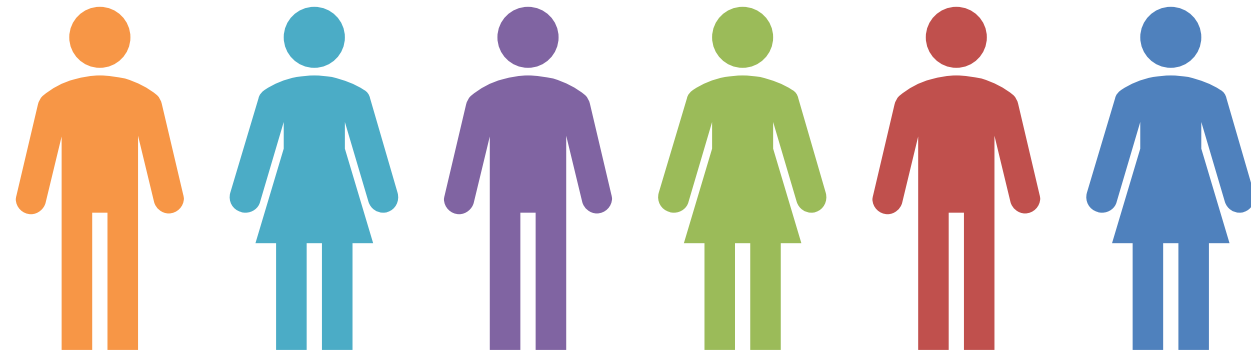


Why, What, Where & How?

Well now, all of this is very interesting you say, but...

- Why is this really important?
- What difference does it make for any individual?
- Where is the science?
- How can I do anything about it?

THIS IS ABOUT PERSONALIZED MEDICINE



Data are one of the most important ingredients to move science forward

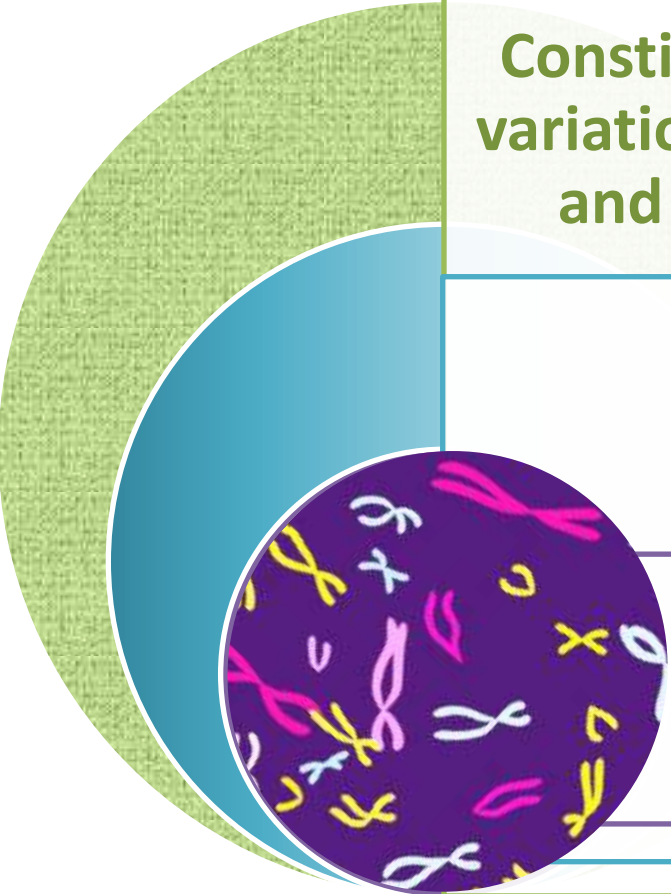
*“Worldview” could be narrow in focus
if data do not represent a
diverse set of patients*

Diverse Populations



Attributes

Valid Clinical Variables



Constitute relevant sources of variation in a number of clinical and subclinical conditions

Affect risk factors, prevalence, age of onset, symptomatology, prognosis, biomarkers, treatment effectiveness

Gender, Ethnicity

Affect behavior, perception, health

**Sex, Age,
Genetic Ancestry**

Alter physiology at the molecular, cellular, and macro-organism level

Attributes



Sex, Gender

Differences reported in **cardiovascular disease**, **pulmonary dysfunction**, **neurological debility**, **irritable bowel syndrome**, **endocrine and autoimmune disorders**, **mental illness**

Age

Older patients and pediatric patients with **age-specific co-morbidities**, **concomitant therapies**, or **development considerations** that impact health

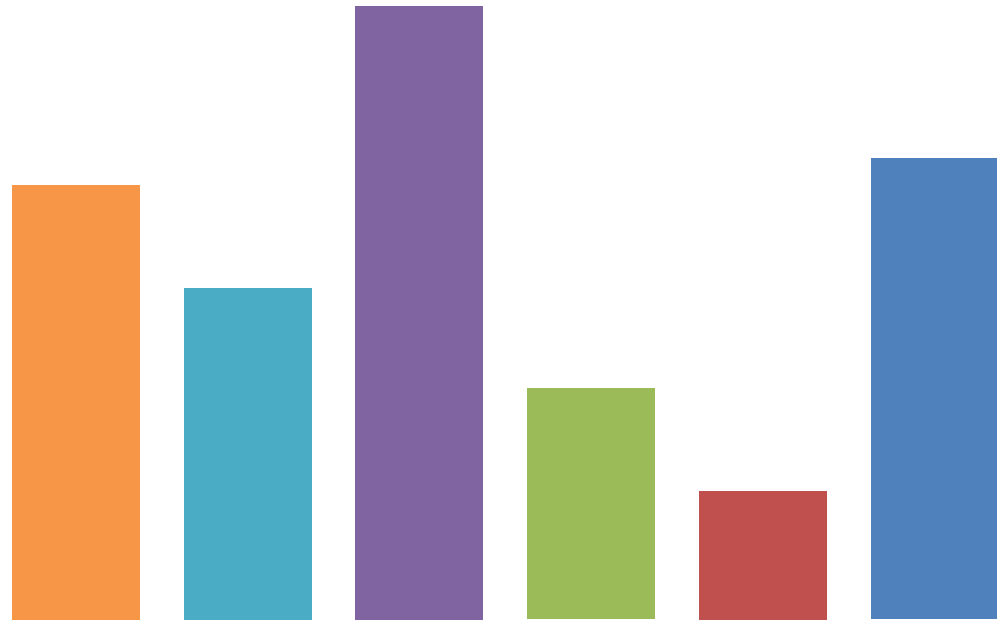
Genetic Ancestry, Ethnicity

Ancestral and ethnic groups experience **different mortality** rates for many health conditions

Generalizability

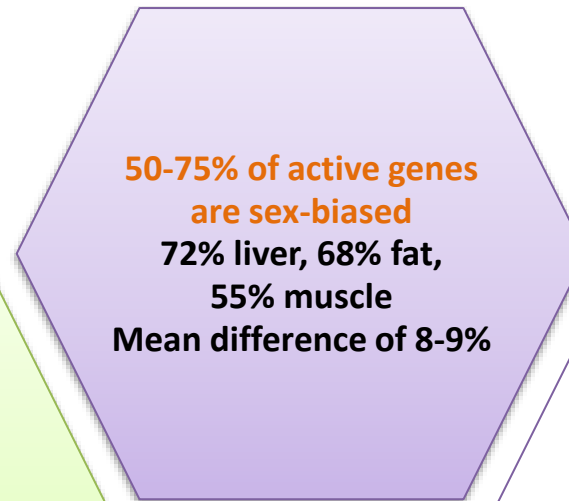
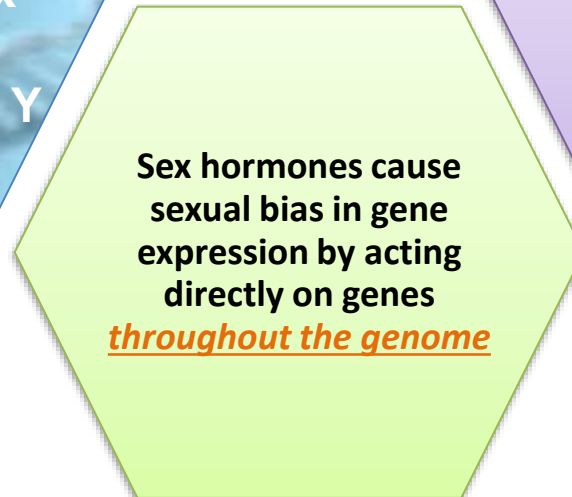


