



# Why is it Critical to Account for Biological Sex in all Analyses of Drug Effects?

Mayo Clinic  
**S**pecialized **C**enter **O**f **R**esearch **E**xcellence  
*on Sex Differences*

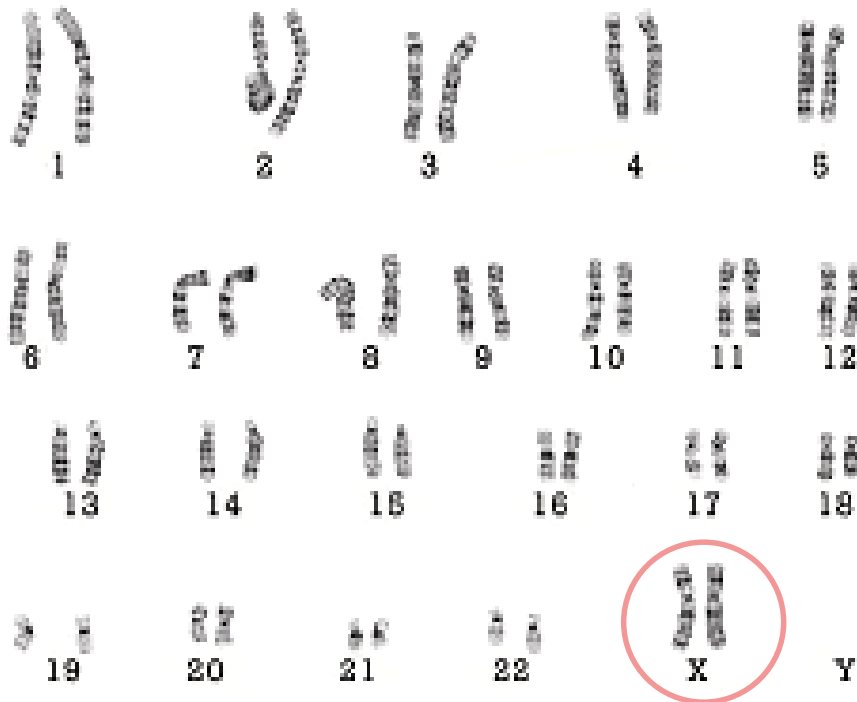
Virginia M Miller, PhD  
FDA Workshop - Subgroup Analysis  
November 28, 2018

# Why is it critical to account for biological sex in all analyses of drug effects?

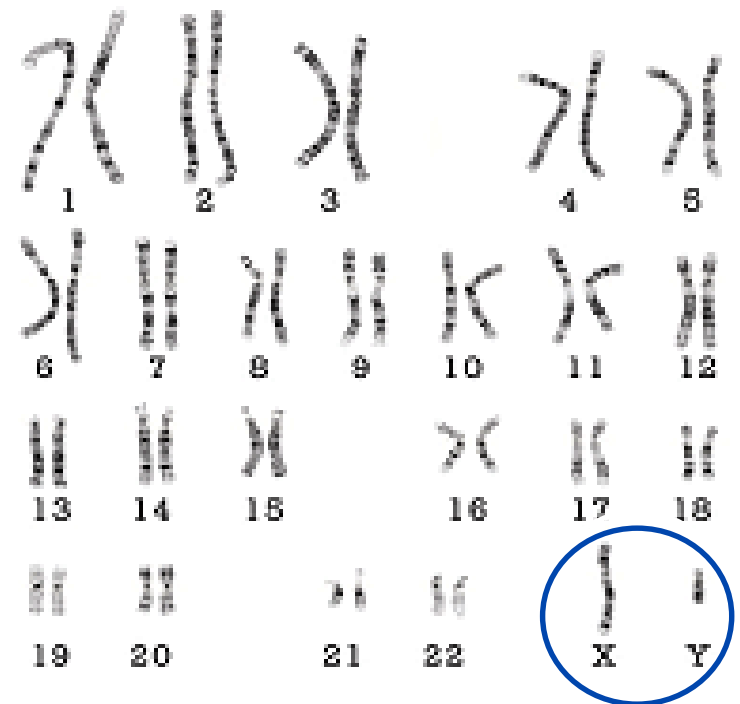
Sex is the basic biological variable that differentiates physiological and pharmacological processes.

