

SESSION II: The Impact of Sex and Hormones on Regenerative Medicine

Monica M Laronda, PhD

Assistant Professor,
Dept. of Pediatrics, Div. of Endocrinology; Dept. of Obstetrics and Gynecology

Director of Research,
Fertility & Hormone Preservation & Restoration Program



Definitions

SEX = biology

chromosomes

hormones

anatomy

GENDER = individuals

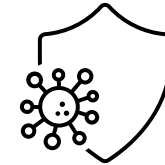
*socially constructed roles, behaviors
different across societies and can
change over time*

not defined by one for another

Sex Differences

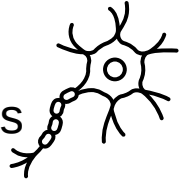
- There are **known differences** between male and female biology:

- Fight disease [immune cell differences in response to influenza]
- Experience pain [International Association for the Study of Pain 2024 report]
- Cardiovascular health [leading cause of death in women in US, CDC]



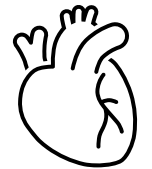
- Still at a **deficit in understanding** because of:

- Historic systemic (and continued) lack of female (and trans and intersex) individuals in clinical trials
- Historic systemic (and continued) lack of female cells and animals used in foundational research
- Lack of consideration for hormonal environment



- **Consequences** include:

- Delayed diagnoses or misdiagnosed
- Adverse effects from treatments
- Limited access to treatments



Biology is not Binary

1:2000 – 1:4500

Clinically DSD / intersex

Chromosomes

XY XXY XYY XXX Xo XX

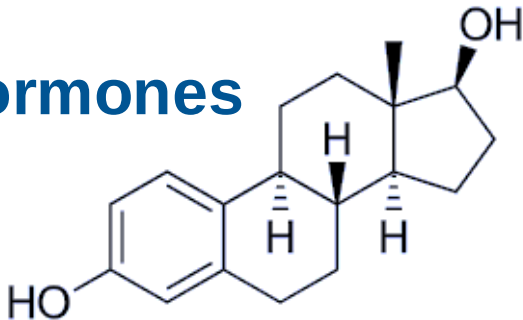


Anatomy



PMID: 7671849

Hormones



Lifespan



2016: Sex as a Biological Variable

NIH funded basic and preclinical research is subject to this SABV policy:

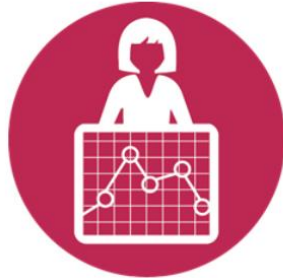
The 4 Cs of Studying Sex to Strengthen Science



Consider

Design studies that take sex into account, or explain why it isn't incorporated

orwh.od.nih.gov



Collect

Tabulate sex-based data



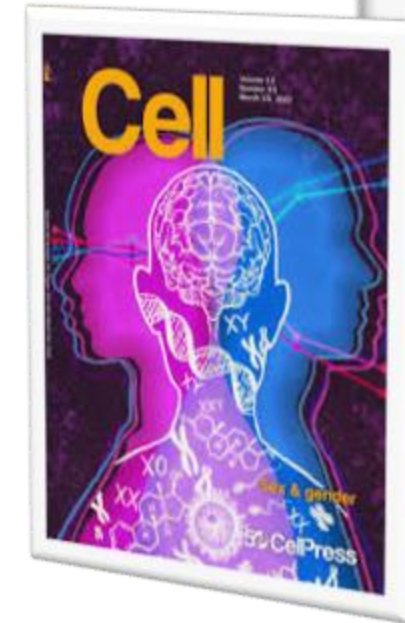
Characterize

Analyze sex-based data



Communicate

Report and publish sex-based data



Based on NIH Inclusion of Women and Minorities policy (NIH Revitalization Act of 1993) which is used for clinical research

SARS-CoV-2 Vaccine Example



2001

Vaccine Trials
5/2020 - 10/2020



5/2021

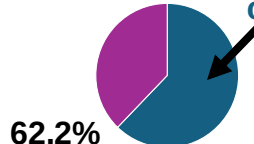
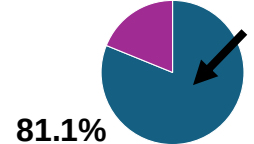
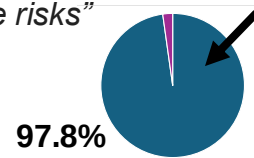