versus



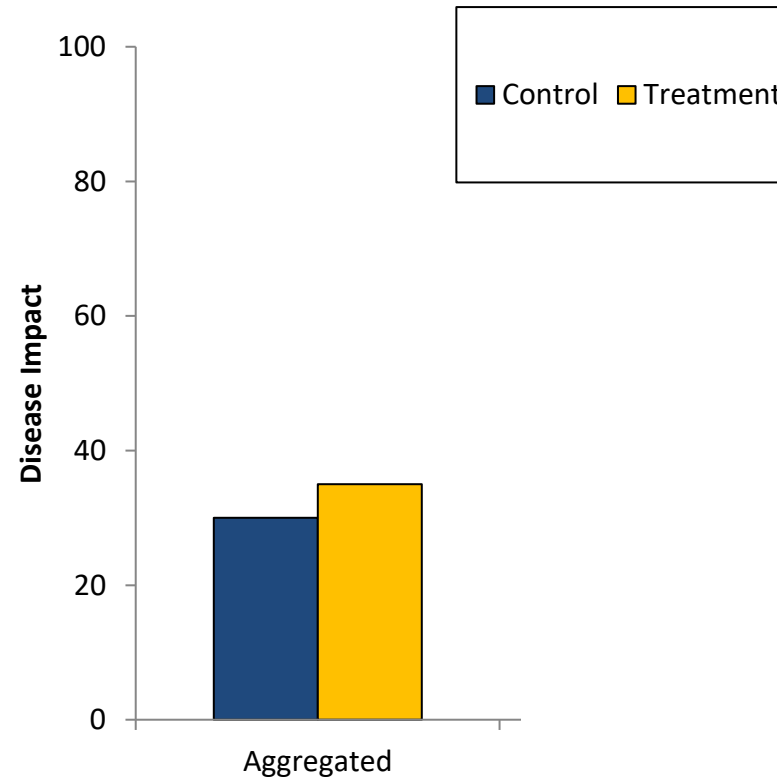
Global Patterns of Gene Expression

Differ in Males and Females

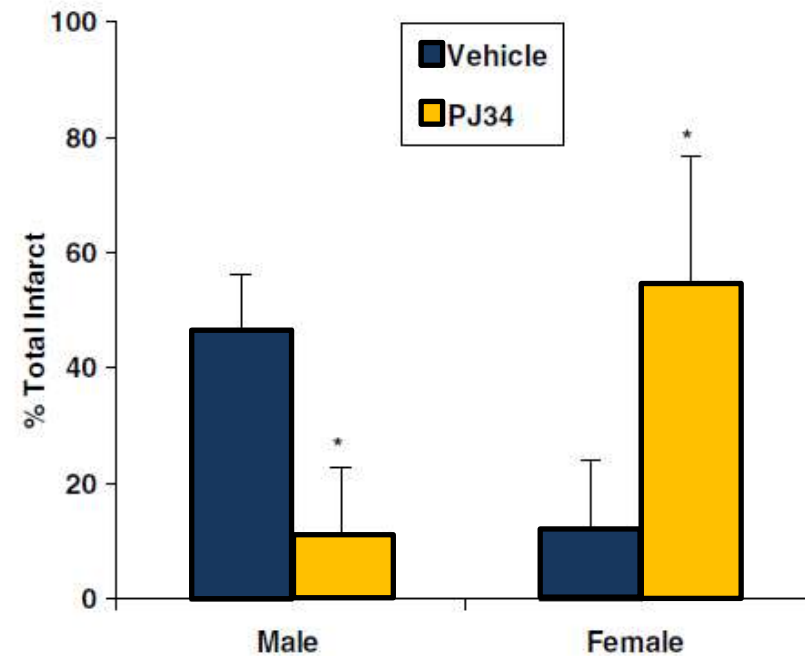


Yang et al. *Genome Res* 2006

Impact of Experimental Design

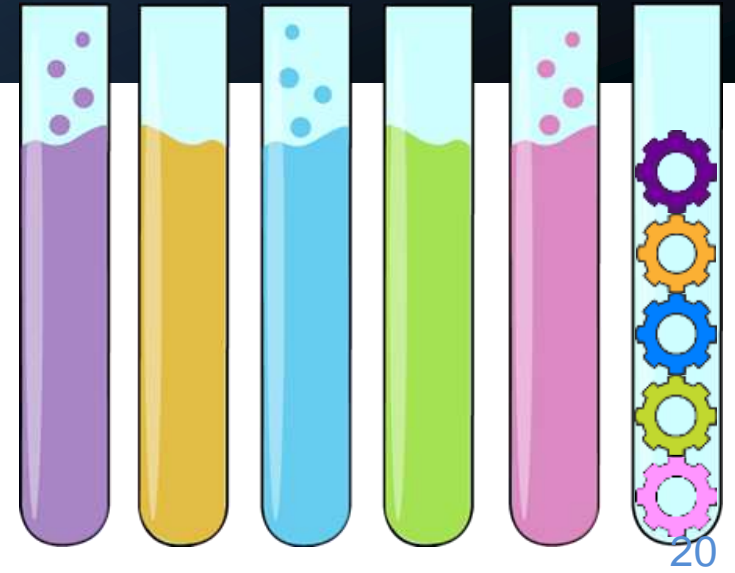


Real Life



The effects of the selective poly-ADP ribose polymerase (**PARP-1**) inhibitor PJ-34 in wild-type (WT) mice of both genders. Treatment with PJ-34 at ischemic onset reduced total infarction in male mice compared with saline-treated controls (* $P<0.001$). A significant increase in ischemic damage was seen in PJ-34-treated females compared with control (* $P<0.001$).

THE SCIENCE OF SEX- AND GENDER-BASED RESEARCH



Inclusion as Preamble

Food Drug & Cosmetic Act 1938

FDA Guidance on Drugs 1993

- *Inclusion of both males and females in clinical studies*
- *Analysis of effectiveness and adverse effects by sex/gender*