# Human Karyotype

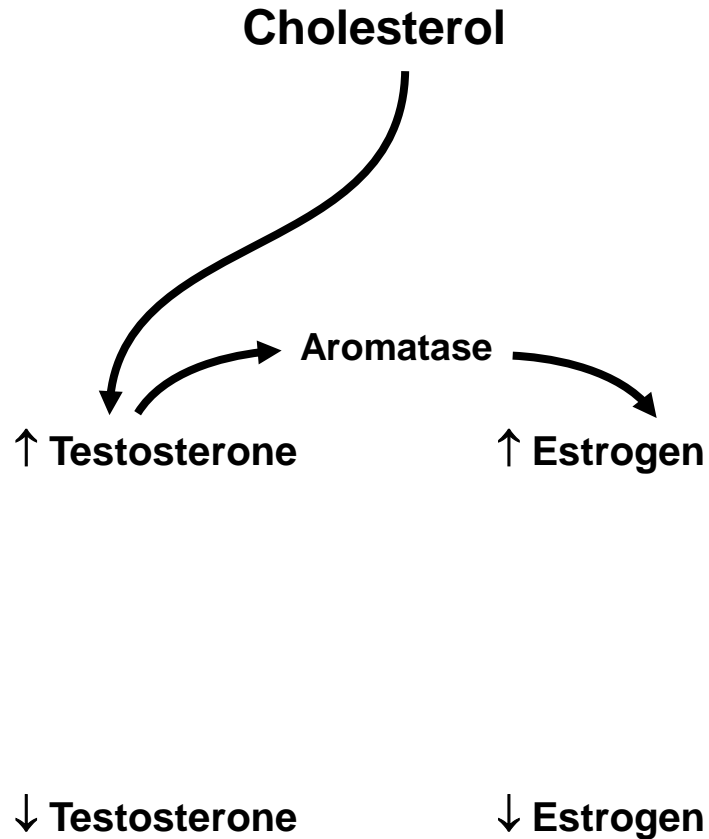
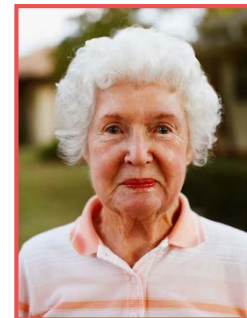
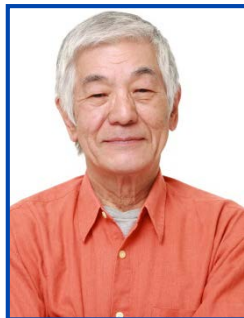
## Female



## Male



# Hormones



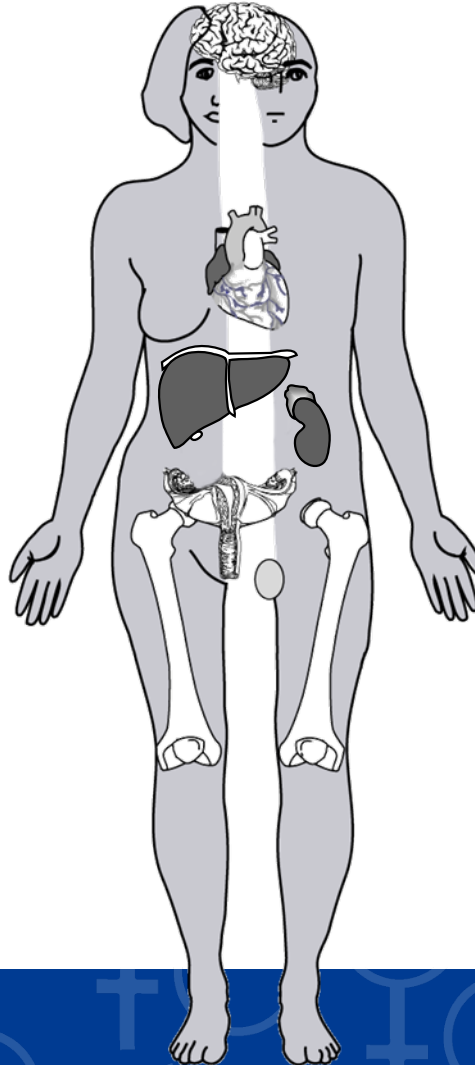
# Pharmacogenomics

## Genes of Interest

Pharmacodynamics

What the drug does to  
the body?

Mechanism of action



Pharmacokinetics

What the body does to the  
drug?

