

# The Science of Sex and Gender

**FDA Small Business Regulatory Education for Industry (REdI)**

June 8, 2022

**Terri Cornelison, MD, PhD**

Chief Medical Officer & Director

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

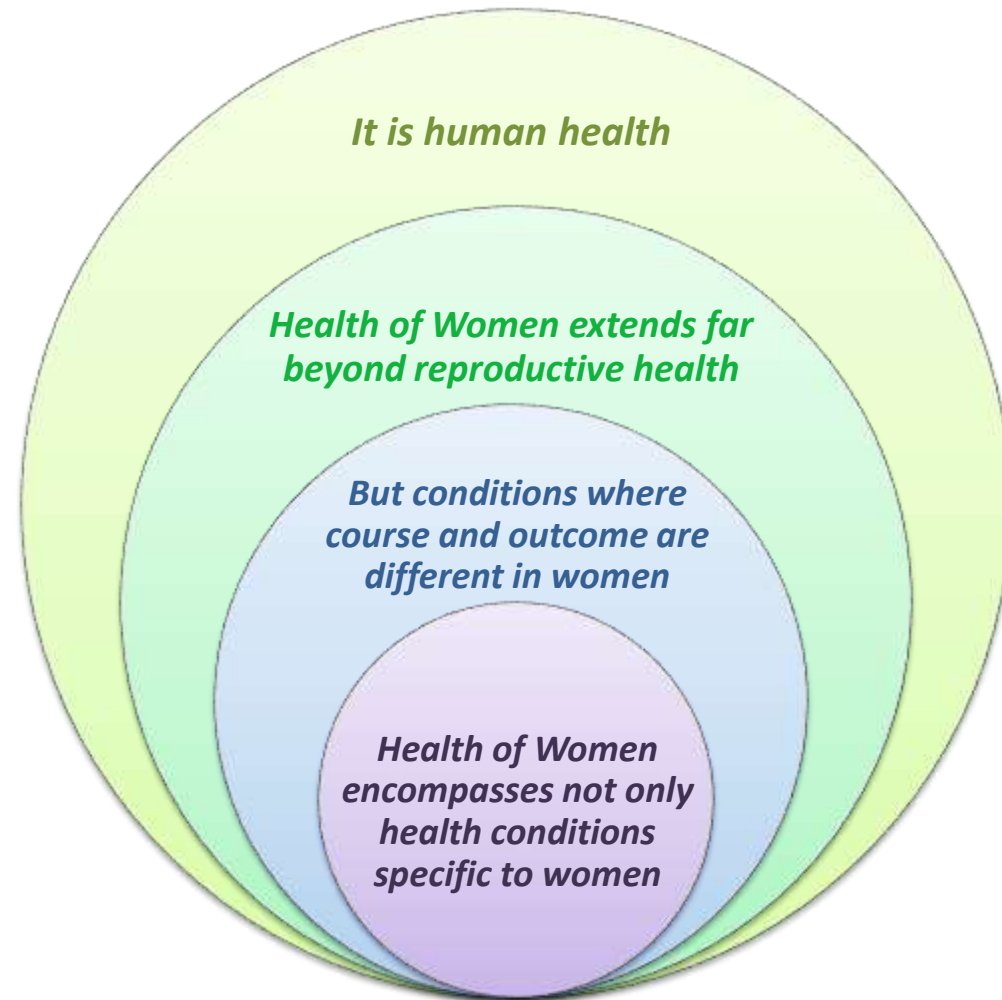




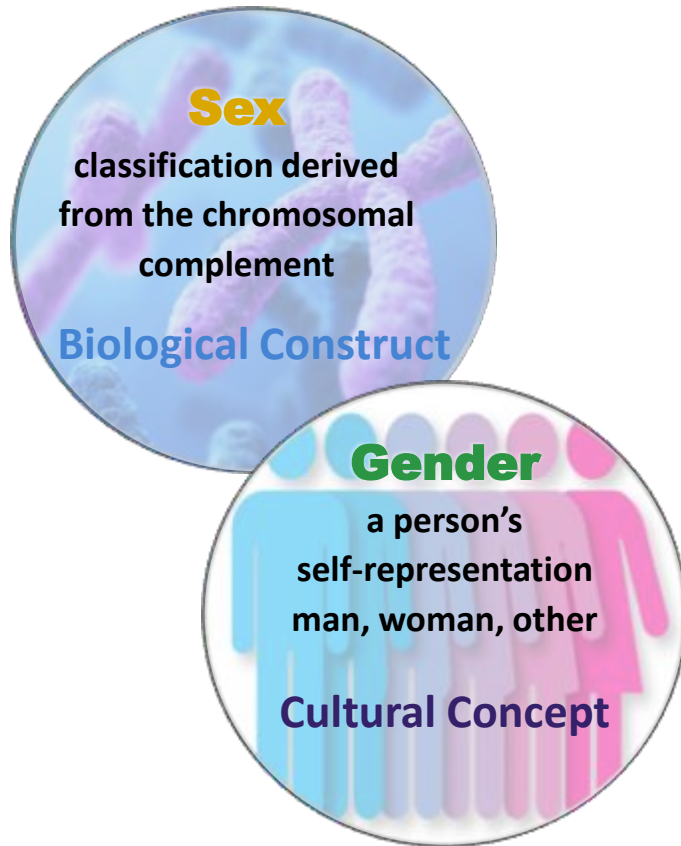
# CDRH Health of Women Program

## Visionary

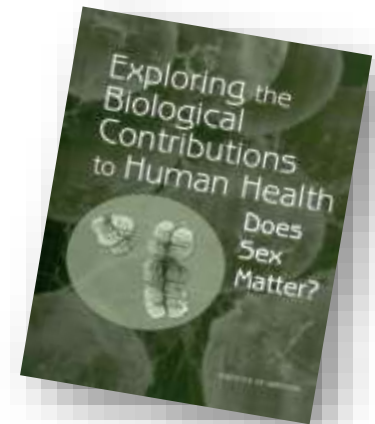
*CDRH has long been interested in a Health of Women framework to explore the unique issues related to the performance of medical devices in women*