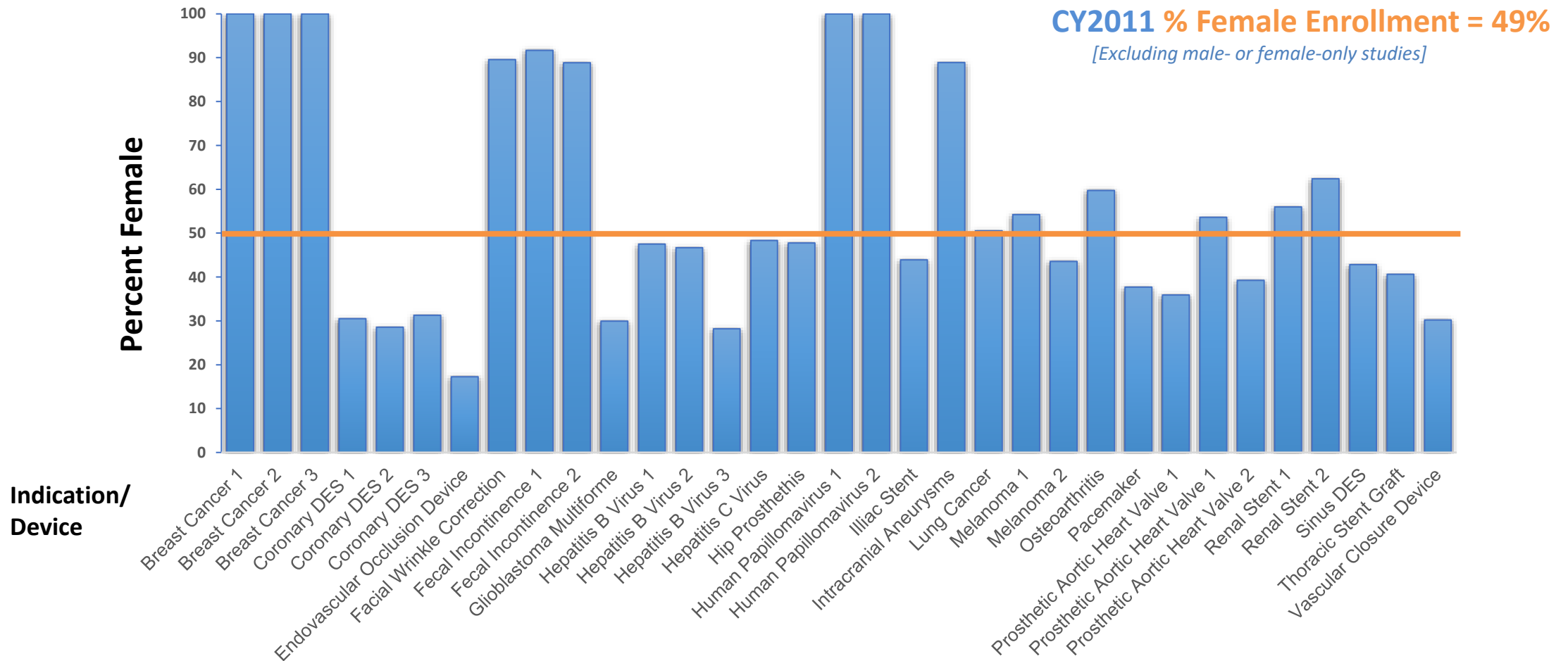
FDAMA 1997

- *Develop guidance on inclusion of women*



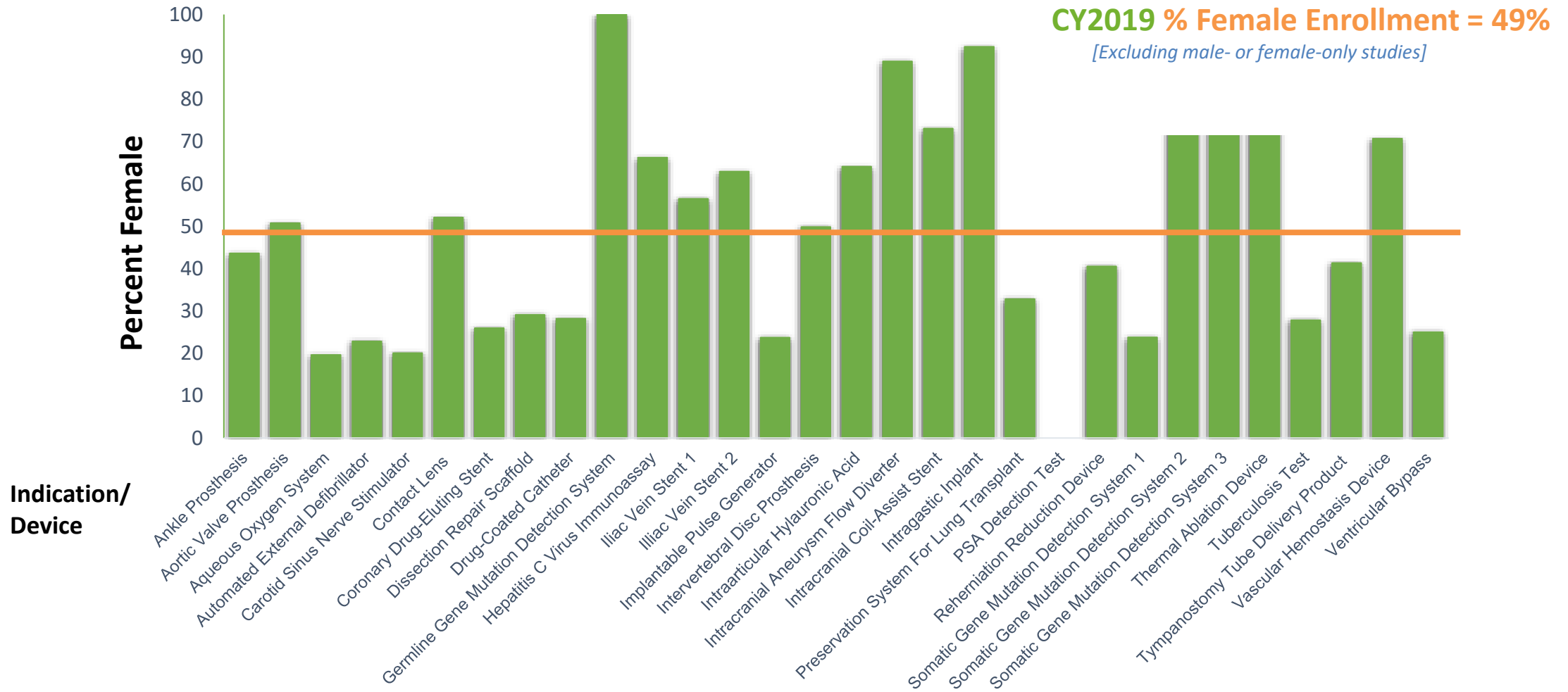
Inclusion as Preamble

Percent Enrollment by Sex/Gender: CDRH PMAs

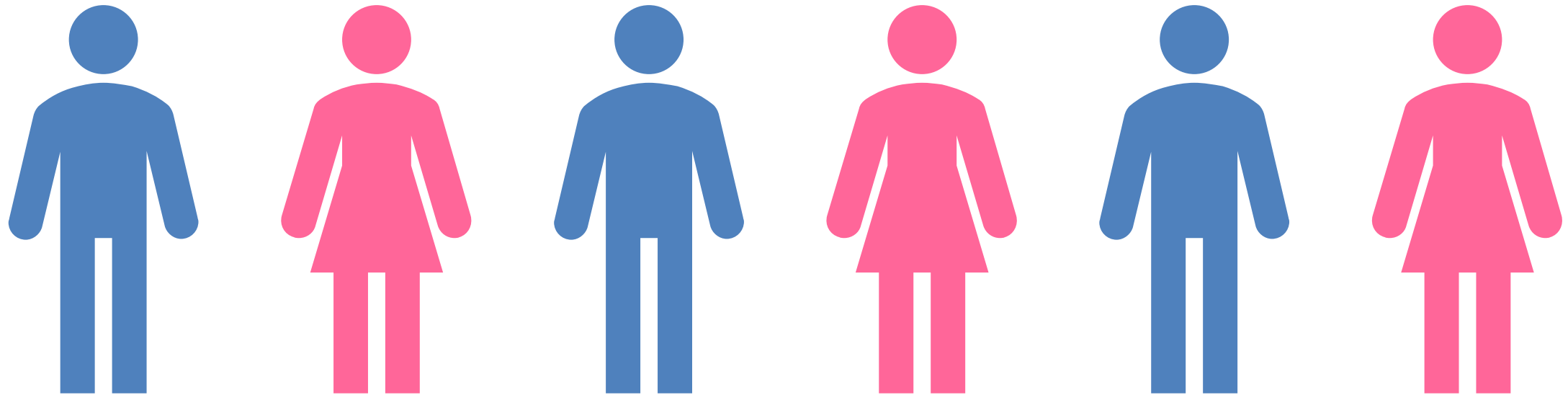


Inclusion as Preamble

Percent Enrollment by Sex/Gender: CDRH PMAs



Inclusion is Only Part of the Story



Sex is a Basic Biologic Variable

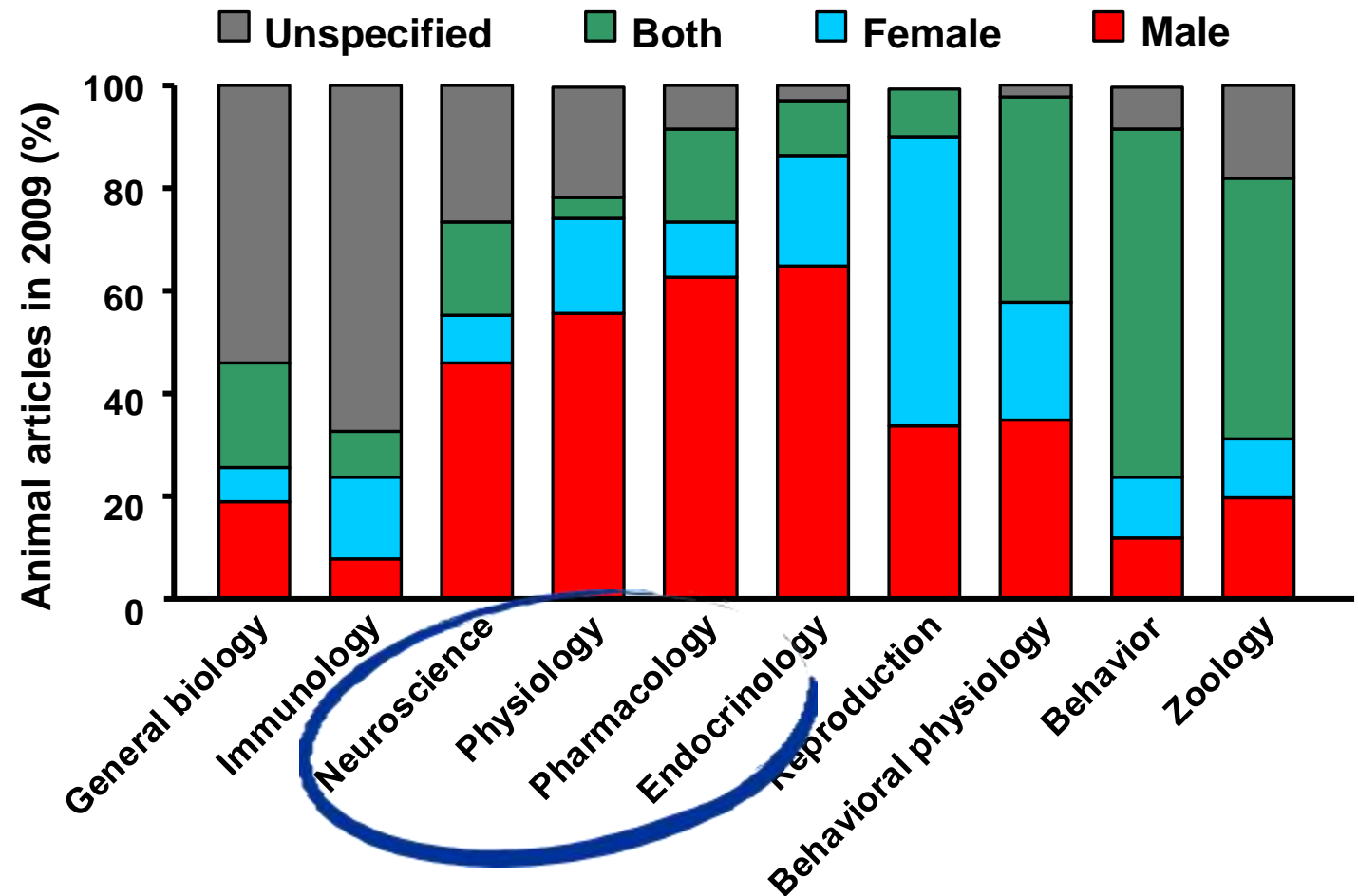
Profound influence on
our daily lives, including
our physiology and
susceptibility to disease



Biomedical science often
assumes that basic
physiological processes are
similar in females and males

Male Predominance

Animal Studies



Zucker and Beery, *Nature* 2010

Male Predominance

Surgical Research



Kibbe

- Evaluated ALL publications in 2011-2012
- 618 articles with animals and cells
- For female-prevalent diseases, of those reports that stated the sex, **only 12% studied female animals**