11/2022



2024

"pregnant and lactating humans should be granted the autonomy to consent for participation in a clinical trial when the anticipated benefits outweigh the risks"

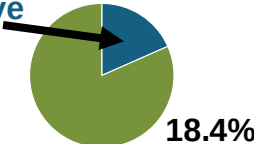
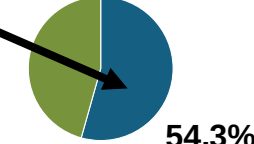
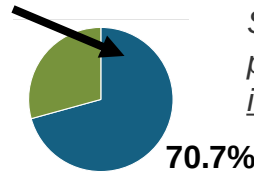


Vaccine trials (90)

Excluded pregnant indiv.

Excluded lactating indiv.

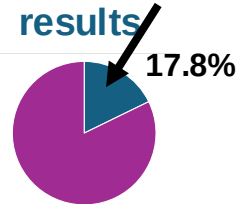
Required contraceptive use



Treatment trials (495)

"...while pregnant patients puzzle over whether they should get vaccinated, evidence is mounting that they have a higher risk of COVID-19 complications and death than people who aren't pregnant. Some studies also suggest that among pregnant patients with COVID-19, disease severity may increase the risk of preterm delivery."

Reported sex-disaggregated results



12/2020

"the spread of anecdotes about menstrual irregularities caused by vaccination amongst individuals has the potential to spread and exacerbate vaccine hesitancy."

NBC NEWS

Covid vaccine trials didn't monitor menstrual

SHARE & SAVE



CORONAVIRUS

Covid vaccine trials didn't monitor menstrual changes. Researchers say it's part of a bigger problem.

Collecting data about menstruation could have prevented confusion and distress and assuaged misguided fears about Covid vaccines, they said.