***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 Center for Devices and Radiologic Health



Cardiovascular

Women-Specific

Orthopedic

Neurologic

Physical Medicine







# FDA Center for Devices and Radiologic Health



Radiology

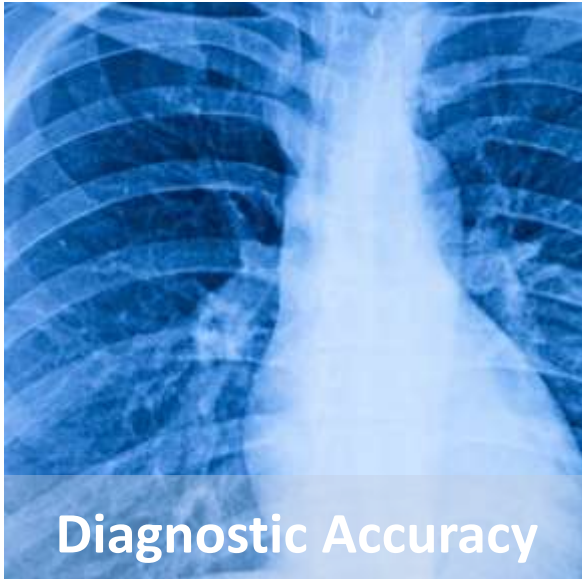
Diagnostics

Biomarkers

Digital Health

Artificial Intelligence

Machine Learning

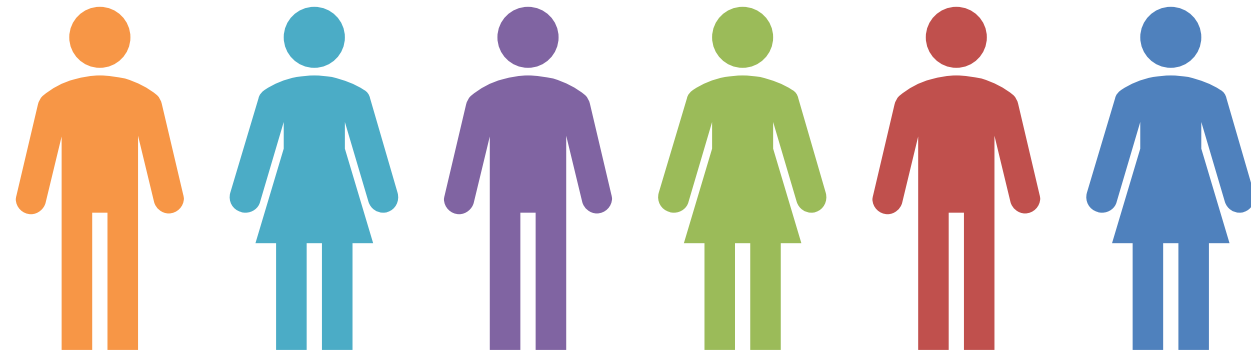


# Why, What, Where & How?

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*

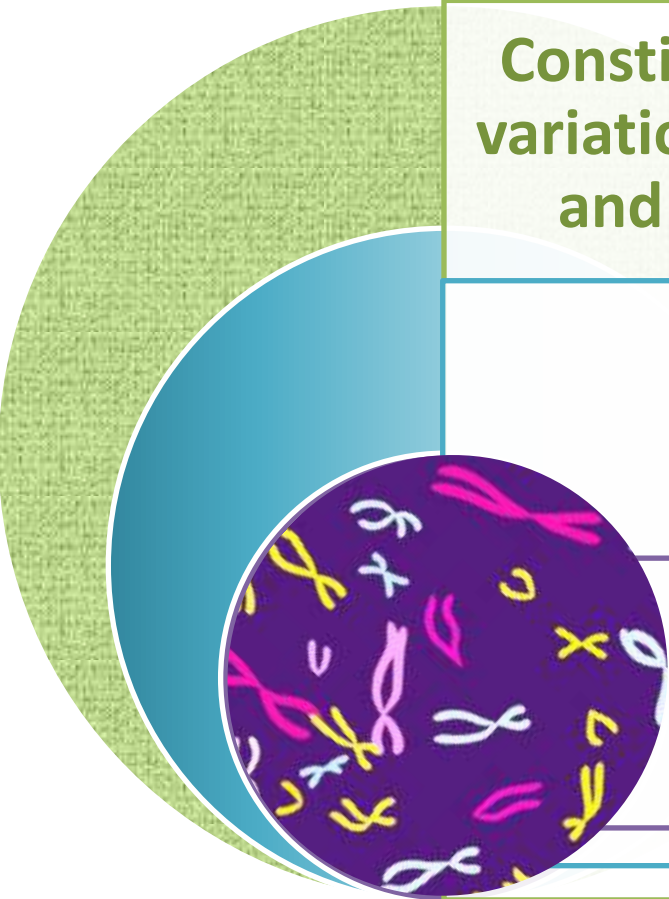


# Diverse Populations



# 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**

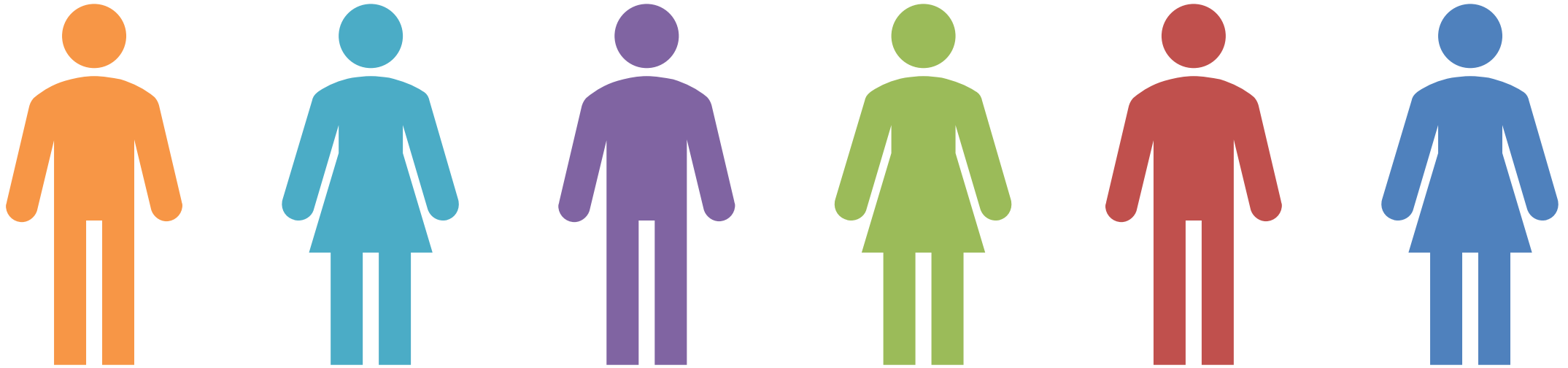
**Gender, Ethnicity**

**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

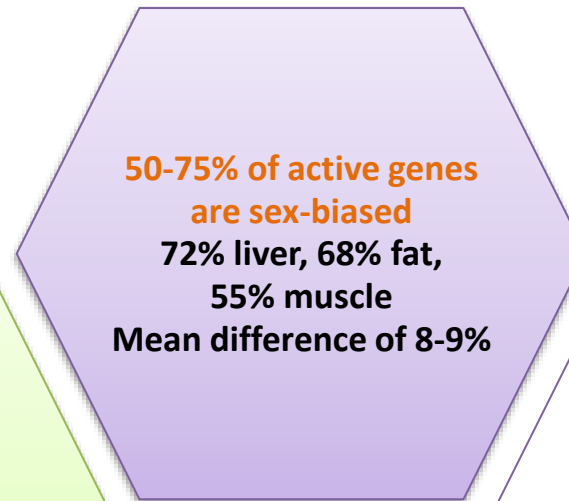
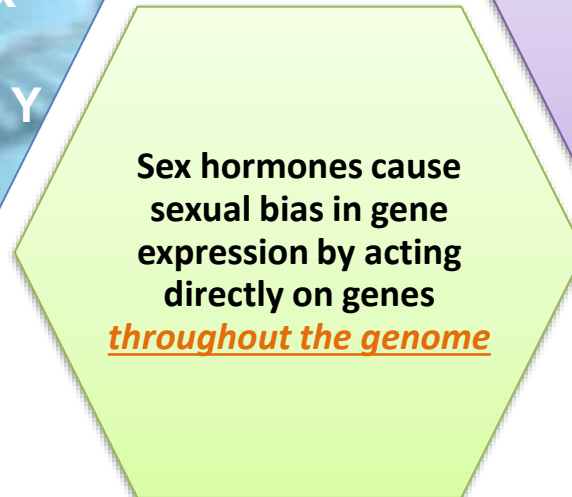
# Generalizability