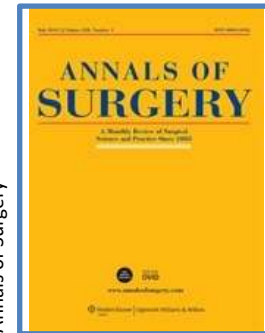
American Journal of Surgery



JAMA Surgery



Annals of Surgery



Journal of Surgical Research



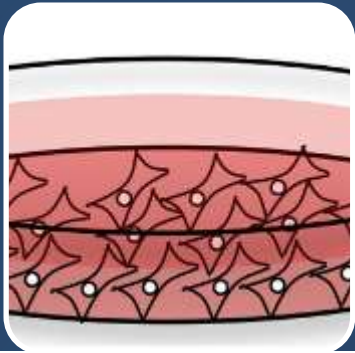
Surgery



Kibbe et al,
Surgery 2014

Male Predominance

Impact on Health Care



Cells

- Undefined
- Male



Animals

- Undefined
- Male

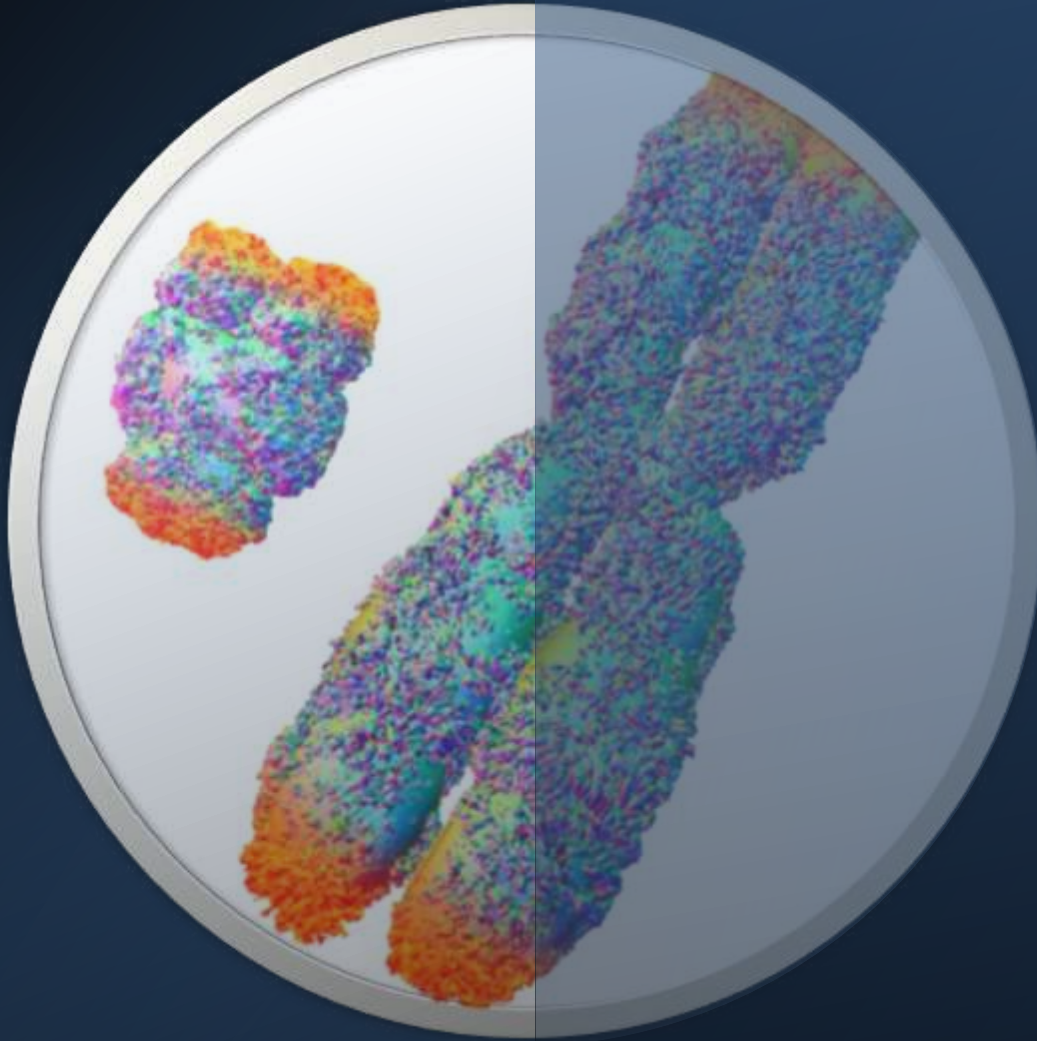


Humans

- Men



Medical Care



Every Cell is Sexed



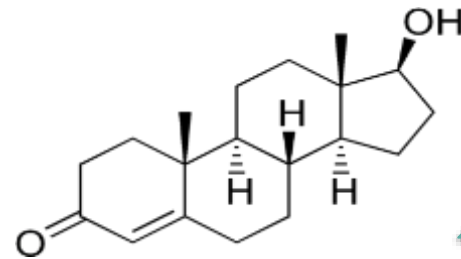
Proximate Factors Causing Sex Differences

Chromosome Effect



Sex Chromosome Effect

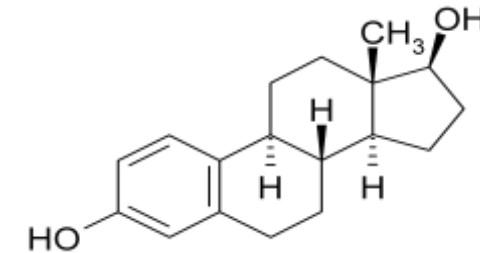
- Direct effects of X and Y genes in non-gonadal tissues



Hormonal “Organizational”

- Permanent differentiating effects of testosterone on genitalia and brain

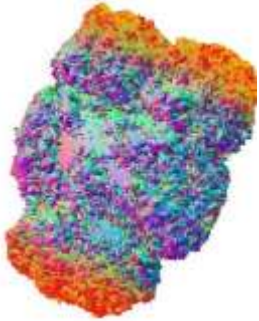
Hormone Effect



Hormonal “Activational”

- Life-long differential effects of gonadal hormones:
 - estrogens
 - androgens
 - progestins

Y Chromosome



Y – No Homologous Counterpart: *SRY*

- Testicular determination

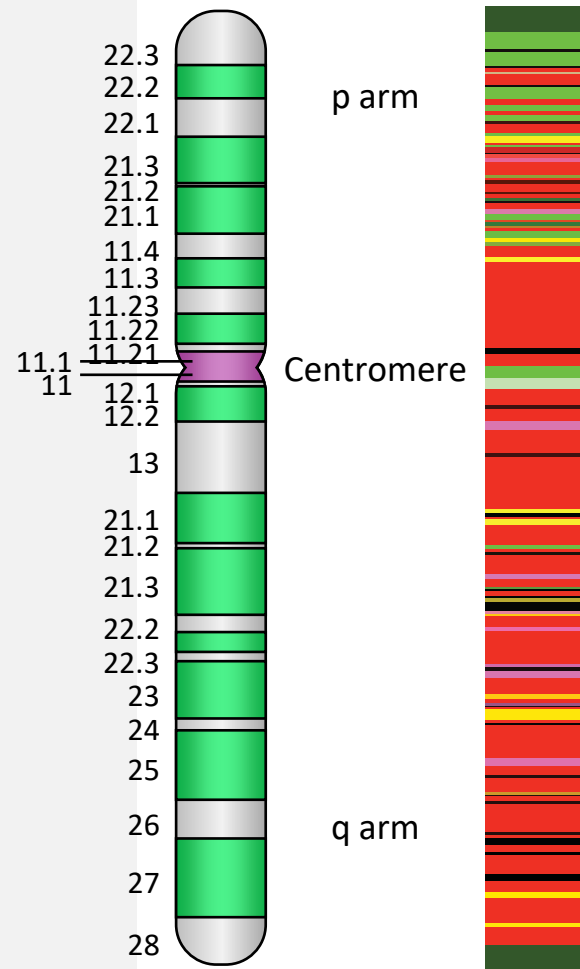
Y – Homologous Counterpart: *RPS4Y*

- Ribosomal protein S4, component of the 40S subunit
- 19 amino acid difference between RPS4X and RPS4Y
- Functionally equivalent isoforms

X Chromosome: Patterns of Inactivation

1,965 genes

- Pseudoautosomal – escapes inactivation
- Escapes inactivation
- Heterogeneous expression
- Subject to X-chromosome inactivation



Brain

Mental retardation, Cognitive function, social,
Cerebellar ataxia, Color blindness/night blindness

