



June 24, 2024



**Barcelona  
Supercomputing  
Center**  
*Centro Nacional de Supercomputación*



EXCELENCIA  
SEVERO  
OCHOA

# Introduction to the complexity of biological sex

Davide Cirillo

Machine Learning for Biomedical Research

Life Sciences Department

# BSC and Bioinfo4Women



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# Barcelona Supercomputing Center

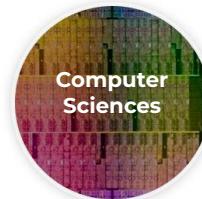


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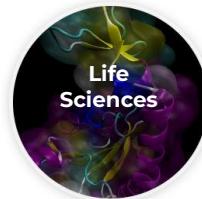


GOBIERNO  
DE ESPAÑA  
 MINISTERIO  
DE ECONOMÍA  
Y COMPETITIVIDAD  
Generalitat de Catalunya  
**Departament d'Economia  
i Coneixement**

 UNIVERSITAT POLITÈCNICA  
DE CATALUNYA  
BARCELONATECH



Computer  
Sciences



Life  
Sciences



Earth  
Sciences



Engineering  
Applications  
(CASE)

# The MareNostrum 5 supercomputer



- Ranked in the **top 20** global supercomputers with a peak of **314 petaflops**.
- Europe's largest scientific infrastructure in Spain, funded at **€202 million**.
- 45.4 petaflop CPU and a 260 petaflop GPU partition with **4,480 NVIDIA Hopper** processors.
- Features **650 petabytes of storage** and an InfiniBand NDR200 network connecting **over 8,000 nodes**.
- Access granted via competitive calls and peer review (see <https://eurohpc-ju.europa.eu/>)

# The Bioinfo4Women initiative at BSC



## Internationalization and networking

- Promote an international collaboration network of women in computational biology
- Research seminars at BSC (remote) including reflection of experiences of women in science
- Participation/organization of events
- B4W Fellows programme

## Research line

- Include the sex and gender perspective in the Life Science department research practice by:
  - Develop guidelines for researchers, providing specific examples of how to implement it within each research group
  - Create a repository (papers, datasets, etc) with scientific evidence regarding this topic

## Communication

- Dissemination of seminars and conferences organised by B4W but also external events of relevance, relevant publications, and inspiring stories that foster changes in the gender and diversity imbalance in research
- Outreach to the research community and beyond

## Strategy, organization and financial engagement

- Strategic decisions aligned with the BSC Life Sciences Department and other European efforts
- Financial aspects of the programme and sustainability strategy
- Implement actions approved

## Support women's scientific career

### Training plan

- Gender dimension in research incorporated into PhD training programme at BSC
- Review BSC soft skills training courses from gender-sensitive standpoint
- Job description writing from non-biased perspective

### Mentoring programme

- Pilot B4W Mentoring programme in 2022 - provide international role models to junior researchers
- Build international network of Bioinfo4Women-related mentors and mentees

# The Bioinfo4Women initiative at BSC

npj | Digital Medicine

[www.nature.com/npjdigitalmed](http://www.nature.com/npjdigitalmed)

REVIEW ARTICLE OPEN

## Sex and gender differences and biases in artificial intelligence for biomedicine and healthcare

Davide Cirillo  <sup>1,10</sup>, Silvina Catuara-Solarz <sup>2,3,10</sup>, Czuee Morey <sup>3,4</sup>, Emre Guney  <sup>5</sup>, Laia Subirats  <sup>6,7</sup>, Simona Mellino <sup>3</sup>, Annalisa Gigante <sup>3</sup>, Alfonso Valencia <sup>1,8</sup>, María José Rementería <sup>1</sup>, Antonella Santuccione Chadha <sup>3</sup> and Nikolaos Mavridis <sup>3,9</sup>