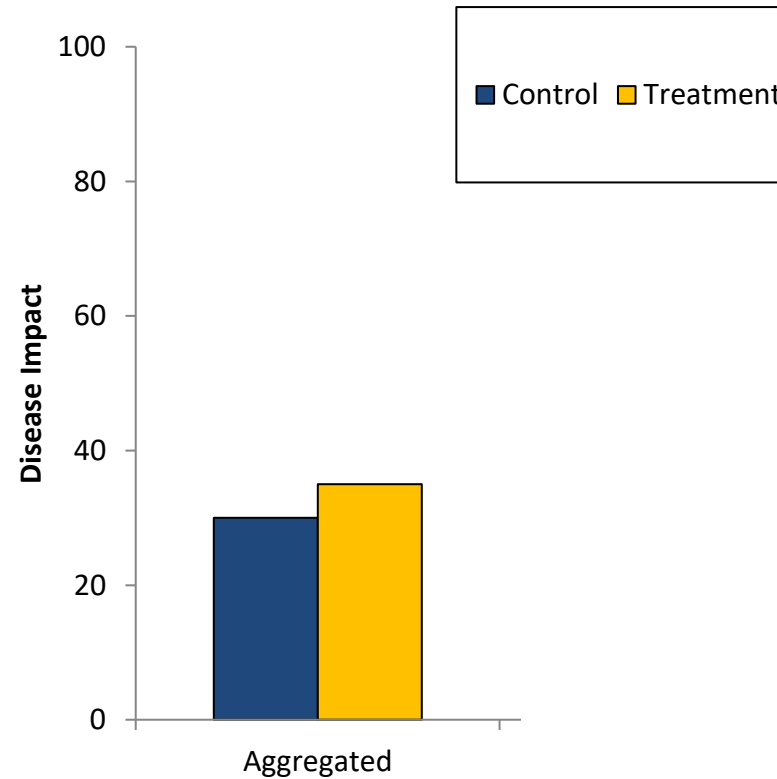
# Global Patterns of Gene Expression

## Differ in Males and Females

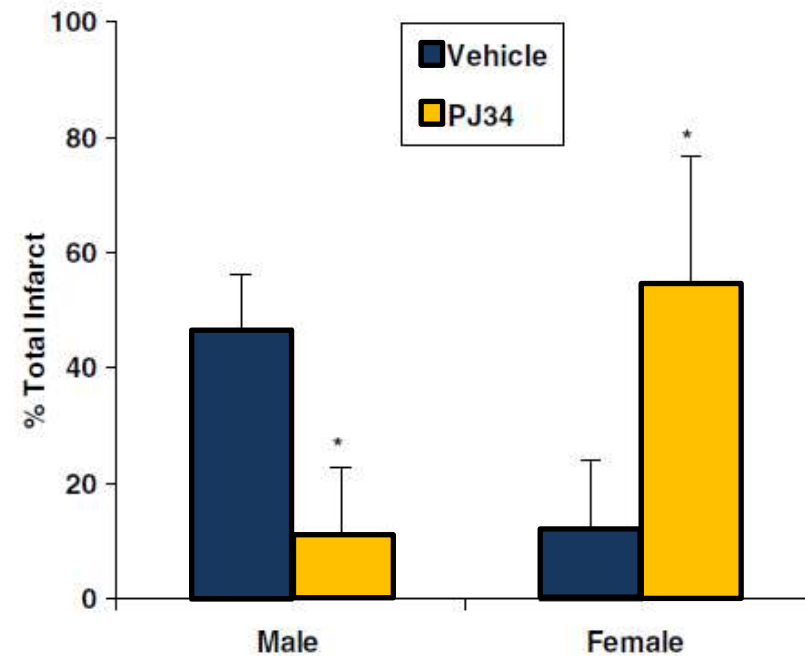


Yang et al. *Genome Res* 2006

# Impact of Experimental Design

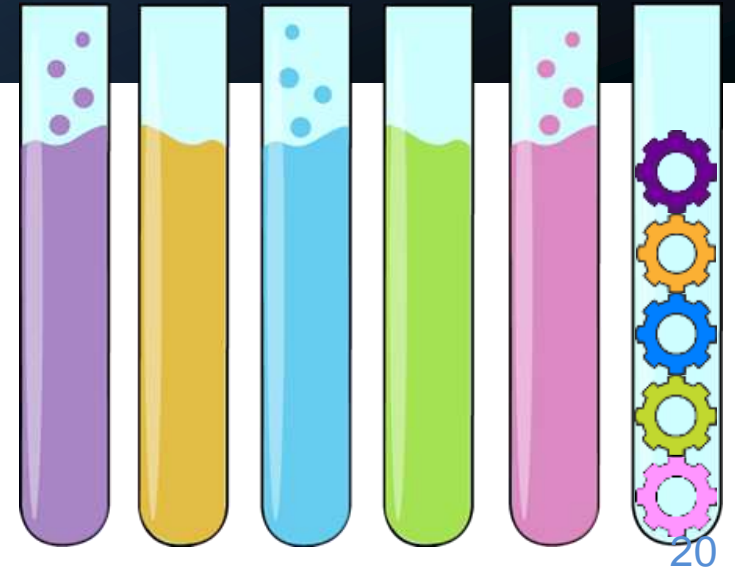


# Real Life



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*

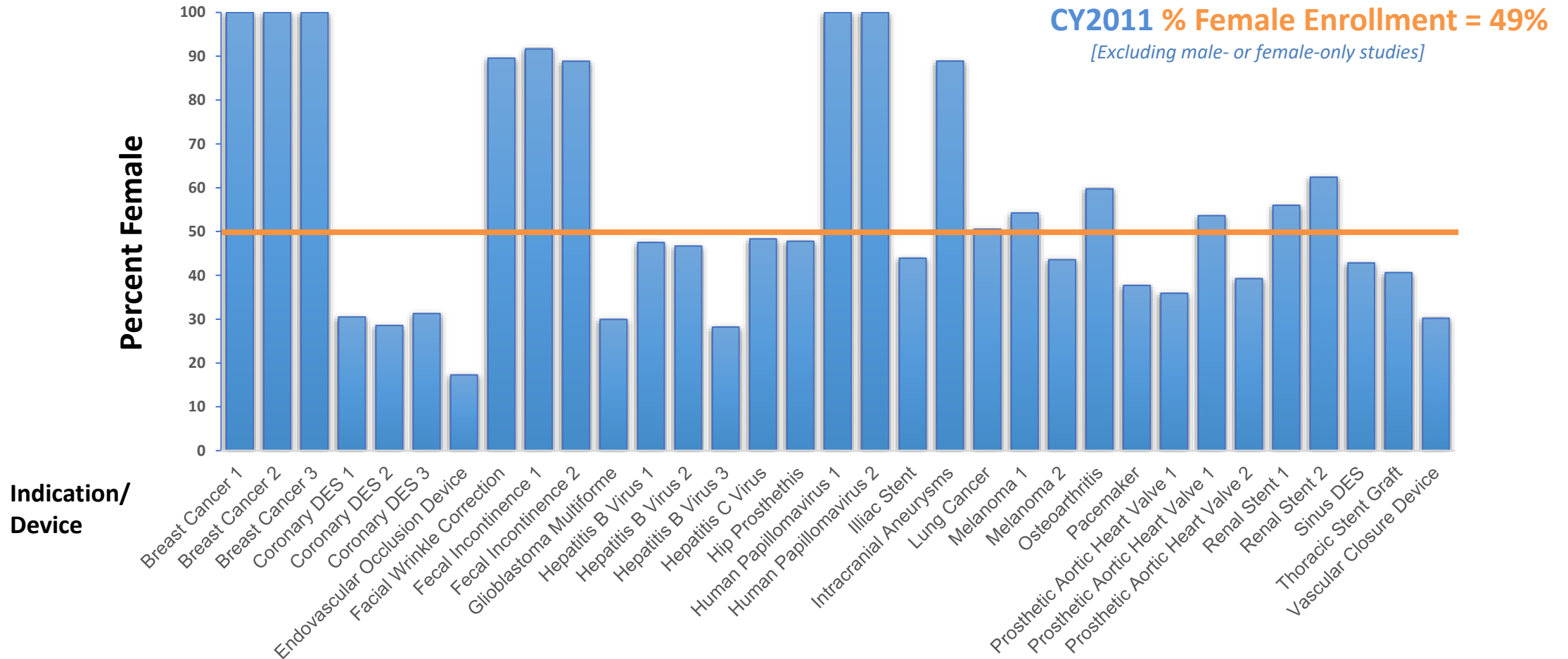
### FDAMA 1997

- *Develop guidance on inclusion of women*



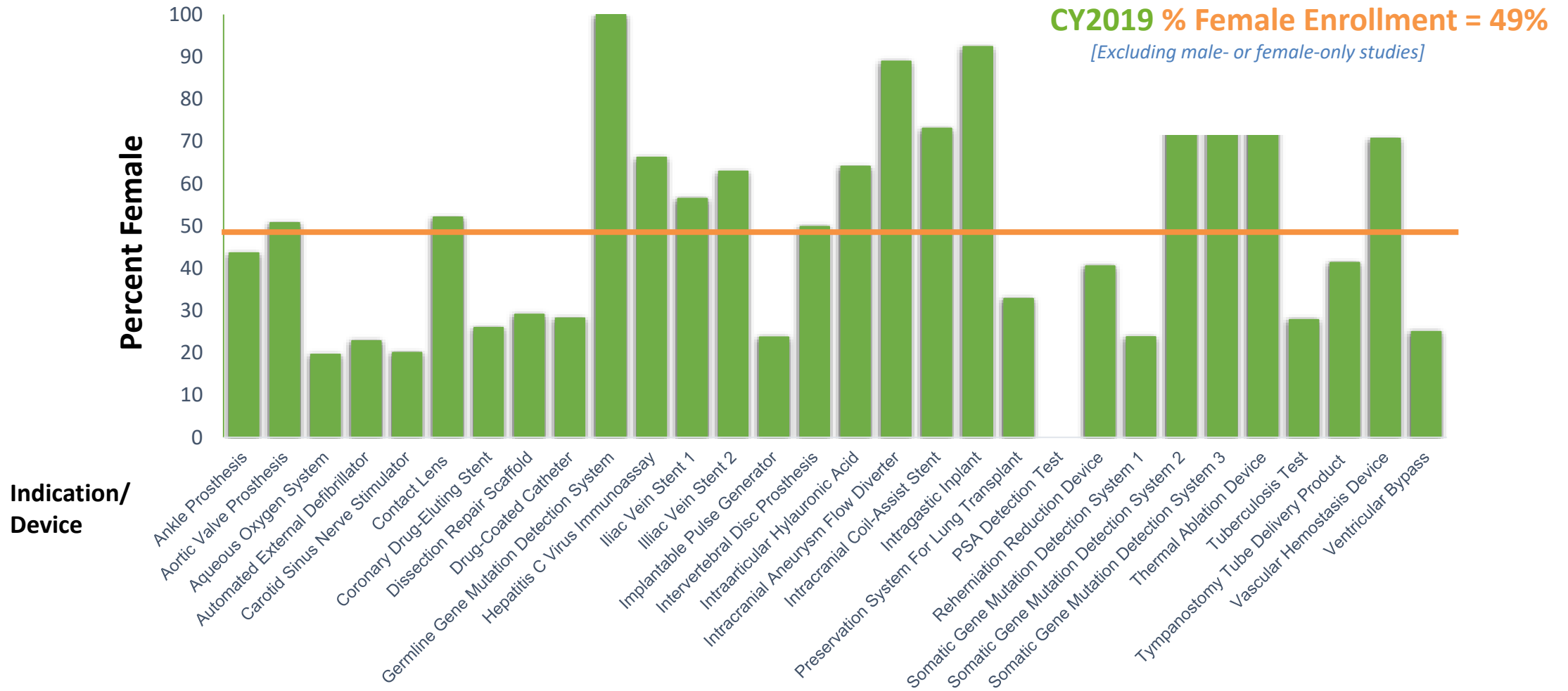
# Inclusion as Preamble

## Percent Enrollment by Sex/Gender: CDRH PMAs

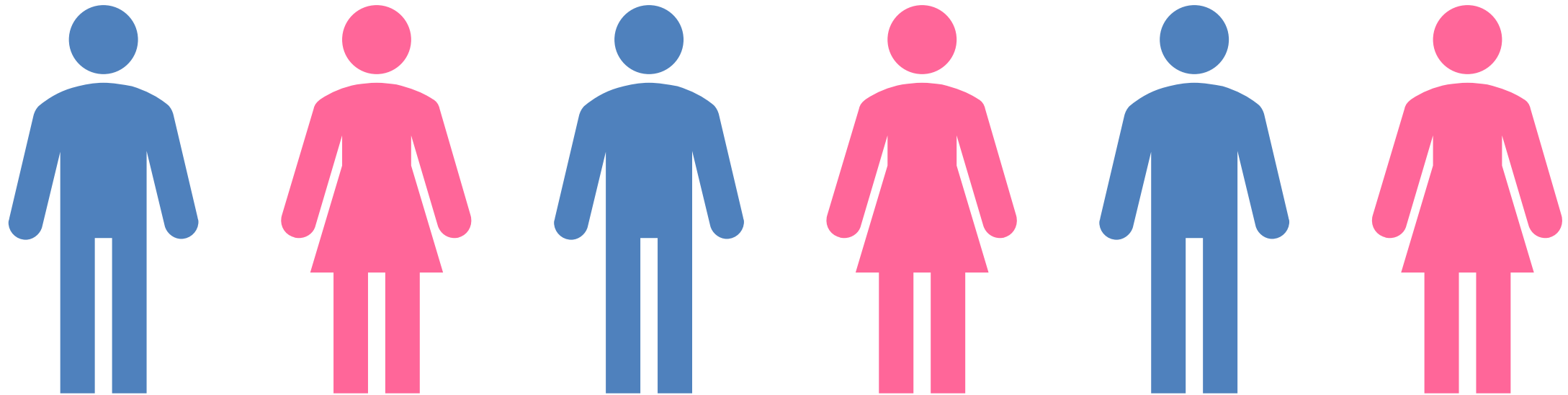


# Inclusion as Preamble

## Percent Enrollment by Sex/Gender: CDRH PMAs



# Inclusion is Only Part of the Story



# Sex is a Basic Biologic Variable

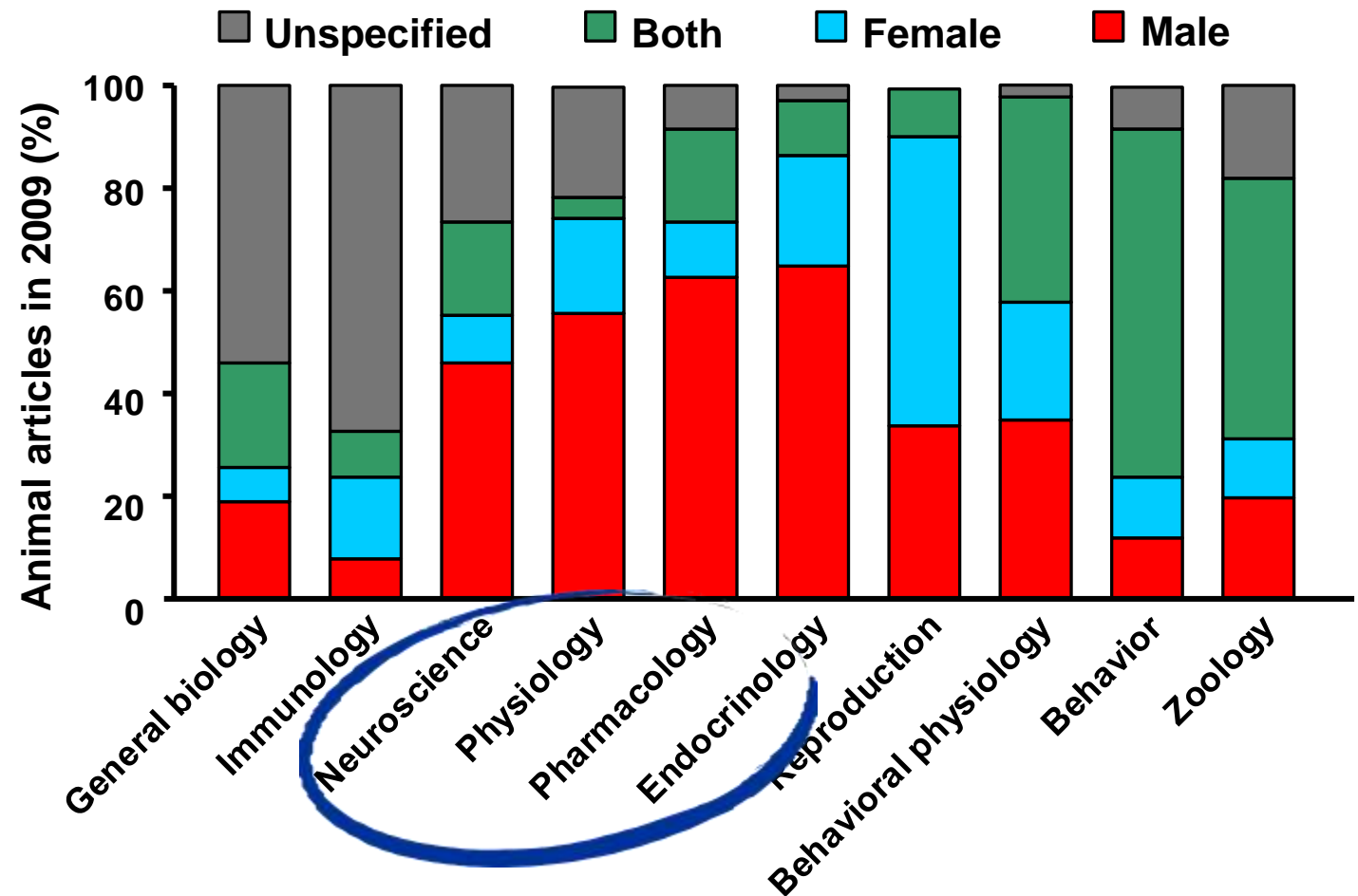
Profound influence on  