Cancer

Melanoma/antigens, Testicular cancer, Prostate cancer

Cardiovascular

Cardiac valvular dysplasia, Dilated cardiac myopathy

Cell regulation and metabolism

Apoptosis inhibitor, Glycogen storage disease
Mucopolysaccharides

Endocrine

Insulin-dependent diabetes mellitus
Hypoparathyroidism

Hematology

Hemoglobin, Hemophilia, Thrombocytopenia

Immunology

Autoimmune immunodeficiency, Mature T cell proliferation

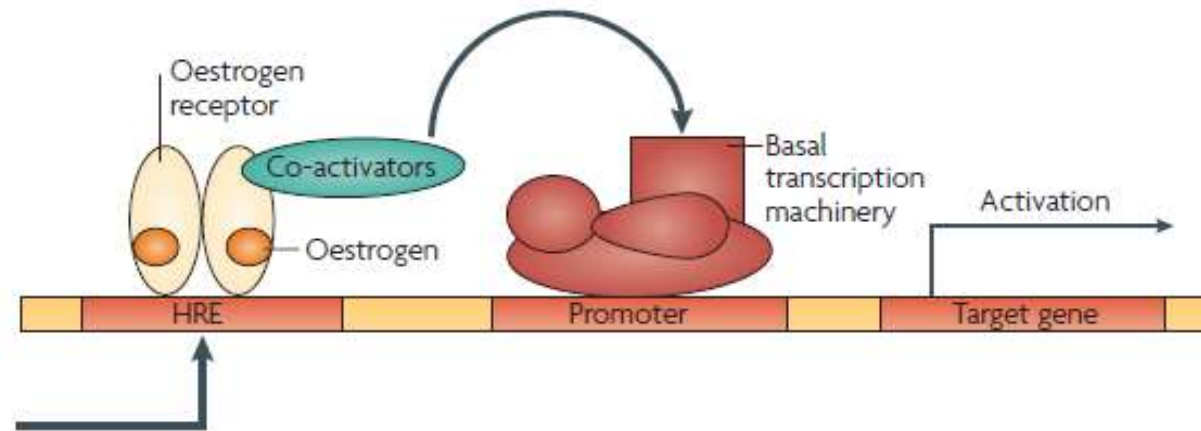
Reproduction

Androgen insensitivity, Premature ovarian failure



Epigenetic Changes

Regulation of gene expression by hormone receptors

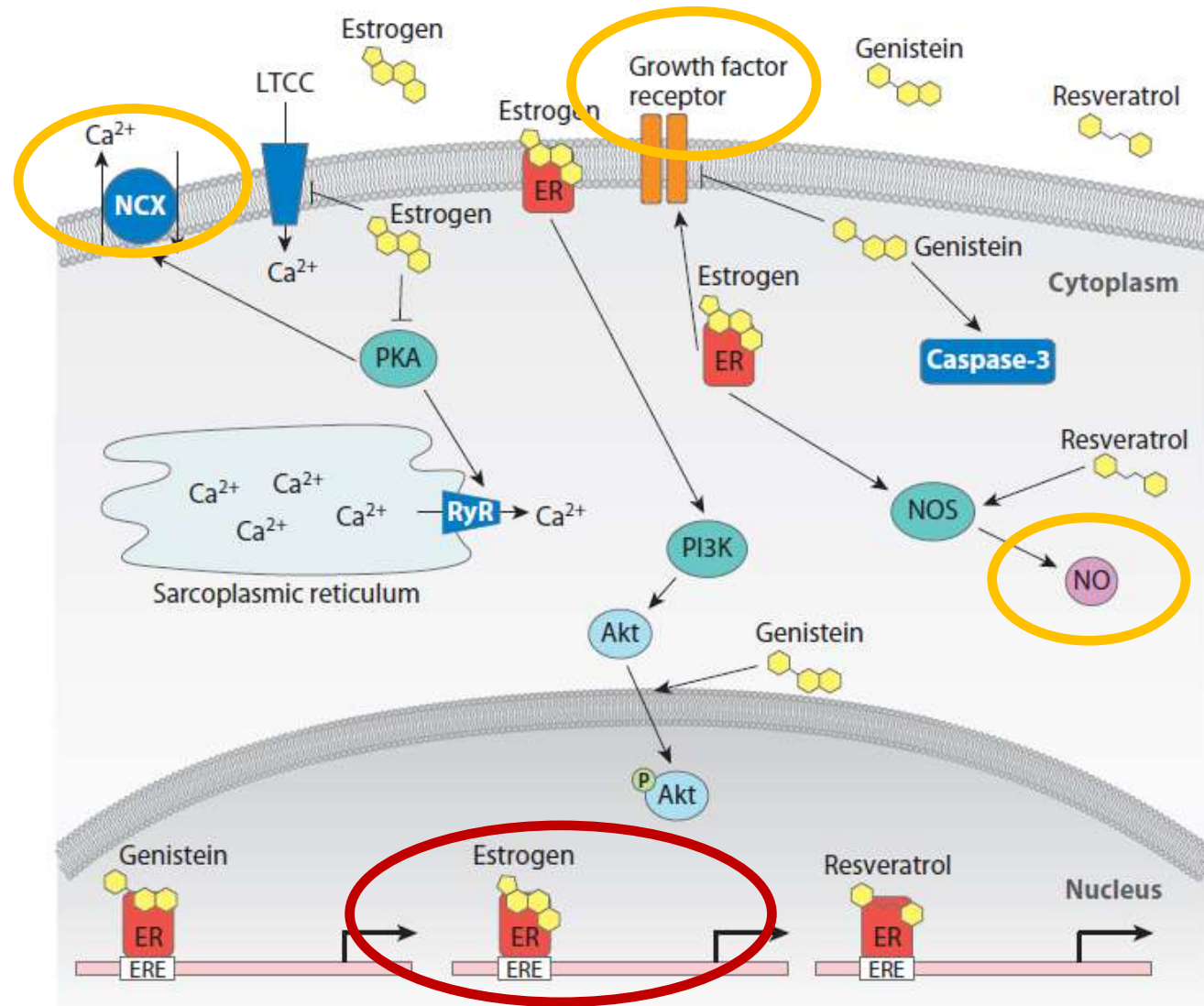


Estrogen-responsive elements

Androgen-responsive elements

Estrogen molecules form a complex with estrogen receptors (ERs)
This complex can then bind a hormone-responsive element (HRE)
The ERE–ER complex interacts through co-activators with the basal transcription machinery to increase the transcription of target genes in a hormone-dependent manner

Estrogen Signaling in the Heart





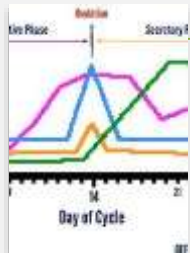
Cardiovascular Risk



Risks differ between women and men



In women, cholesterol plaque spreads evenly throughout the artery wall



Cholesterol levels vary over the course of a menstrual cycle



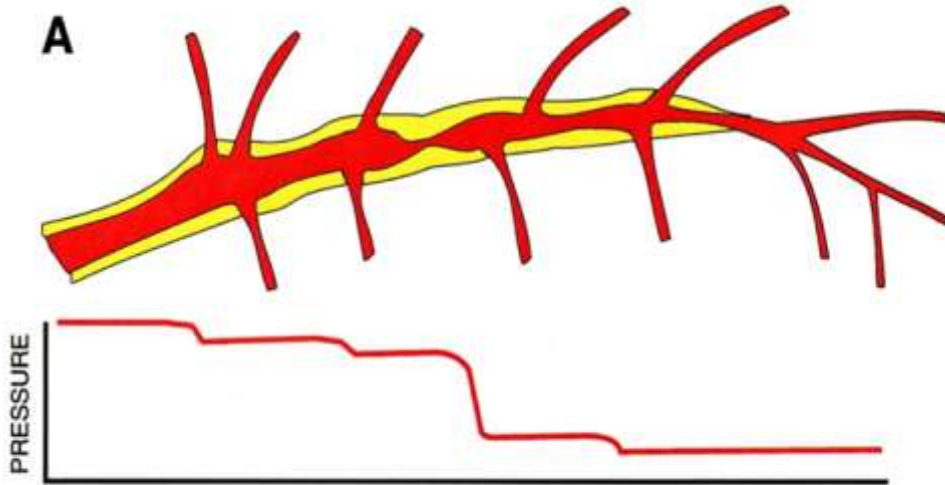
Women have twice the rate of heart failure with preserved ejection fraction



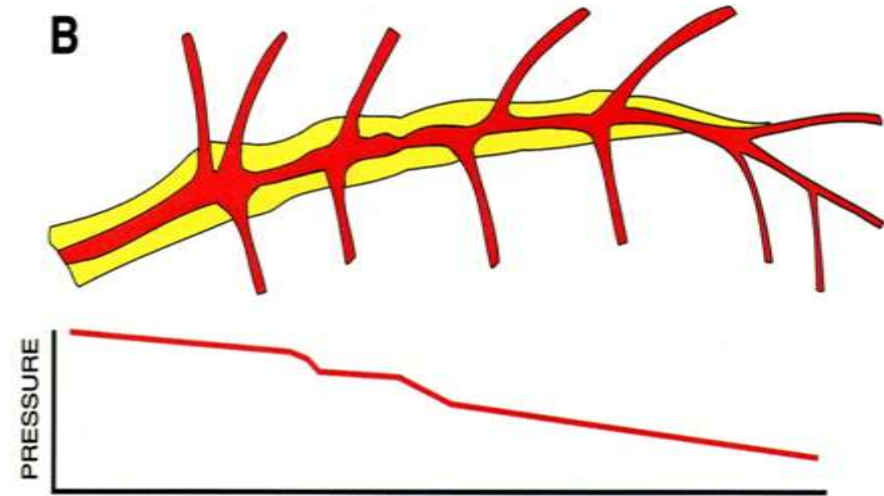
Women with adverse pregnancy hypertensive outcomes have greater risk of cardiovascular disease

Cardiovascular Disease

in women



Single segmental stenoses
Suitable for angioplasty

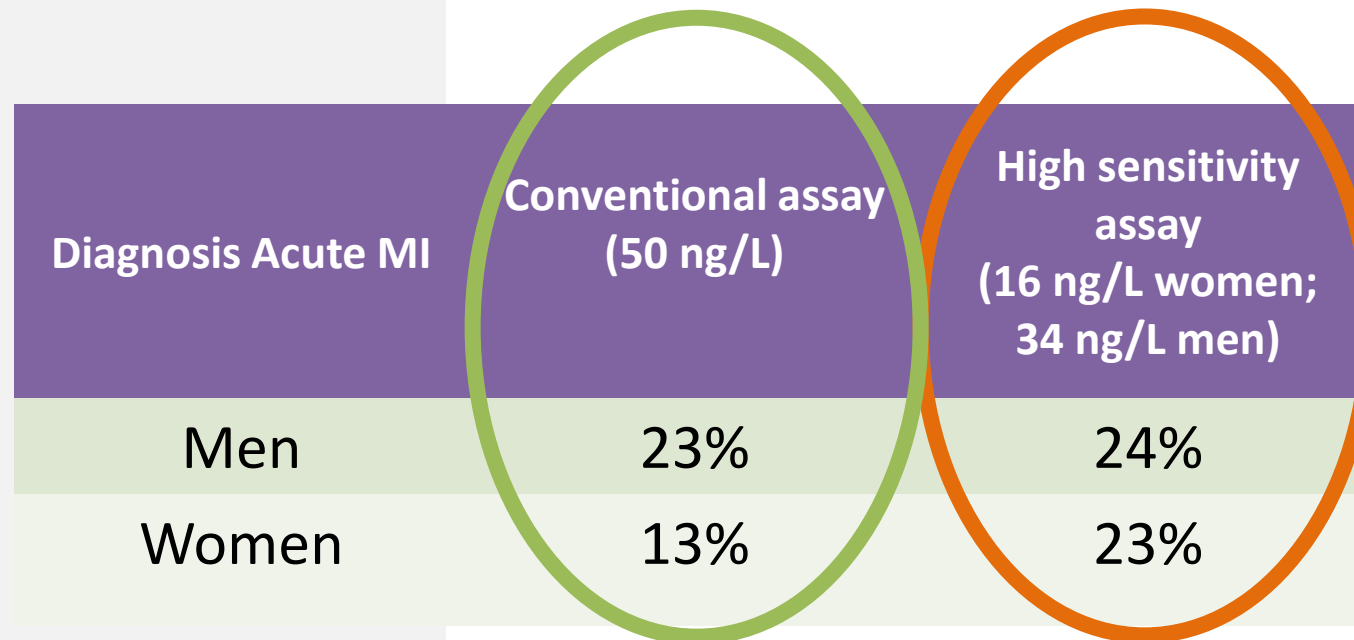


Diffuse disease or multiple stenoses
Not appropriate for angioplasty



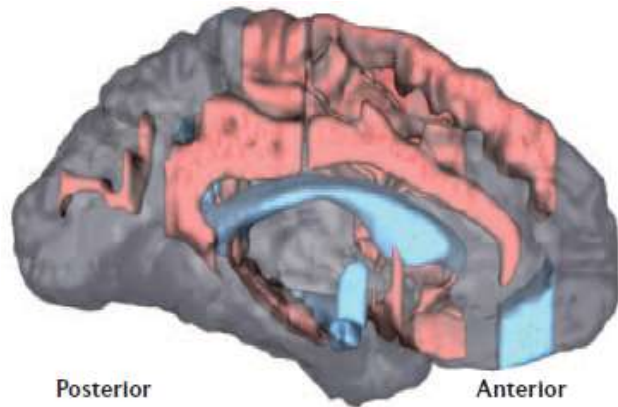
Gender-specific Biomarker Thresholds Urged in MI Diagnosis

High-STEACS (High-sensitivity troponin in the evolution of patients with acute coronary syndrome)



Brain

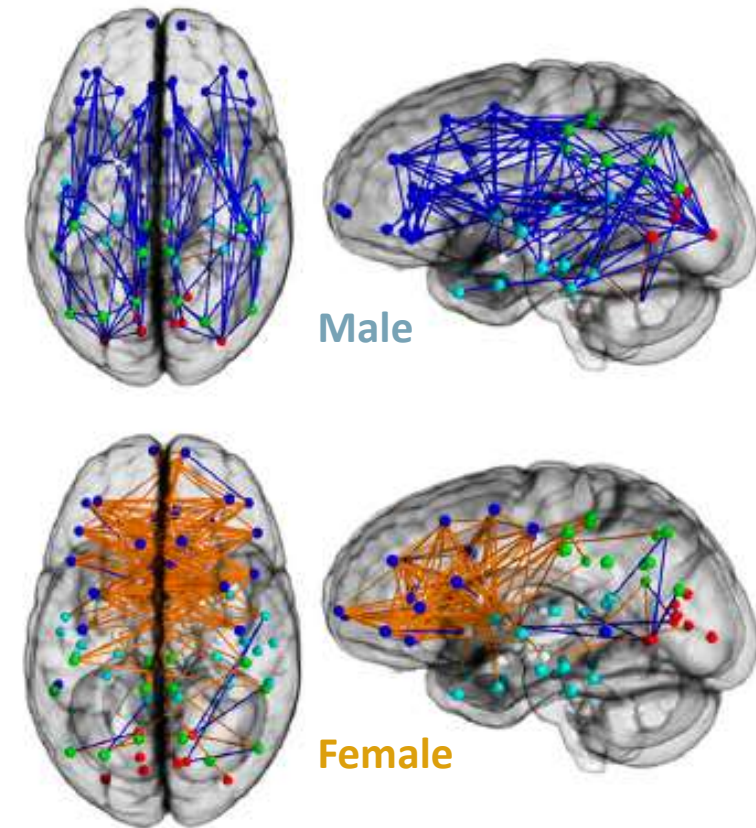
Structural and Functional Dimorphism



Structures that are larger in the healthy **female** brain, relative to cerebrum size