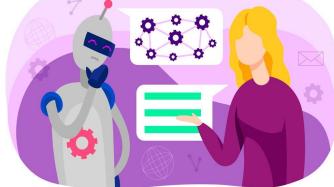
Precision Medicine implies a deep understanding of inter-individual differences in health and disease that are due to genetic and environmental factors. To acquire such understanding there is a need for the implementation of different types of technologies based on artificial intelligence (AI) that enable the identification of biomedically relevant patterns, facilitating progress towards individually tailored preventative and therapeutic interventions. Despite the significant scientific advances achieved so far, most of the currently used biomedical AI technologies do not account for bias detection. Furthermore, the design of the majority of algorithms ignore the sex and gender dimension and its contribution to health and disease differences among individuals. Failure in accounting for these differences will generate sub-optimal results and produce mistakes as well as discriminatory outcomes. In this review we examine the current sex and gender gaps in a subset of biomedical technologies used in relation to Precision Medicine. In addition, we provide recommendations to optimize their utilization to improve the global health and disease landscape and decrease inequalities.

npj Digital Medicine (2020)3:81; <https://doi.org/10.1038/s41746-020-0288-5>

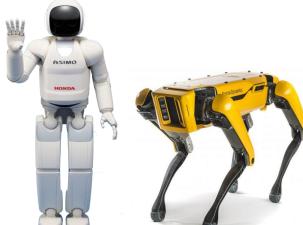
### Big Data Analytics



### NLP



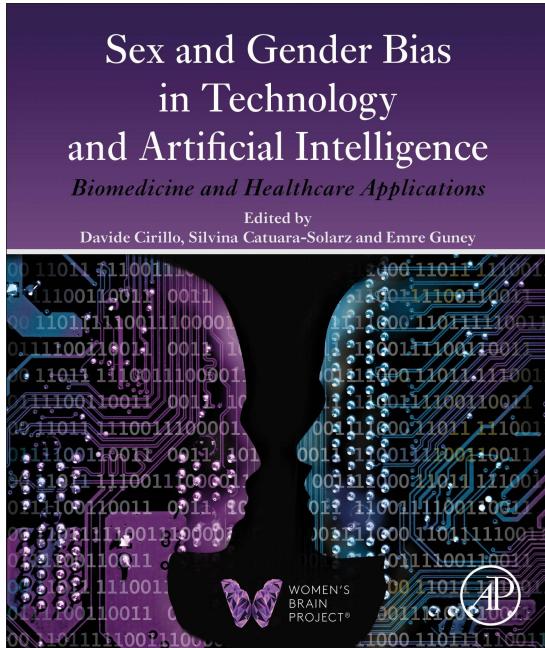
### Robotics



### Digital medicine



# The Bioinfo4Women initiative at BSC



ISBN: 9780128213926

*"It's a must read for anyone working in this area; the materials presented here should be integrated into medical school curricula."*

## Londa Schiebinger

John L. Hinds Professor of History of Science, Stanford University  
Founding director, Gendered Innovations in Science, Health & Medicine, Engineering, and Environment



RESEARCH  
PROGRAMME  
ON BIOMEDICAL  
INFORMATICS





# Auditing the quality of datasets used in algorithmic decision-making systems

## STUDY

Panel for the Future of Science and Technology

EPRS | European Parliamentary Research Service  
EN Scientific Foresight Unit (STOA)

EPMA Journal (2022) 13:299–313  
<https://doi.org/10.1007/s13167-022-00284-3>

RESEARCH



Digital biomarkers and sex impacts in Alzheimer's disease management — potential utility for innovative 3P medicine approach

Robbert L. Harms<sup>1</sup> · Alberto Ferrari<sup>2</sup>  · Irene B. Meier<sup>3</sup> · Julie Martinkova<sup>2,4</sup> · Enrico Santus<sup>2,5</sup> · Nicola Marino<sup>2,6</sup> · Davide Cirillo<sup>2,7</sup> · Simona Mellino<sup>2</sup> · Silvana Cattura Solarz<sup>2</sup> · Ioannis Tarnanas<sup>1,8</sup> · Cassandra Szoek<sup>2,9</sup> · Jakub Hort<sup>4,10</sup> · Alfonso Valencia<sup>7,11</sup> · Maria Teresa Ferretti<sup>2</sup> · Azizi Seixas<sup>12</sup> · Antonella Santuccione Chadha<sup>2</sup>

Received: 15 February 2022 / Accepted: 10 May 2022 / Published online: 6 June 2022  
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ACM DL DIGITAL LIBRARY