SARS-CoV-2 Vaccine Example

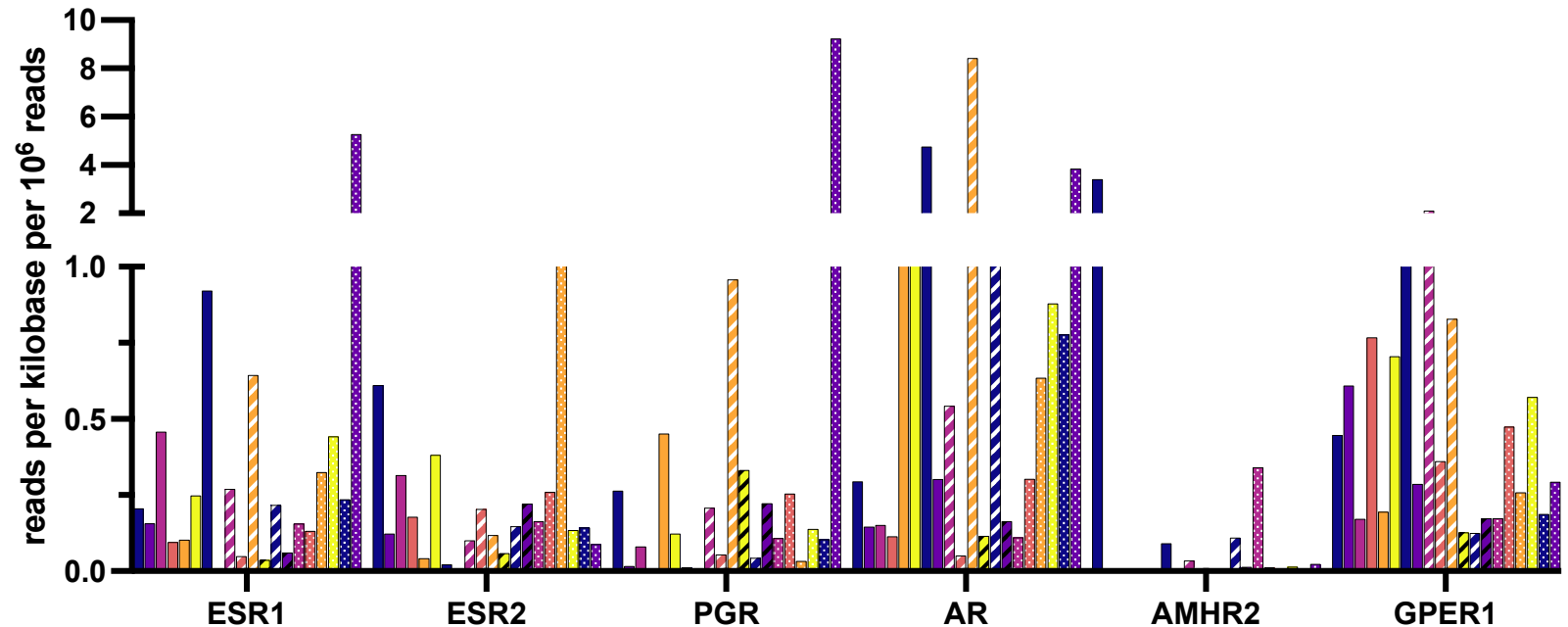
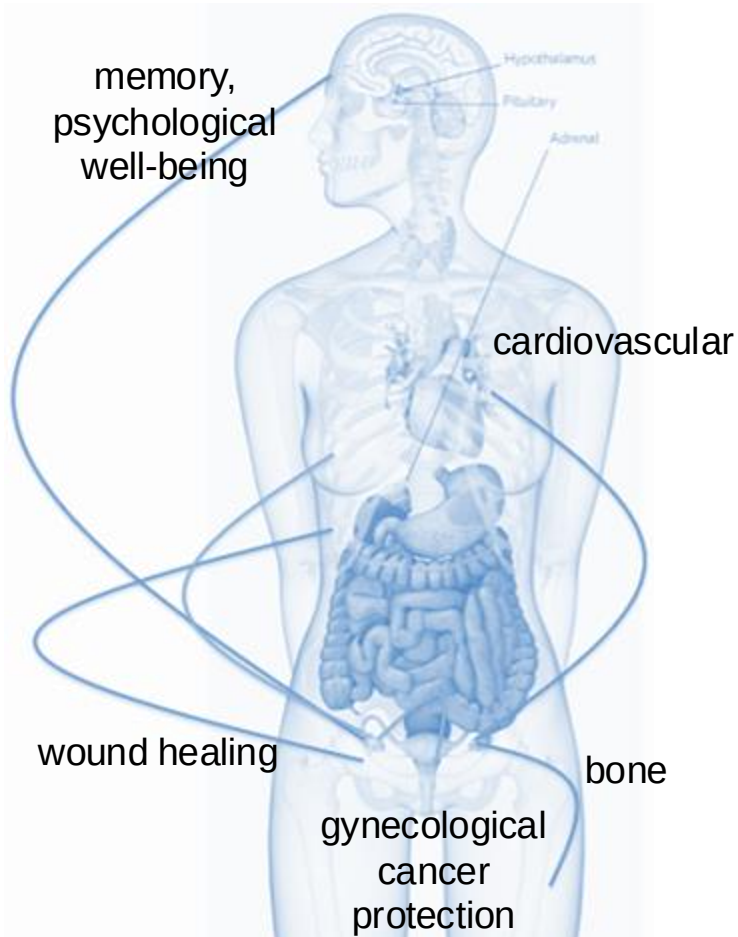
- Regulations are still not followed:
 - pregnant and lactating women **should be granted autonomy** were **excluded** from participating.
 - Sex as a biological variable was **rarely** considered or reported
- Lessons learned?
 - past information would indicate that **menstrual cycles should be tracked** where appropriate (other vaccines known to have an effect)
 - **vacuum** where reliable information was lacking was **filled by anecdotal evidence**, increased distrust and vaccine hesitation

= broad case for sex-based reporting (across lifespan)

Do hormones play a role in understanding sex differences?