Absorption  
Distribution  
Metabolism  
Elimination

# Rat Liver Life Cycle: 3D-PCA

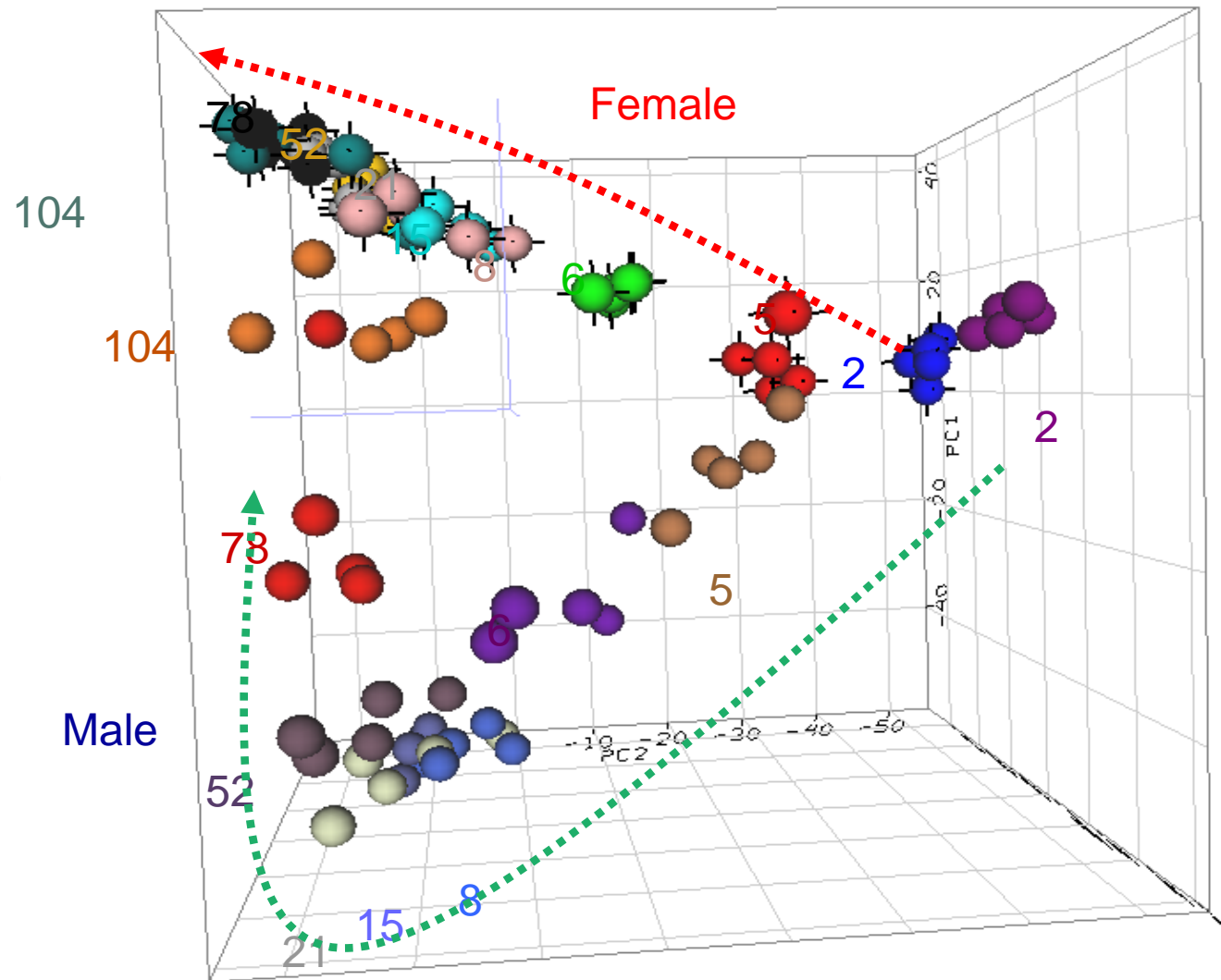
● = 1 animal

Filter criteria:

$P < 0.05$

and fold change  $> 1.5$

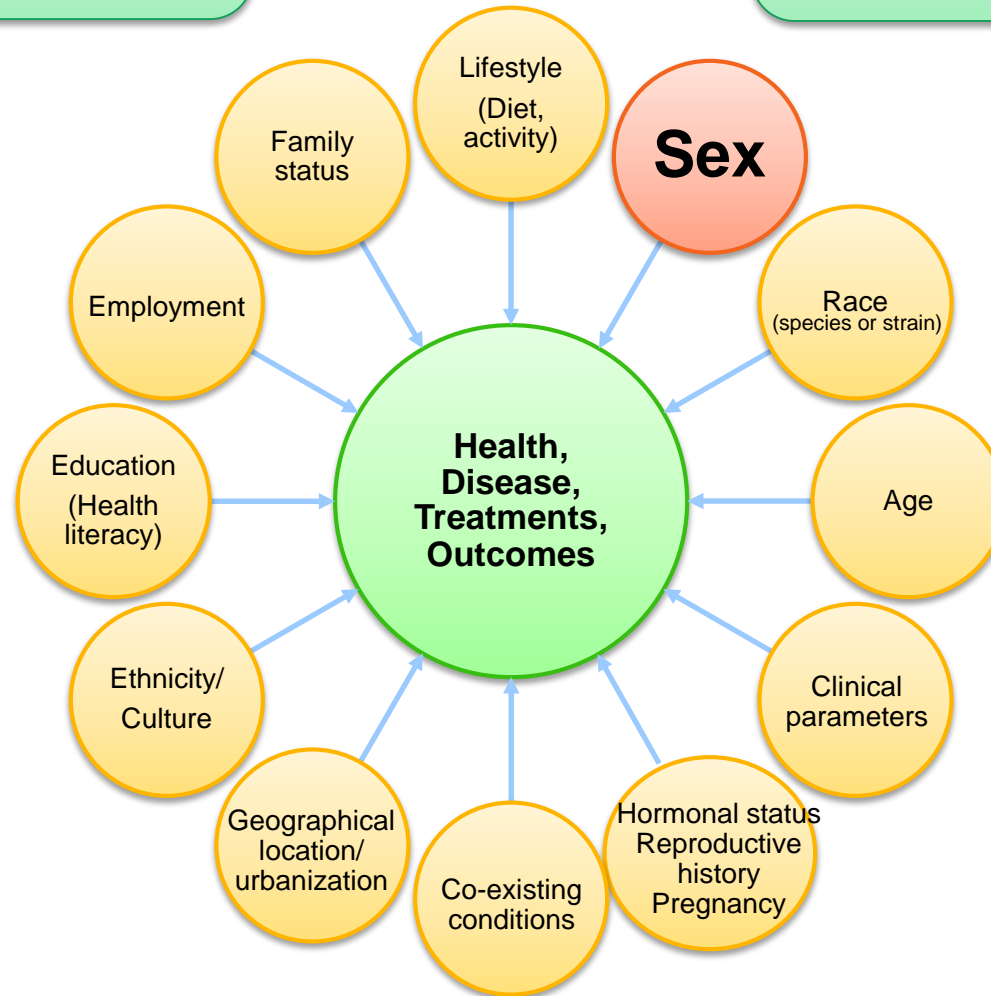
Filtered data set  
(4,164 differentially  
expressed genes)



Gender  
influences  
(extrinsic)



Biological  
influences  
(intrinsic)



# Critical Information

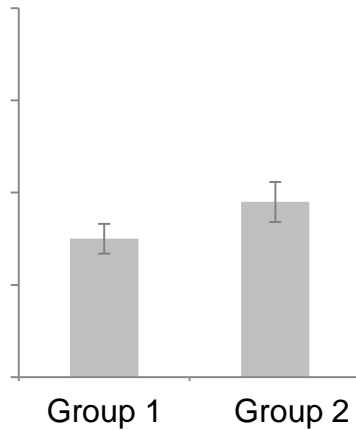
## Basic science variables

- Species/strain
- Sex
- Age
- Reproductive status
- Caging (culture media)
- Temperature
- Food
- Light cycle