WEBCSI ▾

## Abortion and Miscarriage on Twitter: Sentiment and Polarity Analysis from a gendered perspective

Authors:  Olivier Philippe,  María Flores Rodero,  
 Claire Yohalem Furtick,  Laura Planas Simón,  
 María Teresa Ferretti,  Antonella Santuccione Chadha,  
 Laia Subirats Maté,  Davide Cirillo,  María José Rementeria  
[\(Less\)](#) [Authors Info & Claims](#)

WEBCSI '24: Proceedings of the 16th ACM Web Science Conference • May 2024 • Pages 311–319 • <https://doi.org/10.1145/3614419.3644010>



Addressing sex bias in biological databases worldwide

Victoria Ruiz-Serra<sup>1,2</sup>, Nataly Buslón<sup>1,3,4,\*</sup>, Olivier R Philippe<sup>1</sup>, Diego Saby<sup>2</sup>, María Morales<sup>1</sup>, Camila Pontes<sup>1</sup>, Alejandro Muñoz Andirkó<sup>2</sup>, Gemma L. Holiday<sup>4</sup>, Aina Jené<sup>5</sup>, Mauricio Moldes<sup>5</sup>, Jordi Rambla<sup>5</sup>, Alfonso Valencia<sup>1,6</sup>, María José Rementeria<sup>1</sup>, Átia Cortés<sup>1,2,7</sup>, and Davide Cirillo<sup>1,2,8,\*</sup>

Journal Women's Health

TYPE Brief Research Report  
PUBLISHED: 06 September 2023  
DOI: [10.3897/tjwh.2023.970312](https://doi.org/10.3897/tjwh.2023.970312)

Spain 3 DevCenter,  
Centre for Genomic  
Studies Avanzados

g. human genomic

Js. In this context,  
ince they have the  
s at the individual

## Raising awareness of sex and gender bias in artificial intelligence and health

Nataly Buslón<sup>1,2\*</sup>, Átia Cortés<sup>1</sup>, Sil Davide Cirillo<sup>1</sup> and María José R Ufie Sciences Department, Barcelona Supercomputing Center, Guntershausen, Switzerland

Historically, biomedical research has been introduction of Artificial Intelligence (AI) to be discriminatory for other sexes and move towards a fair AI development, diversity both in research practices and promotes the participation of women fosters international collaborations between advances research on sex and gender discuss methodology and results of



## EOSC-Life Handbook

Integration of the sex and gender dimension in life sciences research





## Gender representation in ELIXIR articles

We aim to evaluate gender representation in bibliographic data of ELIXIR publications retrieved from academic search engines, including **Google Scholar** and **BIP! Finder**, to examine gender and visibility biases.



Google Scholar



BIP! Finder



JOIN OUR TEAM  
AT #BioHackEU24!!  
Project #6

{B}{H}

4 November - 8 November 2024  
Barcelona

# Sex



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Center**  
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# Activity time!

What comes to  
mind first when  
you think of sex?