Structures that are larger in the healthy **male** brain, relative to cerebrum size

Goldstein, J. M. et al. *Cereb. Cortex* 2001; 11: 490–497



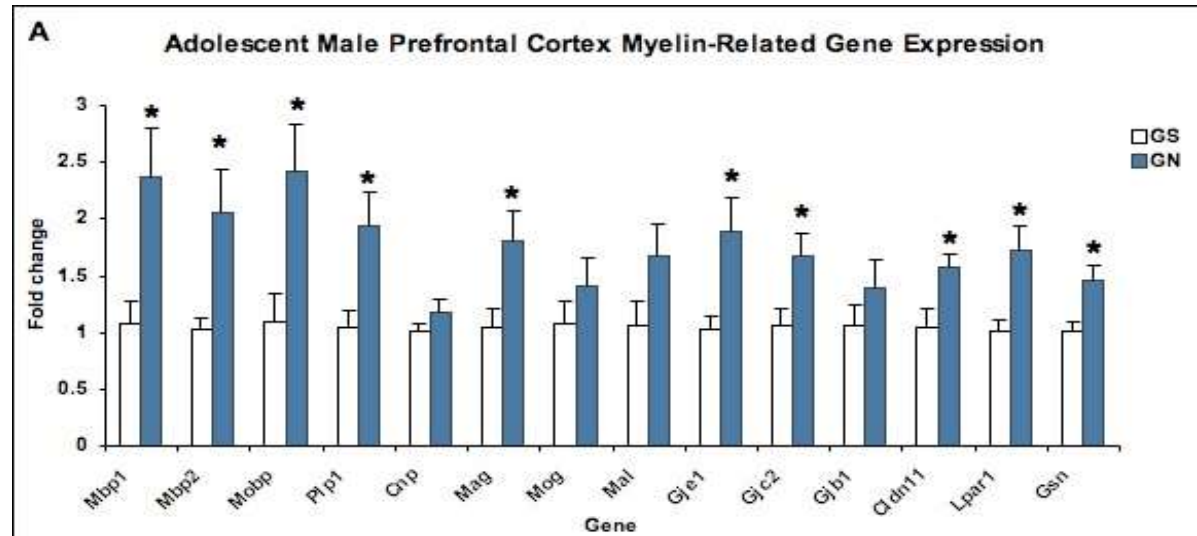
Ingalhalikar M, et al. *Proc Natl Acad Sci USA* 2013

CNS Myelination Defects

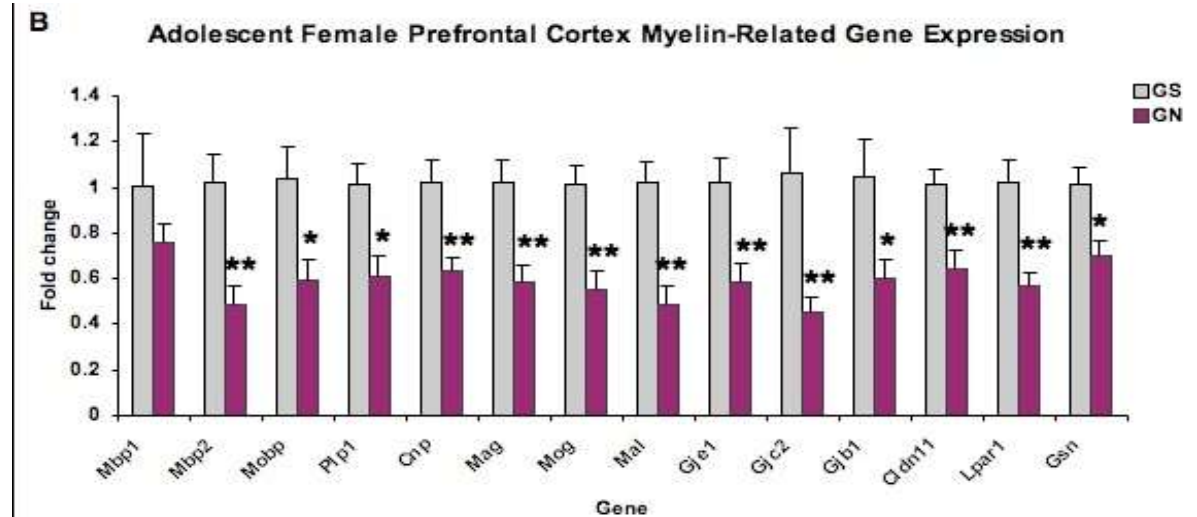
*Gestational Nicotine
modifies myelin-
regulated genes*