Hormones have Systemic Effects on the Body

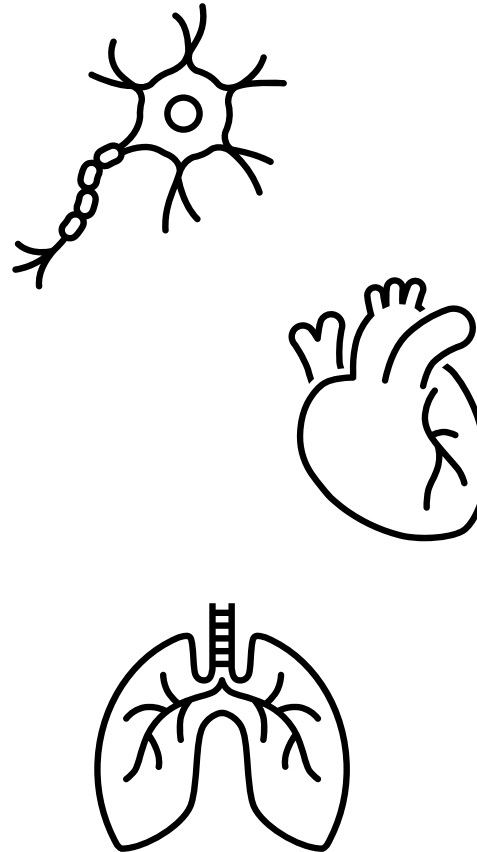


Without hormones (POI) life expectancy is reduced by 2 years from co-morbidities

Description: RNA sequencing of total RNA from 20 human tissues
 BioProject: PRJNA280600
 Publication: PMID 25970244
 Analysis date: Mon Apr 2 15:22:22 2018

Deeper Understanding of Biology and Disease

- *Should not be* seen as burden or multiplier of variables that reduces power
- *Should be* **funded** to support investigations of SABV or repeat previous studies with **understudied conditions**
- SABV = **scientific rigor**:
 - Expanded investigations
 - Inclusive of biological variations
 - Precise descriptions of experimental design
 - Considers developmental timeline



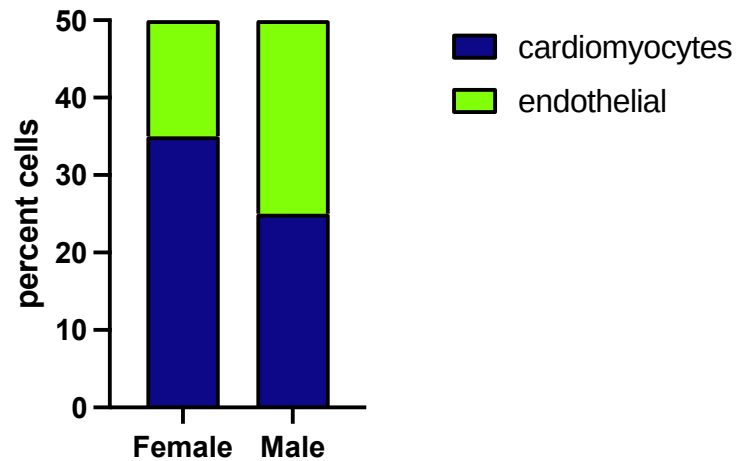
**Diseases
Highlighted Today
*Sex Differences in:***