# Why Visualization Matters for Sex Differences

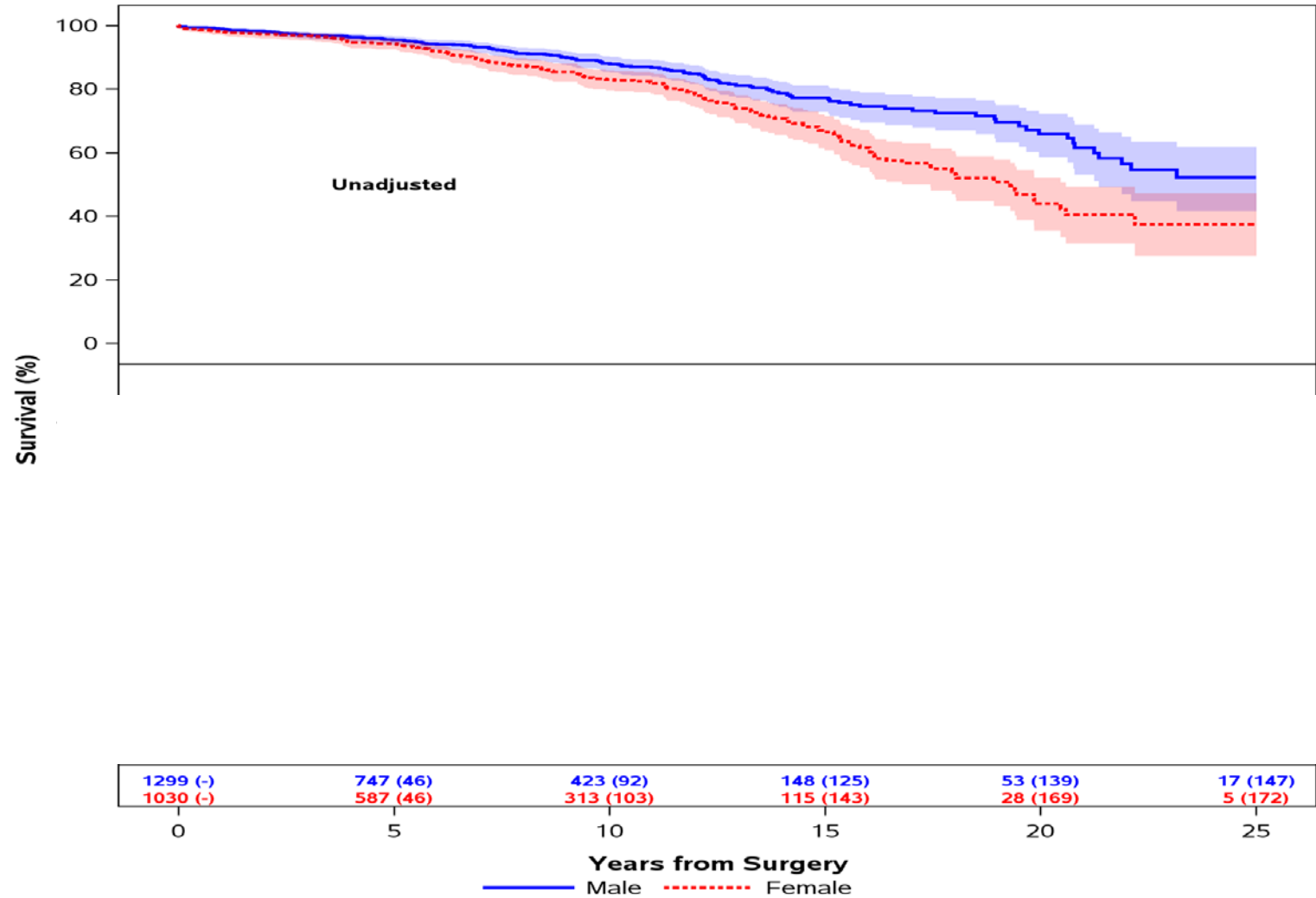
**Bar graph**  
mean  $\pm$  SE,  
males &  
females pooled



# Survival Differences in Men and Women with Obstructive Hypertrophic Cardiomyopathy After Septal Myectomy

Variable	Men (n=1,381)	Women (n=1,127)	P-value
Age (years)	52±13.8	56±15.1	<.001
BMI (kg/m <sup>2</sup> )	30.6±5.4	30.2±6.9	0.006
Hypertension	653 (47.3%)	586 (52%)	0.02
Family history of HCM/SCD	307 (22.3%)	296 (26.4%)	0.016
NYHA Class	2.9±0.5	3±0.5	<.001
LVOT gradient (resting)	54.6±36.6	69.3±41.3	<.001
anteroseptal wall thickness (mm)	20.9±5.2	19.9±4.8	<.001
Posterior wall thickness (mm)	14.0±4.3	13.0±3	<.001
RVSP (mmHg)	35.7±12.3	40.7±17.2	<.001

# Survival



## Recommendation for Reporting Demographic Data for Human Studies

Biological Sex	Ethnicity	Age (by decade of life)					
<b>Female</b>	American Indian or Alaska Native						
	Asian						
	Black or African American						
	Hispanic or Latino						
	Native Hawaiian or Other Pacific Islander						
	White						
<b>Male</b>	American Indian or Alaska Native						
	Asian						
	Black or African American						
	Hispanic or Latino						
	Native Hawaiian or Other Pacific Islander						
	White						
<b>Transgender (m/f) (f/m)</b>	American Indian or Alaska Native						
	Asian						
	Black or African American						
	Hispanic or Latino						
	Native Hawaiian or Other Pacific Islander						
	White						
<b>Decline to report</b>	American Indian or Alaska Native						
	Asian						
	Black or African American						
	Hispanic or Latino						
	Native Hawaiian or Other Pacific Islander						
	White						

# Why is it critical to account for biological sex in all analyses of drug effects?

Sex is the basic biological variable that differentiates physiological and pharmacological processes.

**Mandated by law**  
**H.R.2101 - Research for All Act of 2015**