our daily lives, including  
our physiology and  
susceptibility to disease



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**

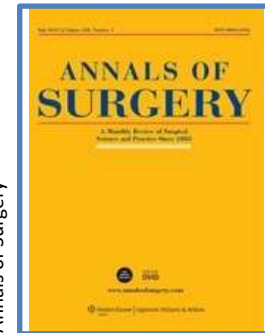
American Journal of Surgery



JAMA Surgery



Annals of Surgery



Journal of Surgical Research



Surgery

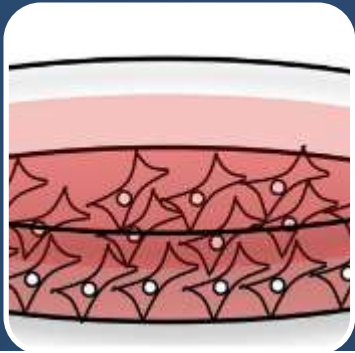


Kibbe et al,  
Surgery 2014



# Male Predominance

## *Impact on Health Care*



### Cells

- Undefined
- Male



### Animals

- Undefined
- Male

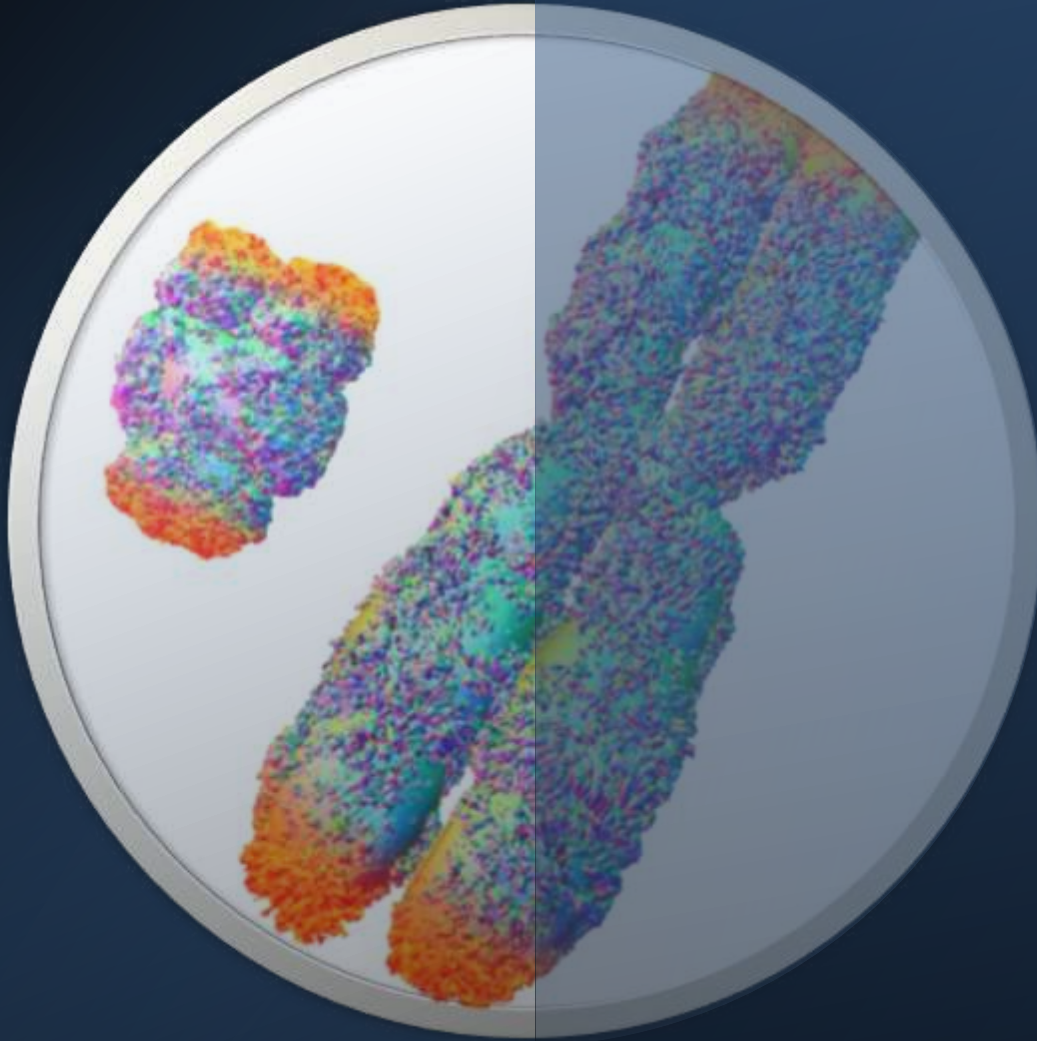


### Humans

- Men



### Medical Care



# Every Cell is Sexed



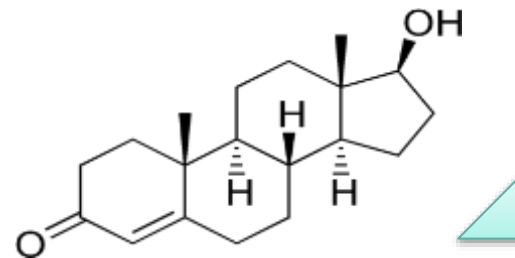
# Proximate Factors Causing Sex Differences

## Chromosome Effect



### Sex Chromosome Effect

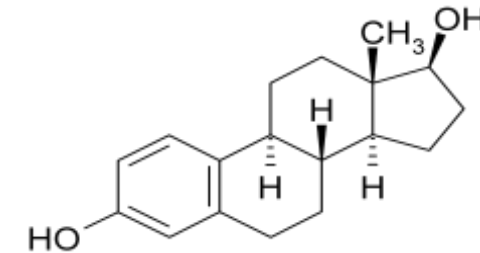
- Direct effects of X and Y genes in non-gonadal tissues