*Onset
Presentation
Pathology
Treatment?*

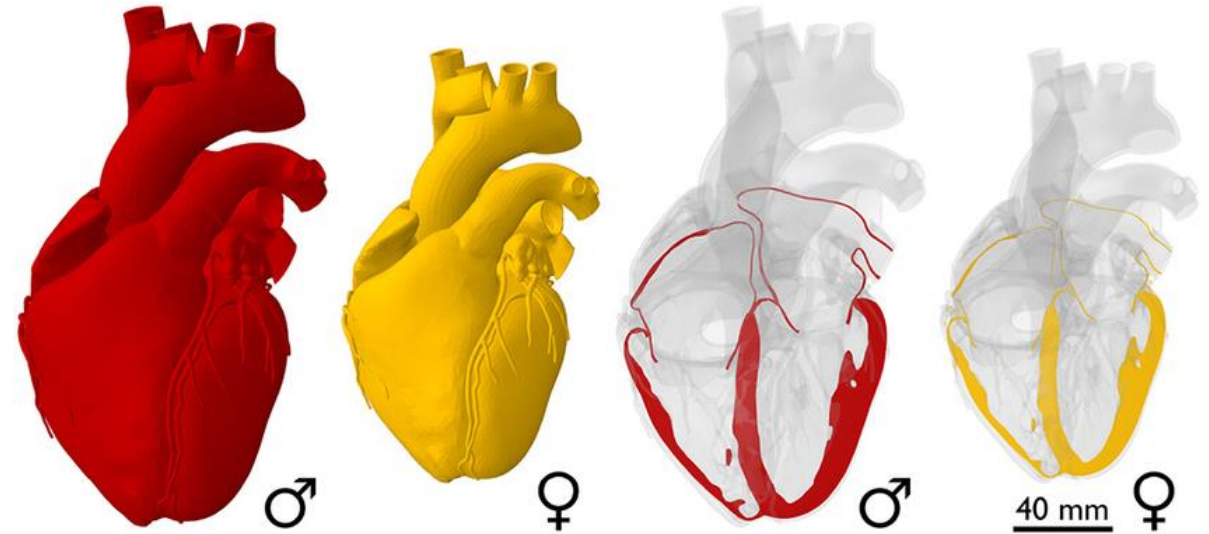
→ Regenerative Medicine

- Do our **models represent patients** we intend to help?
- Were our **therapies developed** accounting for sex differences?

- *Right cell type?*
 - *Right size?*
- *Behave appropriately in right hormonal milieu?*



Sex Differences in Healthy Heart Size



Front. Physiol., 21 March 2022
Sec. Computational Physiology and Medicine
Volume 13 - 2022 | <https://doi.org/10.3389/fphys.2022.831179>

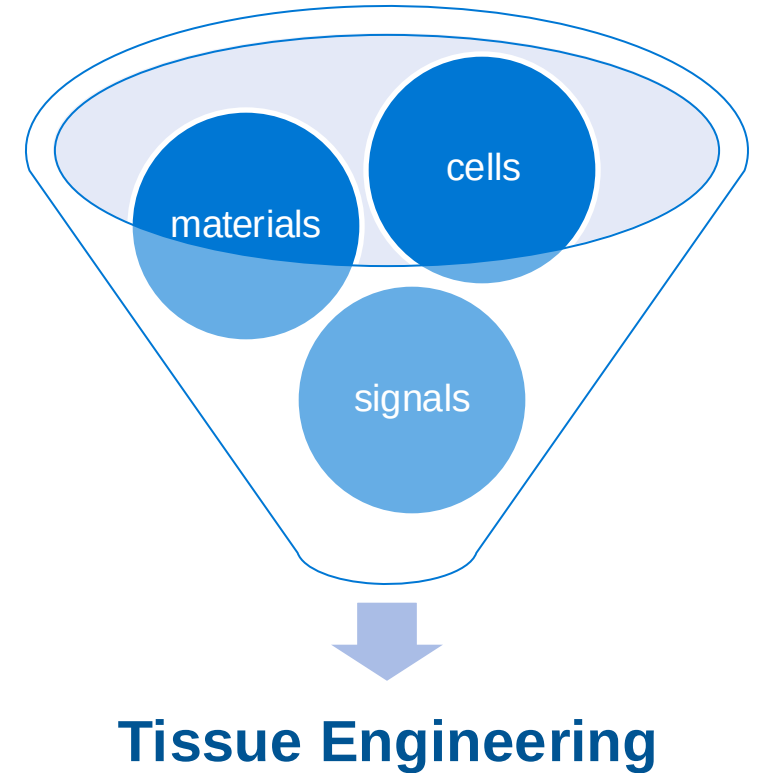
Strengths and Limitations of Model Organisms

- When it is **appropriate** for molecular mechanism, initial discoveries
- Need for **flexibility** in right model organism for the right question
 - Examples of ovary studies
 - Mechanism of follicle growth and meiosis progression – mouse
 - Ovary compartmentalization and physical properties – cow
 - Extracellular matrix components – cow, pig
 - Oophorectomy and transplant procedures in adolescent – mini-pig
- **Gaps:** primordial follicle activation, aging, egg quality, representation of developmental time-line (infancy, puberty, pregnancy, menopause)

**Have human
references**

Challenges to Studying Human Tissues

- Lack of
 - **access** to non-diseased fresh human tissues (esp. across developmental, reproductive, age timelines)
 - **off the shelf platforms** that support functional human tissues (reproductive endo)
- Call for funding “physiomimetic” tissue engineering platforms for human tissues
- ... in presence of hormones



Bring back to why?

Deeper Understanding of Biology and Disease

- Positive impact on female and non-binary health – as groups that have been **historically** and **currently** neglected in research
- **Regenerative medicine** discovered and tested under **inclusive** and **precise** designs would increase likelihood of positive **impact for all**

Women's
Health
Access
Matters®

The WHAM Report shows that funding women's health research has huge economic impacts. **Investing \$350 million generates \$14 billion to our economy.**

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