*Increase in male—
Decrease in female rats*

Male



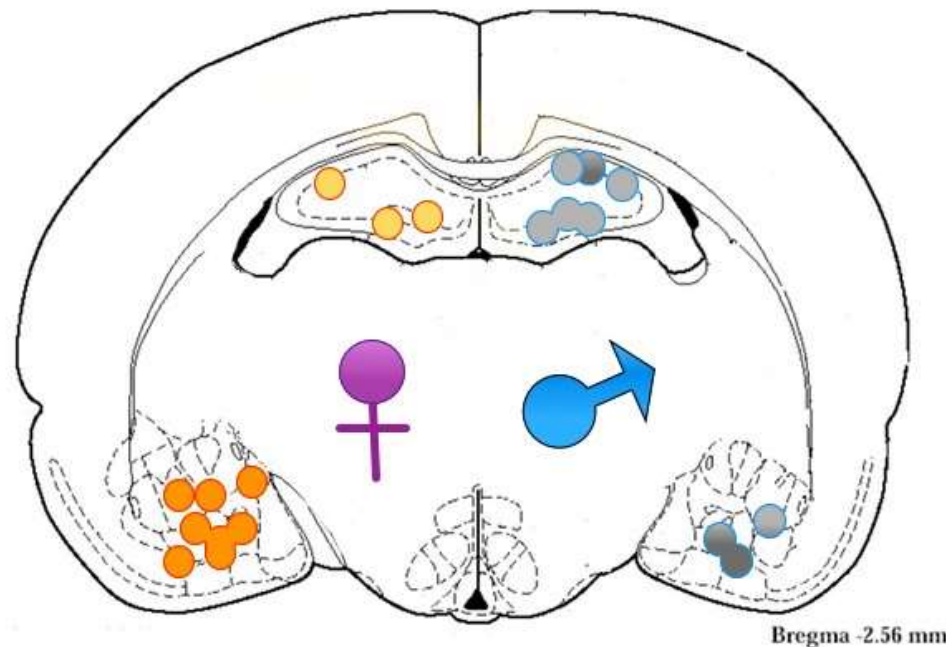
Female



Cell genesis is different in males and females in the telencephalon

Newborn
females have
more new
neurons and
astrocytes in
the amygdala
as males

Amygdala

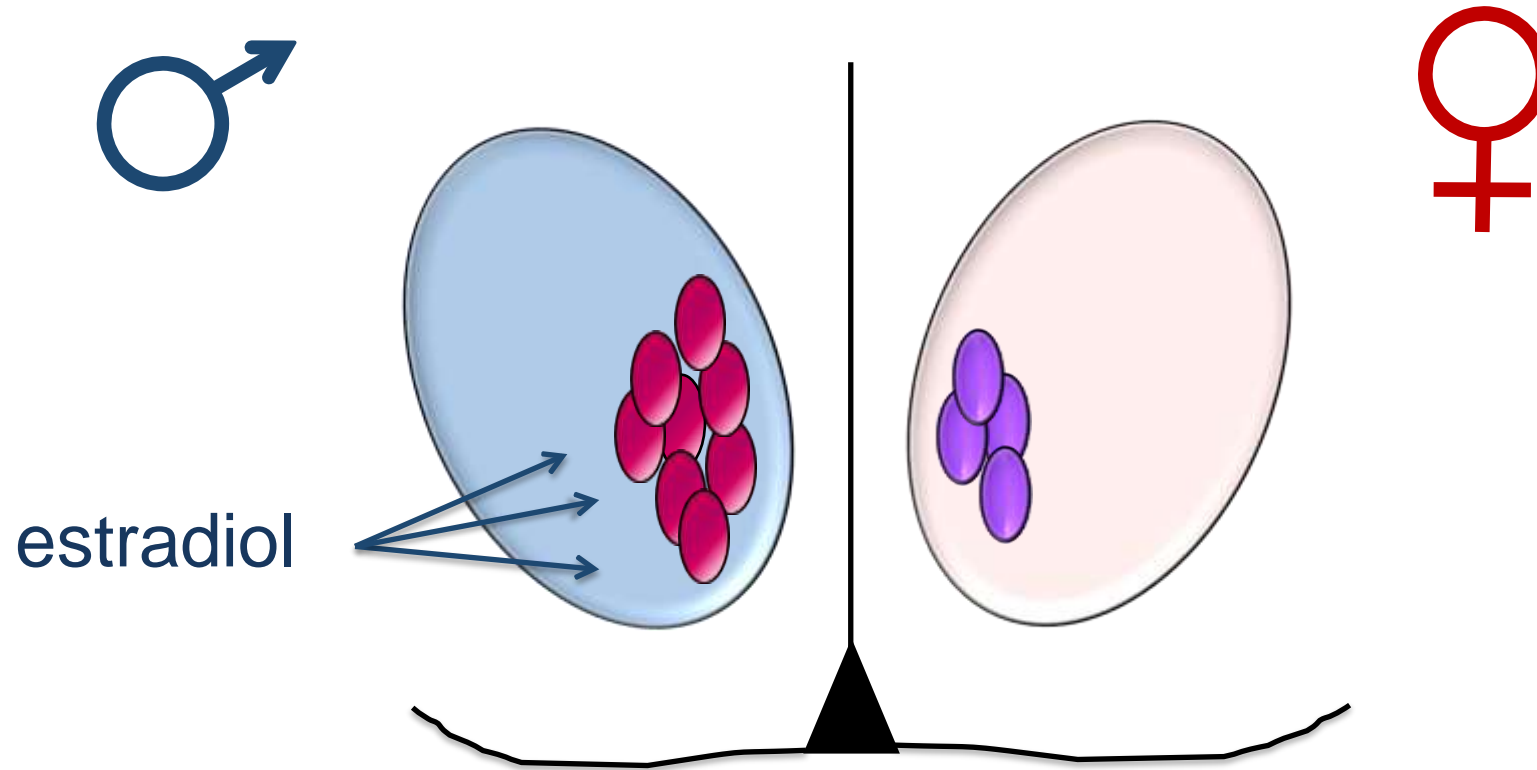


Hippocampus

Newborn males
make twice as
many new
hippocampal
neurons as
females

Testosterone / estradiol in SDN

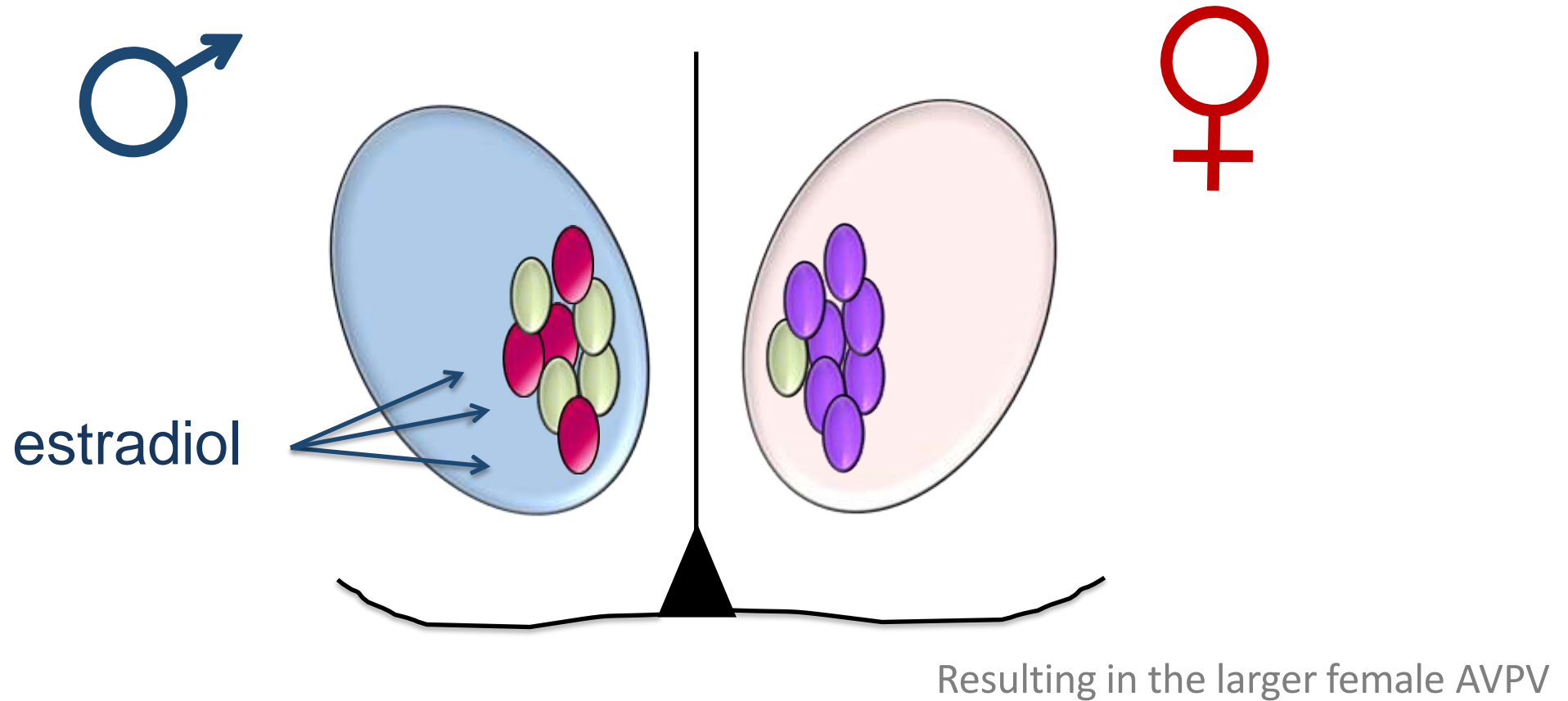
promotes survival of neurons



Resulting in the larger male SDN

But in the AVPV estradiol KILLS

in a selective and directed manner



Response Differences to: oxidative stress and ischemia



**Differences in sensitivity
to oxygen tension**

- **Male hippocampal neurons:**
 - survive longer under normoxic conditions than female
 - but are **more sensitive to ischemia**
- Male neurons **more sensitive to nitrosative** (ONOO^-) stress and excitotoxicity

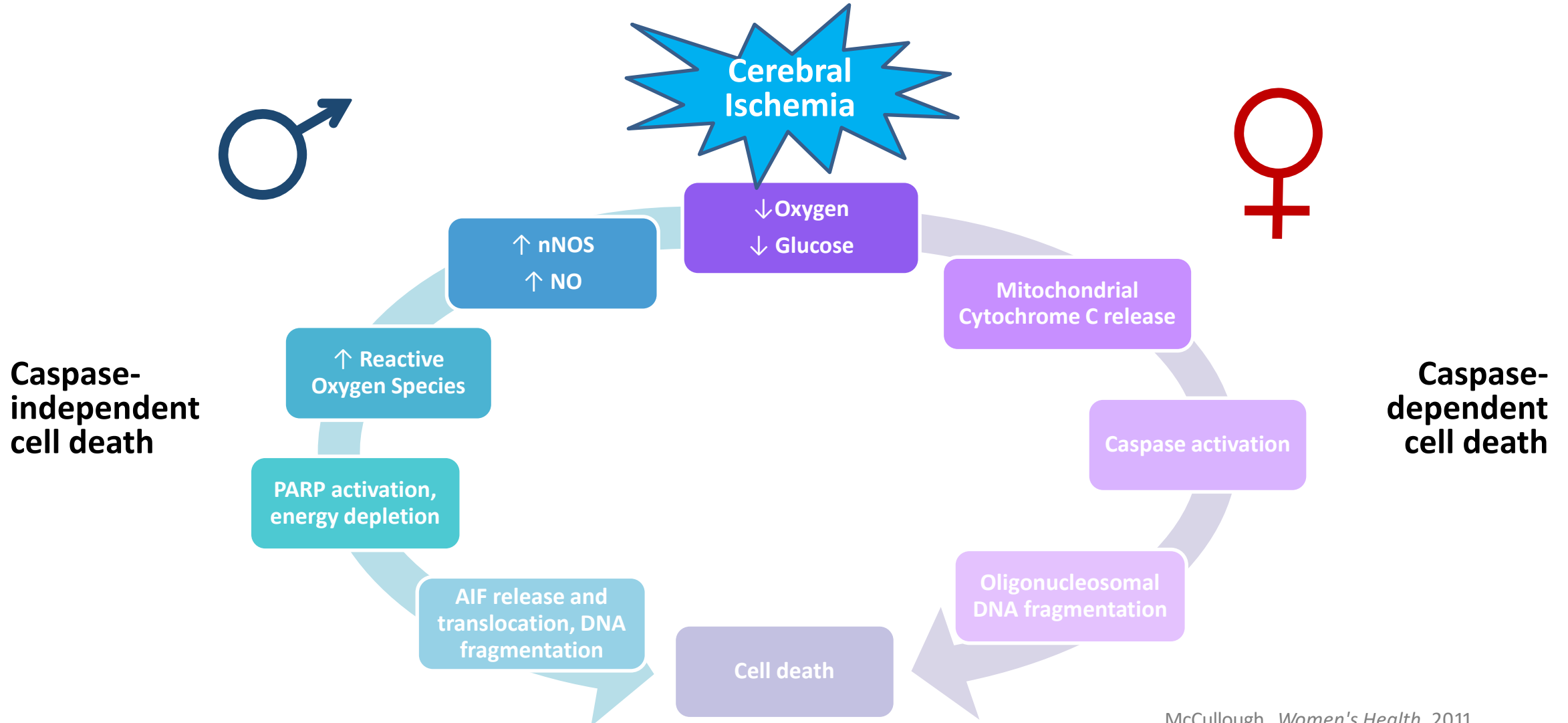
**Differential sensitivity to
cytotoxic agents**

- **Female neurons more sensitive to etoposide- and staurosporine-induced apoptosis**
 - Female neurons: programmed cell death via cytochrome c-dependent pathway
 - Male neurons: programmed cell death via apoptosis-induced pathway

**Differences in glutathione
levels**

- **Male neurons unable to maintain** high levels of intracellular **reductant glutathione**

Sexual dimorphism: ischemic stroke



Distinct Sexual Dimorphism



Rat

Kidney/Spleen

- Female kidney cells significantly **more sensitive** to ethanol- and camptothecin-induced **apoptosis** than male
- Female splenocytes **less sensitive to nitrosative stress** and more sensitive to staurosporine

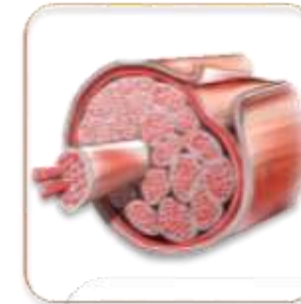


Human

Liver

- **CYP1A1 more responsive** in females
 - CYP1A1 prominent role in metabolism of polycyclic aromatic hydrocarbons
- **CYP3A in higher concentration** in female liver cells
 - CYP3A actions account for metabolism of half of pharmacopeia drugs

72%



Mouse

Muscle

- Female muscle-derived stem cells:
 - **Less sensitive to oxidative stress**
 - **Regenerate** skeletal muscle **more efficiently**
- Better able to survive stress