### Hormonal “Organizational”

- Permanent differentiating effects of testosterone on genitalia and brain

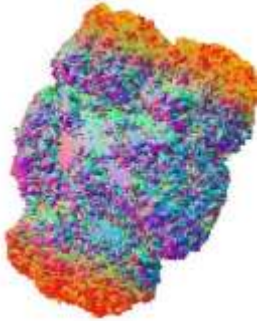
## Hormone Effect



### Hormonal “Activational”

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

# Y Chromosome



Y – No Homologous Counterpart: *SRY*

- Testicular determination

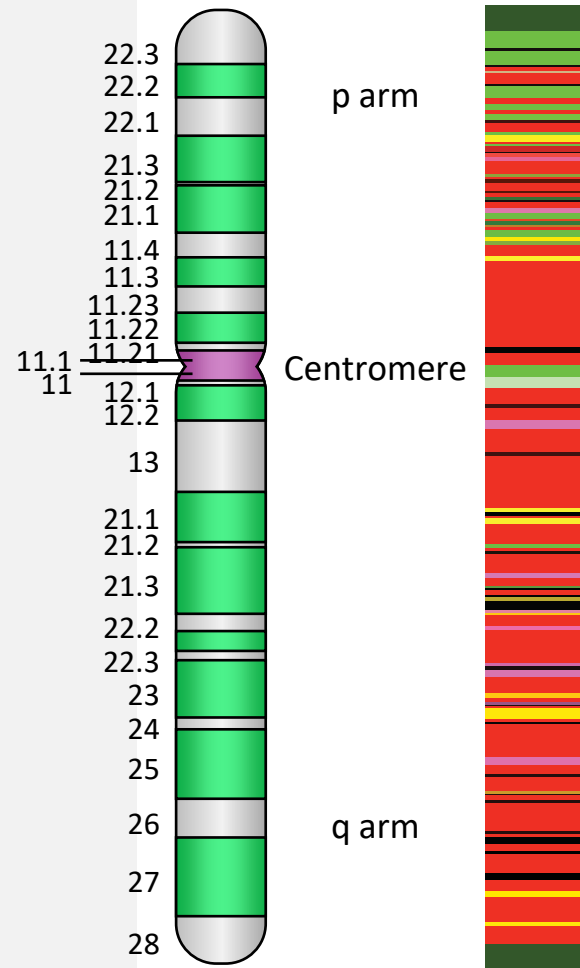
Y – Homologous Counterpart: *RPS4Y*

- 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

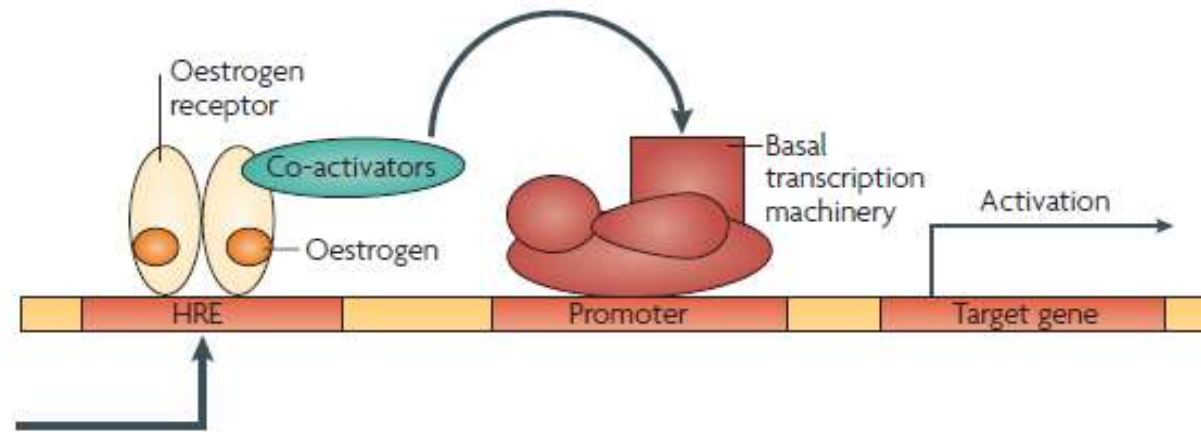
## Reproduction

Androgen insensitivity, Premature ovarian failure



# Epigenetic Changes

Regulation of gene expression by hormone receptors



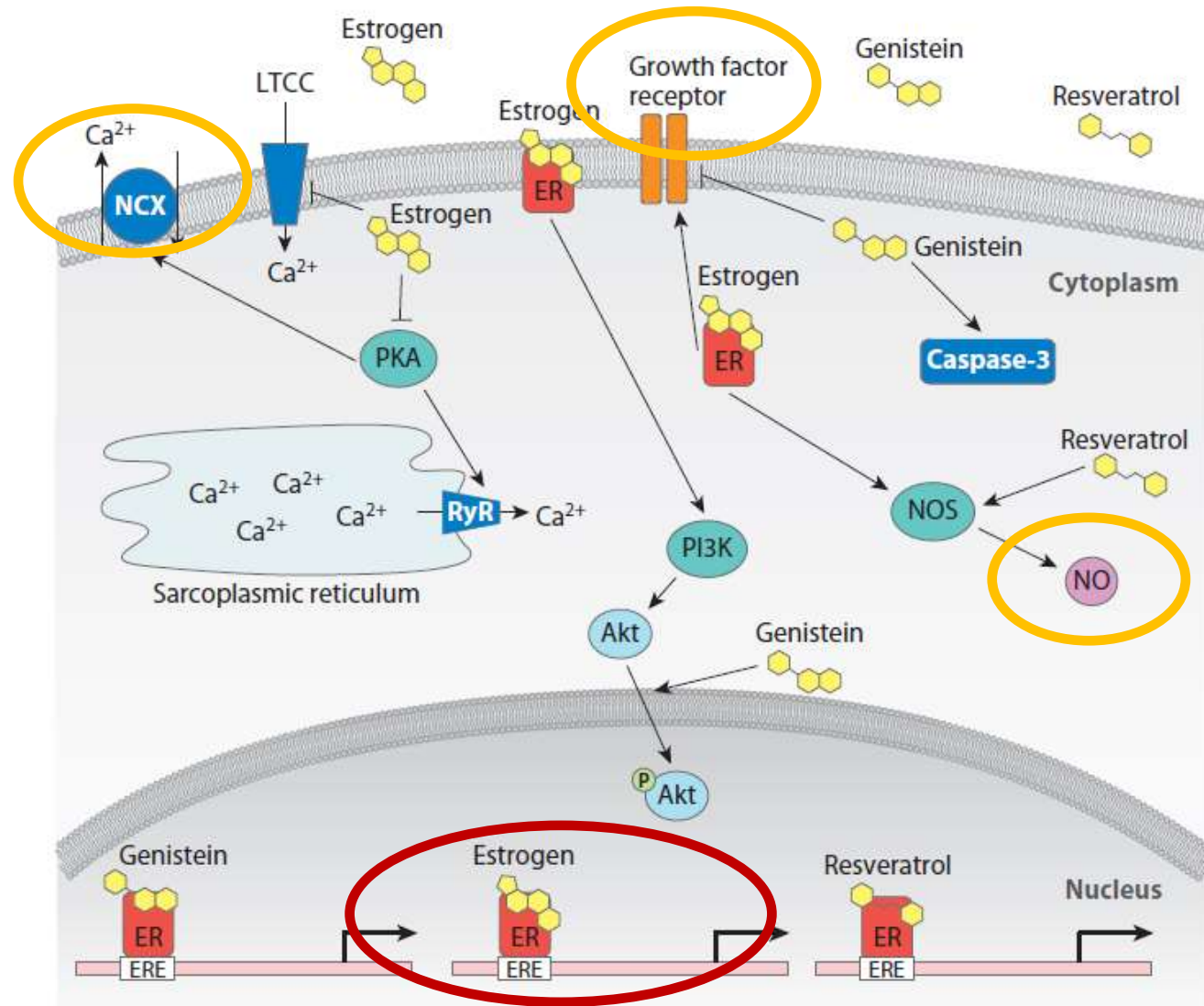
## Estrogen-responsive elements

## 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







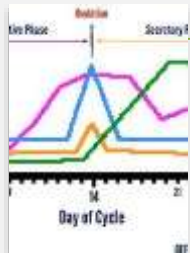
# Cardiovascular Risk



**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**



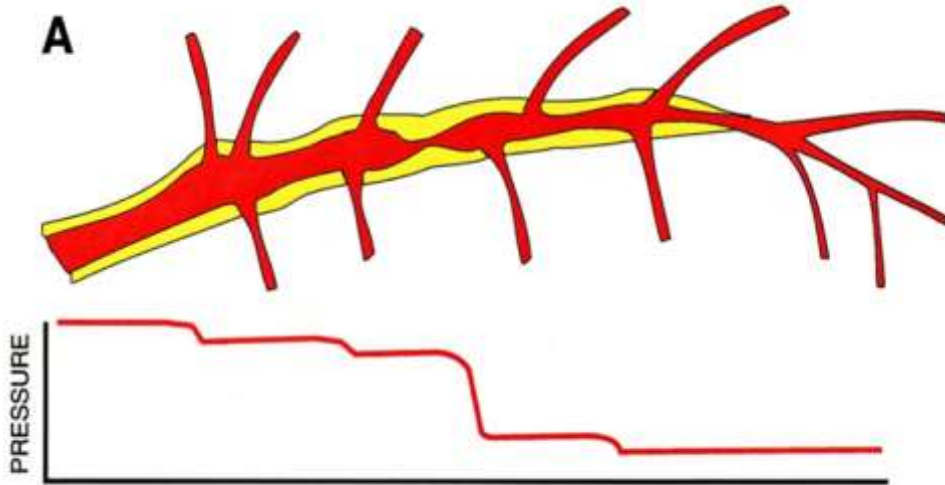
**Women have twice the rate of heart failure with preserved ejection fraction**



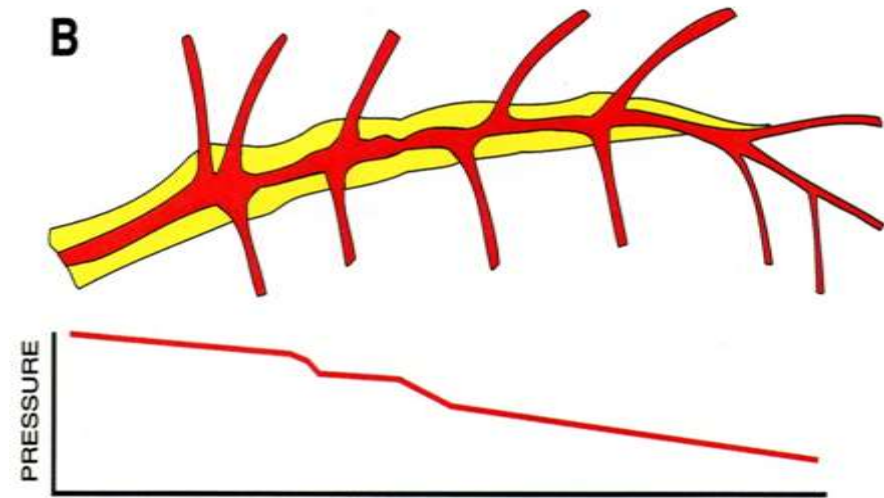
**Women with adverse pregnancy hypertensive outcomes have greater risk of cardiovascular disease**

# Cardiovascular Disease

## in women



Single segmental stenoses  
Suitable for angioplasty

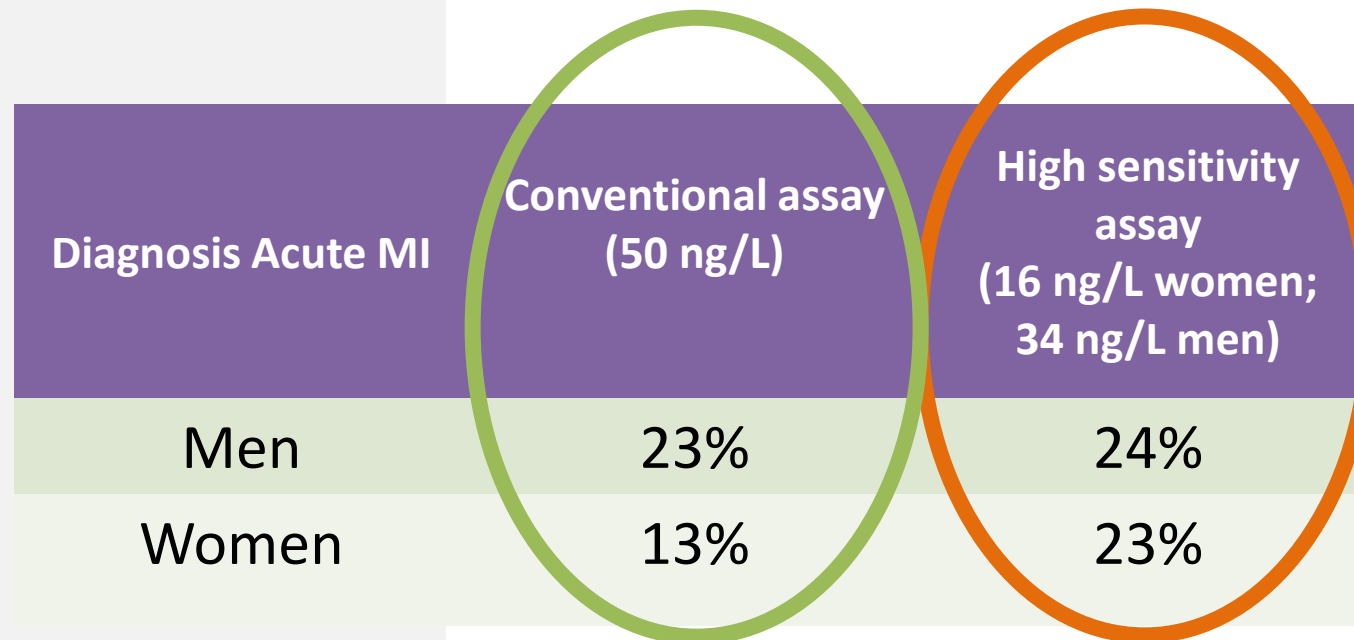


Diffuse disease or multiple stenoses  
**Not appropriate for angioplasty**



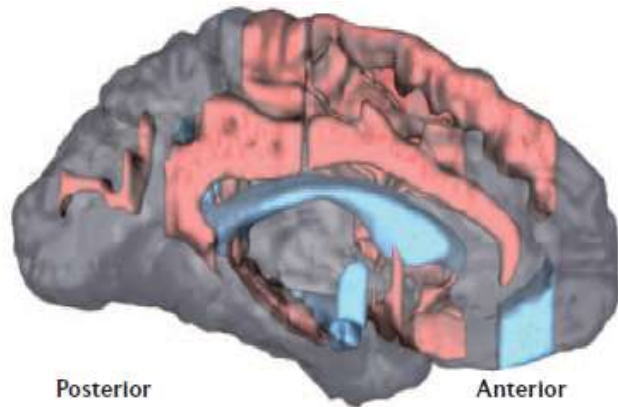
# Gender-specific Biomarker Thresholds Urged in MI Diagnosis

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



# Brain

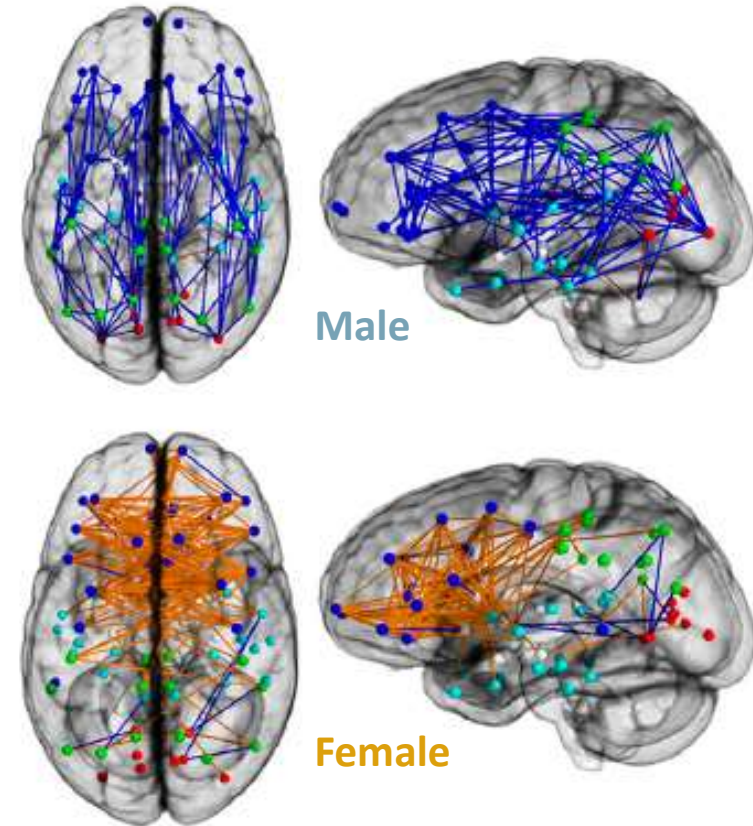
## Structural and Functional Dimorphism



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



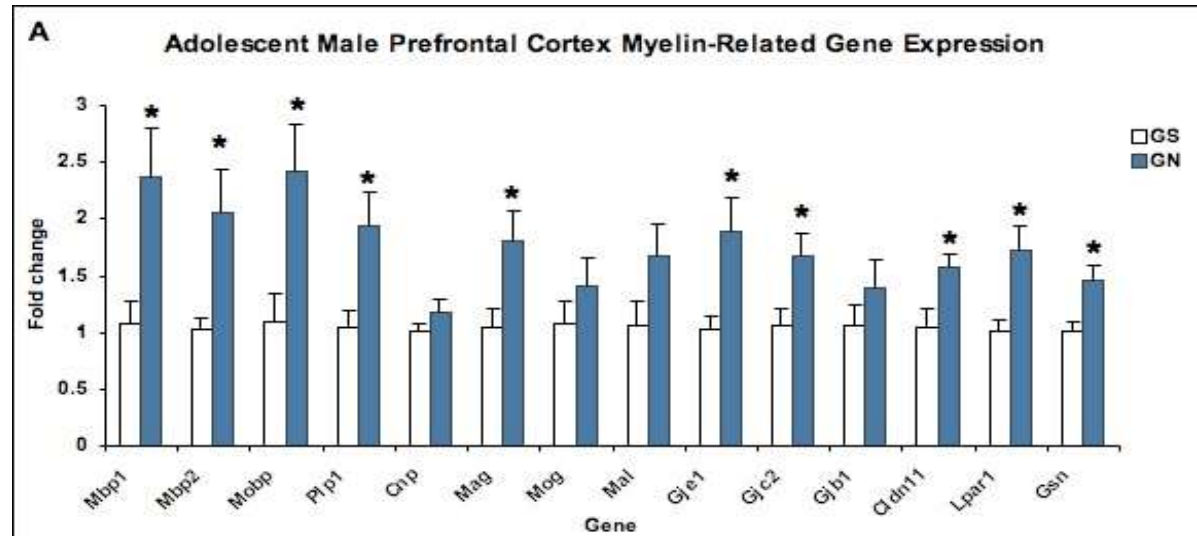
Ingalhalikar M, et al. *Proc Natl Acad Sci USA* 2013

# CNS Myelination Defects

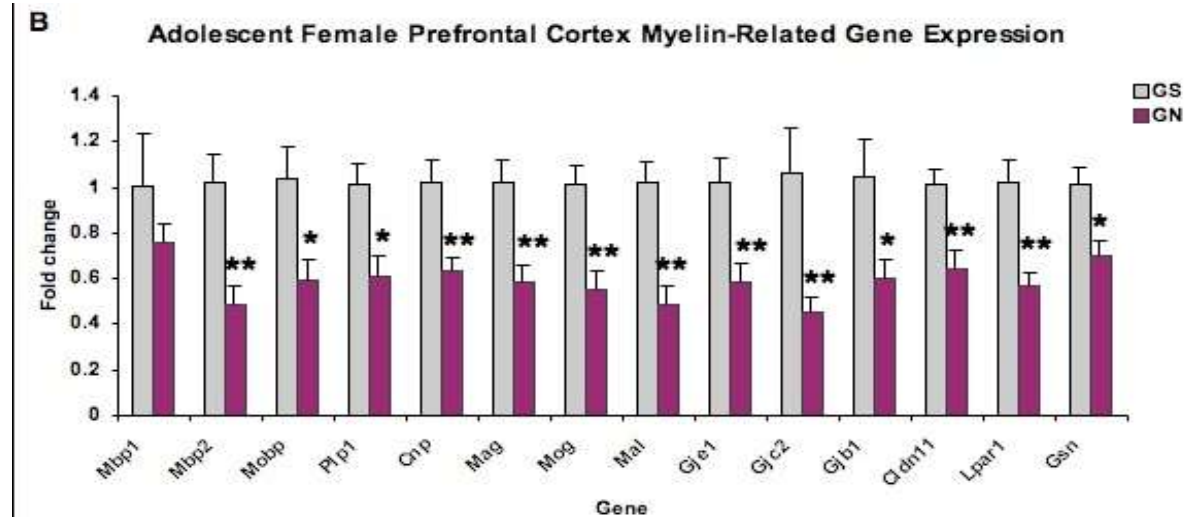
*Gestational Nicotine  
modifies myelin-  
regulated genes*