55%

Function of dimorphic genes

Mice

Liver

- Protease inhibitor
- Steroid hydroxylase
- Defense response
- **Immune response**
- Carboxylic acid metabolism
- Fatty acid metabolism
- Electron transport
- Monooxygenase activity
- **Oxidoreductase activity**
- **Lipid metabolism**
- **Steroid biosynthesis**
- **Steroid metabolism**
- Serine-type endopeptidase inhibitor activity

Adipose

- Calcium/metal ion binding
- Ion cation transporter
- **Immune response**
- Cell motility/adhesion
- Morphogenesis
- Organogenesis
- Muscle contraction
- Muscle development
- **Oxidoreductase activity**
- **Lipid metabolism**
- **C21 steroid hormone biosynthesis**
- **C21 steroid hormone metabolism**
- Hormone biosynthesis/metabolism
- Androgen and estrogen metabolism

Muscle

- Ribosome biosynthesis/assembly
- RNA Binding
- Translation
- Polyamine metabolism
- Biogenic amine metabolism
- Spermine metabolism

Brain

- RNA helicase activity
- ATP-dependent RNA helicase activity
- RNA-dependent ATPase activity

Yang, et al. *Gen Res* 2006



FDA Center for Devices and Radiologic Health



Cardiovascular

Women-Specific

Orthopedic

Neurologic

Physical Medicine



MOVING SCIENCE FORWARD



Our Vision

Sex/Gender-Specific Analysis & Reporting



Data Disaggregated by Sex and/or Gender



FDASIA 907

Food and Drug Administration Safety and Innovation Act Section 907 (2012)

Directed the FDA to address to what extent clinical trial participation and safety and effectiveness data by demographic subgroups (sex, age, race, ethnicity) are included in applications submitted to FDA



FDASIA 907 Report 2013



CDRH:

- ☒ 88% pre-market approval (PMA) applications analyzed data by sex
- ☒ 63% presented publicly

CDER:

- ☐ 73-97% NMEs (new drug applications (NDAs) and biologics license applications (BLAs)) analyzed data by sex
- ☐ 90-100% presented publicly

CBER:

- ☐ 0% BLAs analyzed data by sex
- ☐ 100% presented publicly

It's All About Science

Science is Ready

- Advancements in Science

It's All About Science

Science is Ready

- Advancements in Science

Scientists are Primed

- 1998 NDA Regulation

SEX ANALYSIS
REQUIRED BY REGULATION FOR
NEW DRUG APPLICATIONS

It's All About Science

Science is Ready

- Advancements in Science

Scientists are Primed

- 1998 NDA Regulation
- 2014 FDASIA 907 Action Plan

FDA Report

FDA ACTION PLAN TO ENHANCE THE COLLECTION AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA

Improve the completeness and
quality of demographic subgroup
data collection, reporting, and
analysis

Make demographic subgroup data
more available and transparent

It's All About Science

Science is Ready

- Advancements in Science

Scientists are Primed

- 1998 NDA Regulation
- 2014 FDASIA 907 Action Plan
- **2014 CDRH Guidelines**

Evaluation of Sex-Specific Data in Medical Device Clinical Studies

Guidance for Industry and Food and Drug Administration Staff

**Sex-specific patient enrollment, data
analysis, and reporting of study
information**

- *Consideration of sex during the
study design*
- *Sex-specific statistical analyses of
study data*
- *Reporting sex-specific information*

It's All About Science

Science is Ready

- Advancements in Science

Scientists are Primed

- 1998 NDA Regulation
- 2014 FDASIA 907 Action Plan
- 2014 CDRH Guidelines
- **2016 NIH SABV Policy**
- **2017 21st Century Cures Act**

Consideration of Sex as a Biological Variable in NIH-funded Research

Notice Number: NOT-OD-15-102

Key Dates

Release Date: June 9, 2015

Related Announcements

[NOT-OD-15-012](#)

[NOT-OD-15-011](#)

[NOT-OD-15-103](#)

Explain how relevant biologic variables such as SEX, are factored into research designs and analyses of studies in vertebrate animals and humans

- Applies to basic, preclinical, and clinical research
- Studies proposing to use only one sex should provide strong justification
- Cost alone and absence of known sex differences are inadequate justifications

Consider Sex and Gender

Balanced by Least Burdensome Approach



We want the innovator/researcher to truly consider, to re-think, how (if at all) sex and/or gender may be

We do not want the innovator/researcher to adhere to a guidance **just** to adhere to a guidance

In their experimental materials

In their study design

In the data

In how the data are analyzed

In how the data are interpreted

In how the data are reported

Consider Sex and Gender



How sex/gender are factored into research designs, device development, and analyses of studies in humans, vertebrate animals, tissue cultures and primary cell lines

Applies to non-clinical and clinical research – throughout the total product life cycle

Balanced by a least burdensome approach

Collect

Analyze

Report

Benefit

CDRH at the Forefront of Science



Streamlines Process

- **Consistent approach** to research, analysis, and reporting across government



Saves Resources

- Considering possible role of sex and/or gender **early in the research continuum** may save resources



Improves Data Quality

- **Valid results** depend on well-designed research that considers all variables that may influence outcome

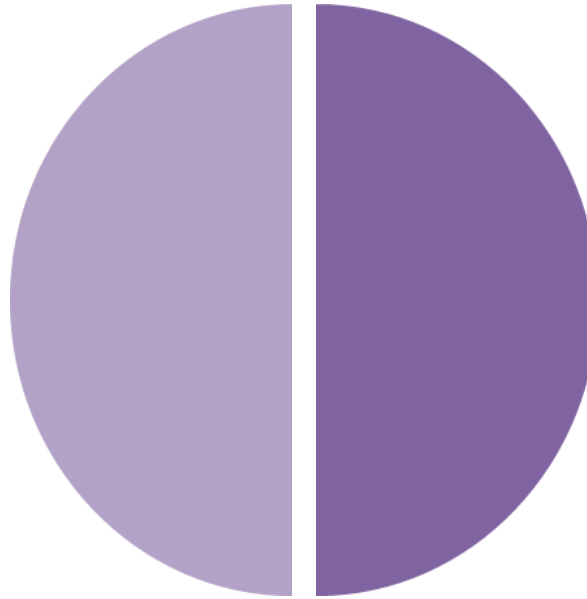


Strengthens Science

- Reporting more sex- and gender-specific data **builds a stronger knowledge base** to enhance efficiency of future regulatory research

Unified Process

Subgroup Analysis



Age

Sex/Gen

Genetic Ancestry

Ethnicity

Simply This...

Does sex and/or
gender affect your
observation?

If no, why not? If yes, how?



U.S. FOOD & DRUG
ADMINISTRATION

Center for Devices and Radiological Health Health of Women Strategic Plan



FDA

FDA STATEMENT

FDA Releases CDRH Health of Women Strategic Plan to Better Inform Medical Device Research and Regulation for All Women

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January 18, 2022

- *CDRH initially issued a proposed strategic plan in September 2019*
- *Considered public feedback to inform this strategic plan*
- *Lays out the framework to further the FDA's mission by protecting and promoting the health of all women*

<https://www.fda.gov/media/155461/download>

Strategic Plan

Outlines three priority areas to protect and promote the health of women

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

Improve availability, analysis, and communication of sex- and gender-specific information

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

Strengthen internal health science programs and initiatives across CDRH

Priority 3 – Research Roadmap

Develop a research roadmap for the health of women medical device ecosystem



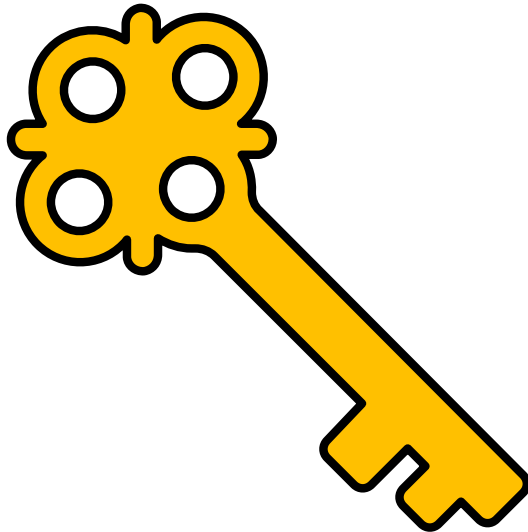
Closing

Help ensure diverse patient demographics and the full spectrum of disease are adequately represented in our clinical trials and data sets

Analyze the data disaggregated by subgroup(s) to better inform the science and drive development of innovations that perform best in all populations for which intervention is intended

Improving data quality, strengthening the science, enriching patient information – brings us closer to precision medicine

Key Takeaway



The study of sex and gender as valid clinical variables is key to better science, and ultimately better health for everyone.

Knowledge Check #1

Science increasingly reveals that sex and gender differences may play significant roles in the course and outcome of conditions that affect all human organ systems.

- A. True**
- B. False**

Knowledge Check #2

Sex and gender are synonymous terms in biomedical research.

- A. True**
- B. False**

Knowledge Check #3

To move the science forward, a critical question for innovators and researchers to ask should be: ***Does sex and/or gender affect the observation? If yes, how? If no, why not?***

- A. True
- B. False

CDRH Health of Women Program

Webpage: CDRH Health of Women Program | FDA

<https://www.fda.gov/about-fda/center-devices-and-radiological-health/cdrh-health-women-program>

Mailbox: CDRHHealthofWomen@fda.hhs.gov.



Center for Devices and Radiological Health
Health of Women Strategic Plan





HEALTH OF WOMEN

CENTER FOR DEVICES &
RADIOLOGICAL HEALTH

Thank You

Health of Women Steering Committee and Ambassadors

Current

Terri Cornelison
Sharon Andrews
Claudette Brooks
Katie Capanna
Jacqueline Cunkelman

Sahar Dawisha
Donna Engleman
Shlomit Halachmi
Danica Marinac-Dabic
Denise Sanchez

Michelle Tarver
Katherine Vorvolakos
Kristina Wiegelmink
Terry Woods

Former

Karoll Cortez
David Gebben
Martin Ho

Ana Loloei
Genevieve McRae
Monica Pagán Motta

Adrianne Phenix
Veronica Price
Jessica Ritsick

Health of Women Program

Current

Terri Cornelison
Antoinette Hazlett

Morgan Kolarich (Pathways
Intern)

Karen Liu (University of
Maryland student)

Former

Carol Krueger

Questions?