*Increase in male—  
Decrease in female rats*

Male



Female

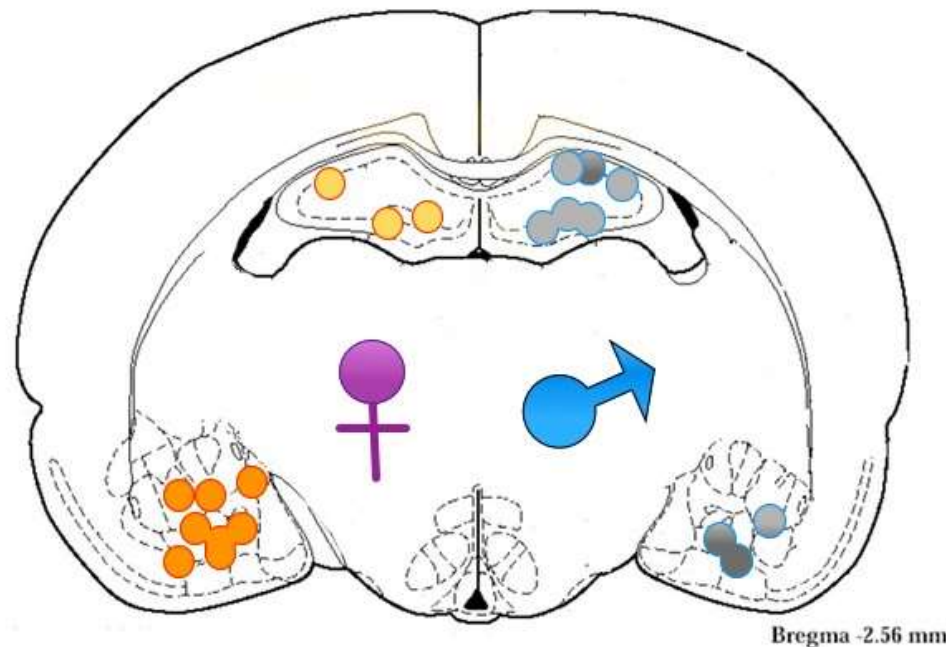




# Cell genesis is different in males and females in the telencephalon

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

## Amygdala

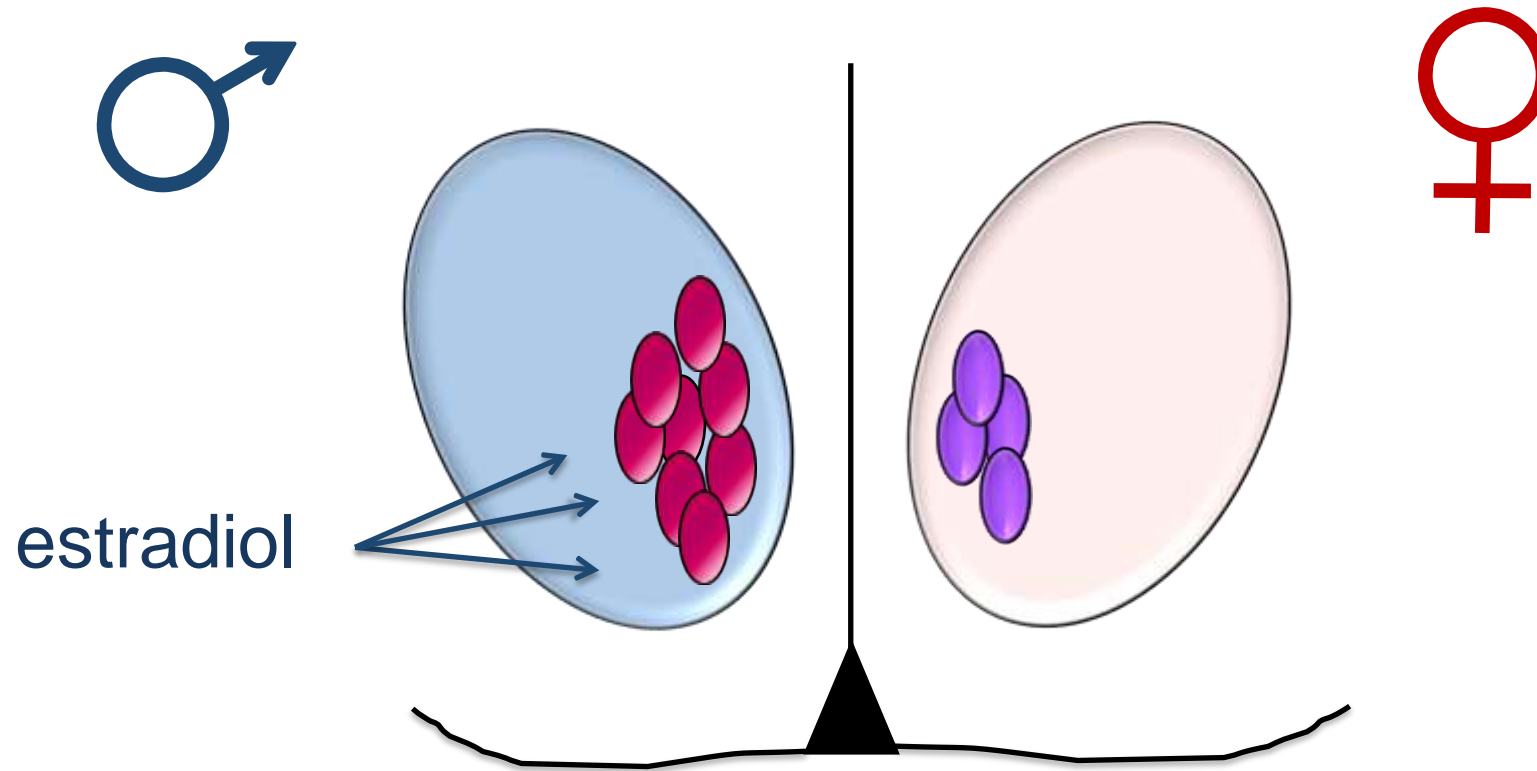


## Hippocampus

Newborn males  
make twice as  
many new  
hippocampal  
neurons as  
females

# Testosterone / estradiol in SDN

promotes survival of neurons

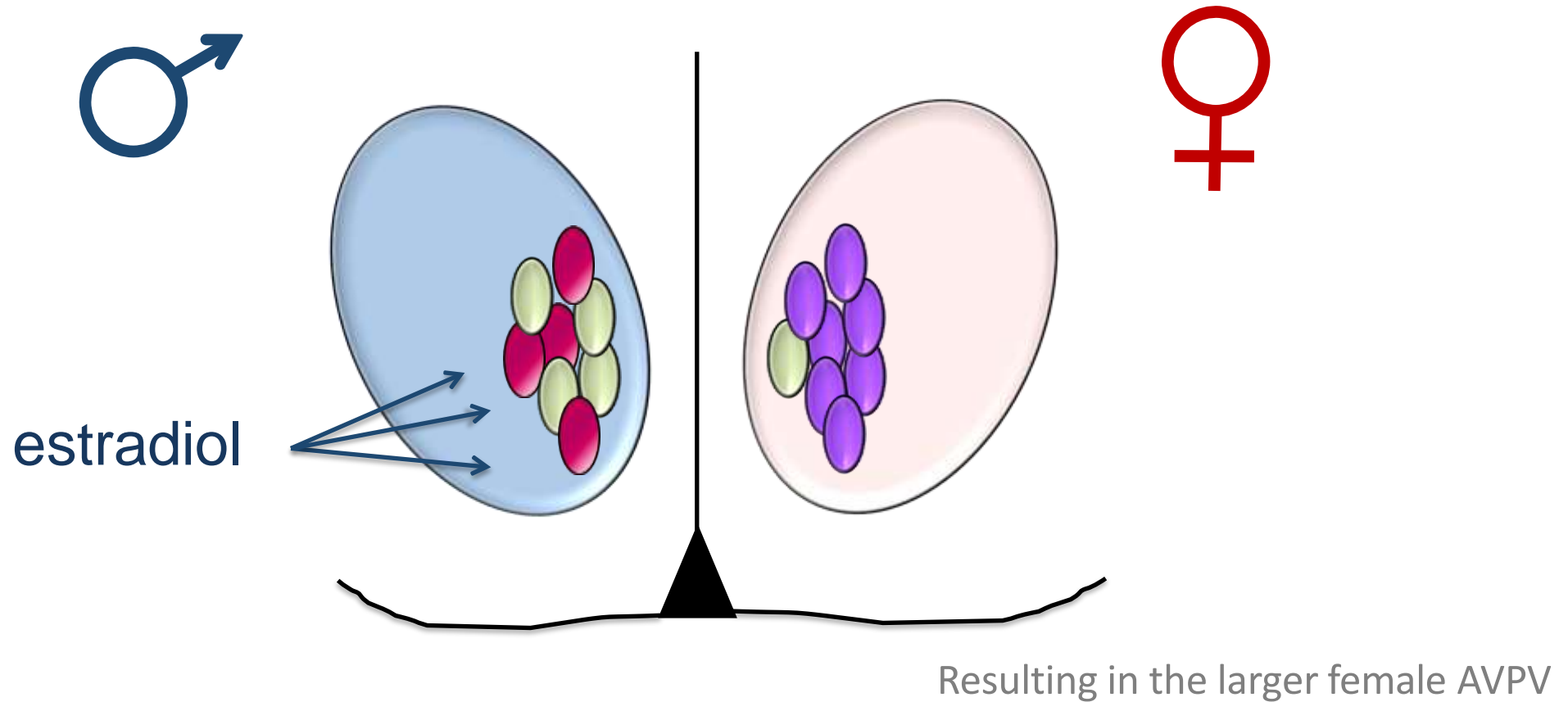


Resulting in the larger male SDN



# 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** ( $\text{ONOO}^-$ ) stress and excitotoxicity

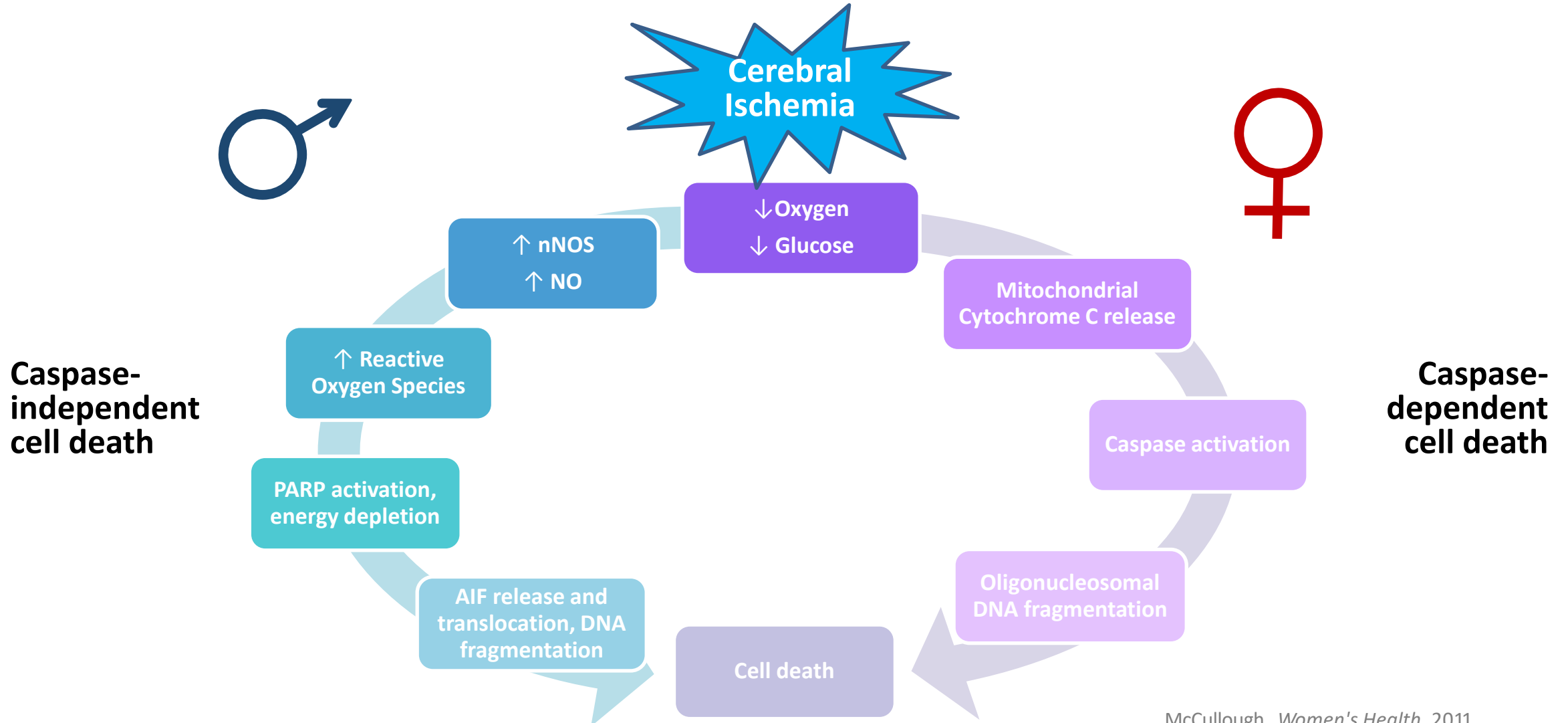
**Differential sensitivity to  
cytotoxic agents**

- **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

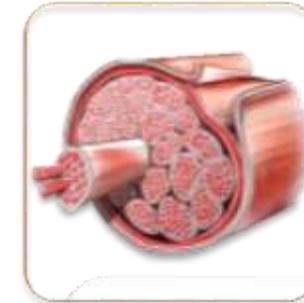


Human

## 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



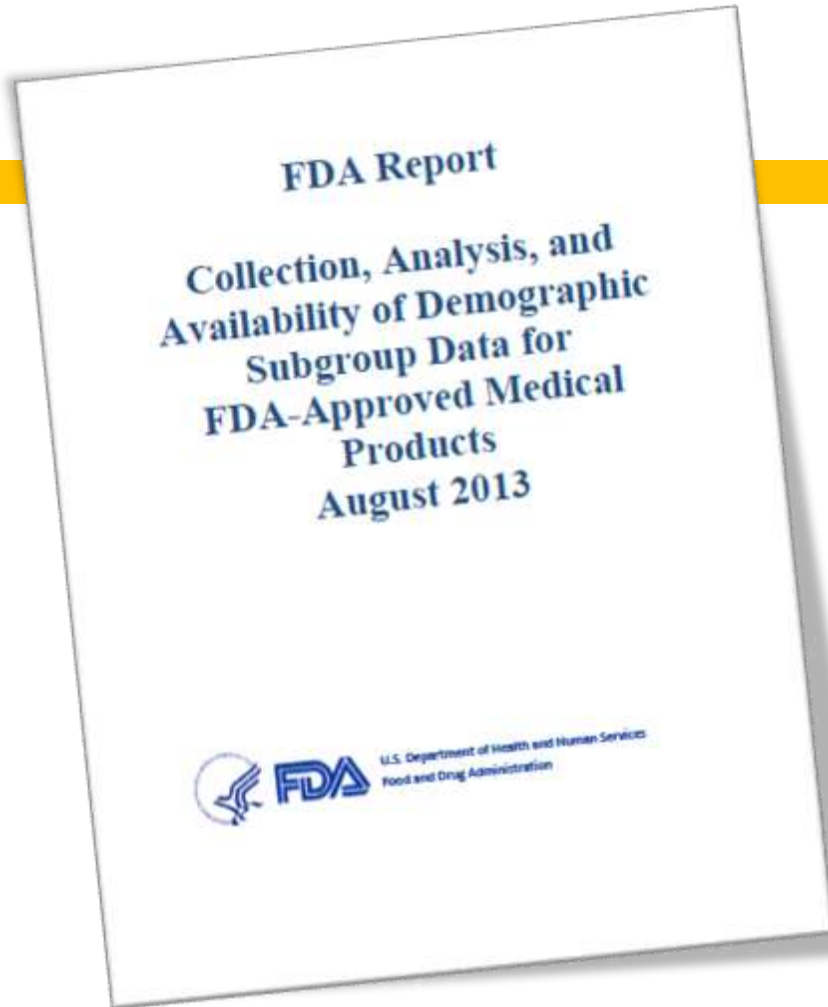
# FDASIA 907

## 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 21<sup>st</sup> 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](#)

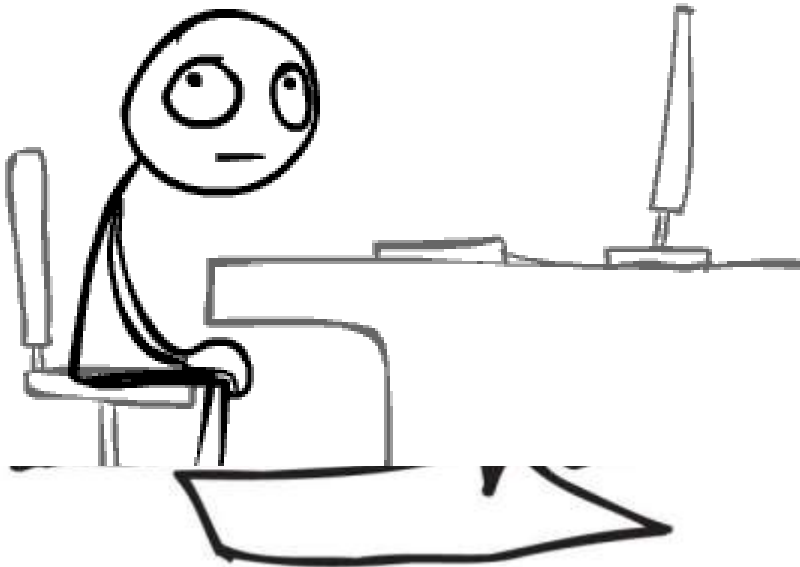
[NOT-OD-15-103](#)

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

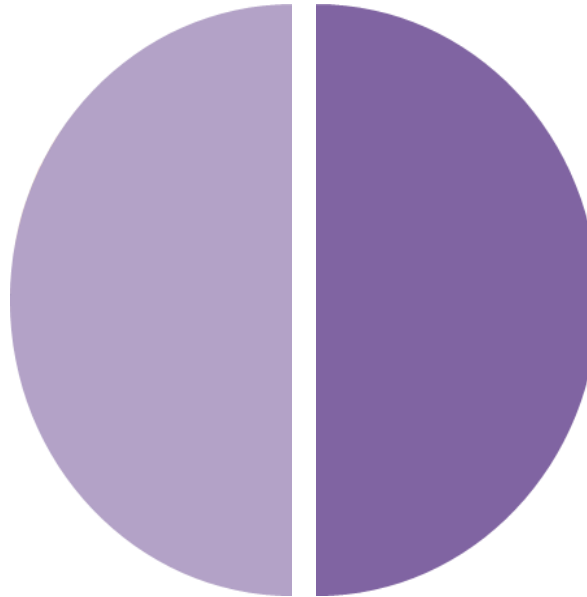


### Strengthens Science

- 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?*

Center for Devices and Radiological Health  
**Health of Women Strategic Plan**



FDA STATEMENT

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

[f Share](#) [t Tweet](#) [in LinkedIn](#) [✉ Email](#) [🖨 Print](#)

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

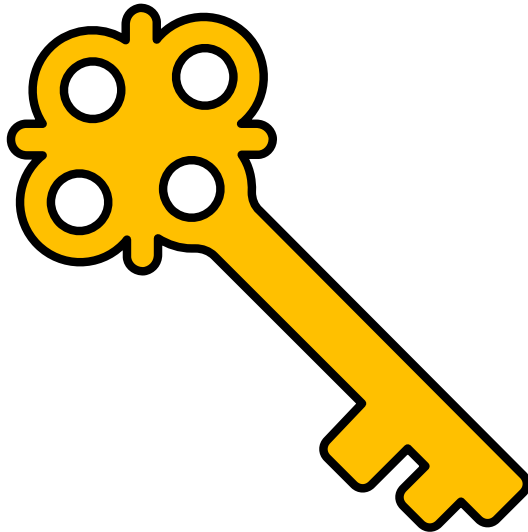
Help ensure diverse patient demographics and the full spectrum of disease are adequately represented in our clinical trials and data sets

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](mailto: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?