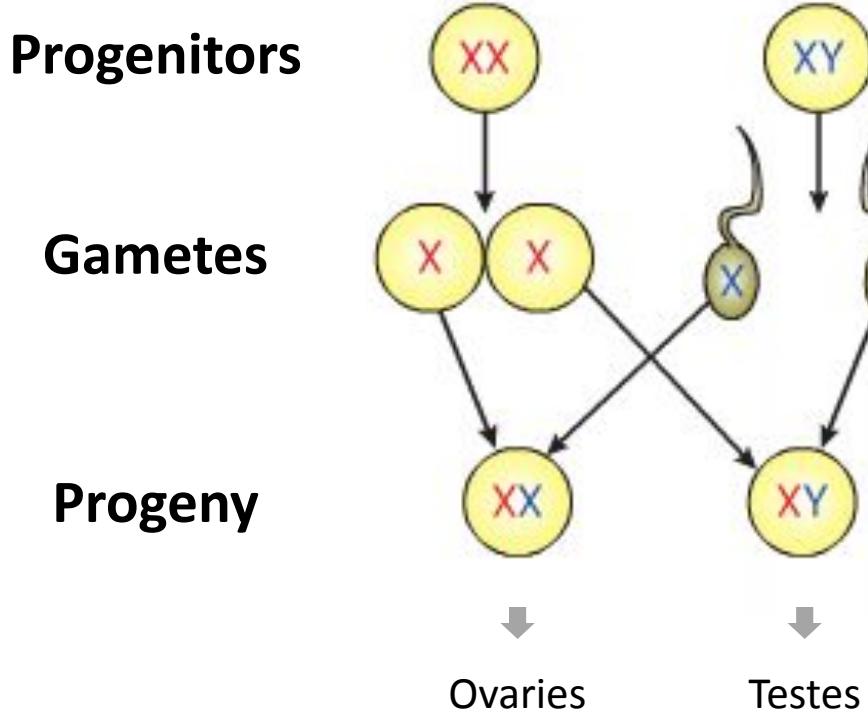
# Sex

Sex refers to a set of **biological attributes** in humans and animals. It is primarily associated with physical and physiological features including **chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy**. Sex is usually categorised as female or male but **there is variation in the biological attributes** that comprise sex and how those attributes are expressed.

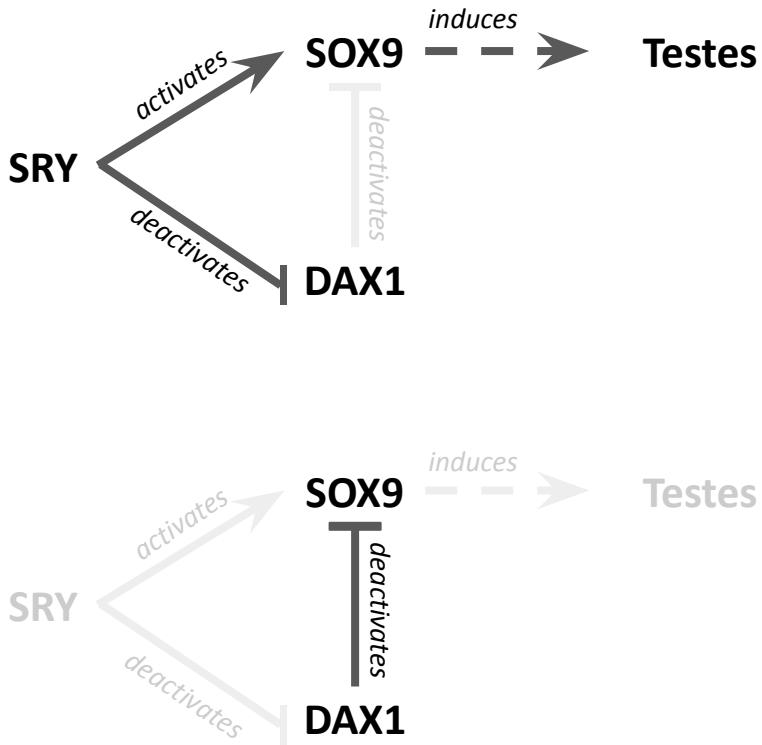
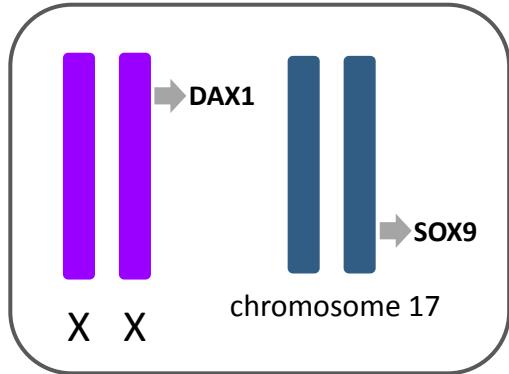
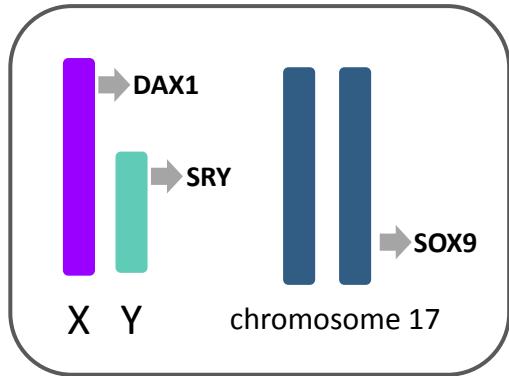
*CIHR Institute of Gender & Health. What Is Gender? What Is Sex? 2020.*

Available online: <https://cihr-irsc.gc.ca/e/48642.html>

Is sex binary?

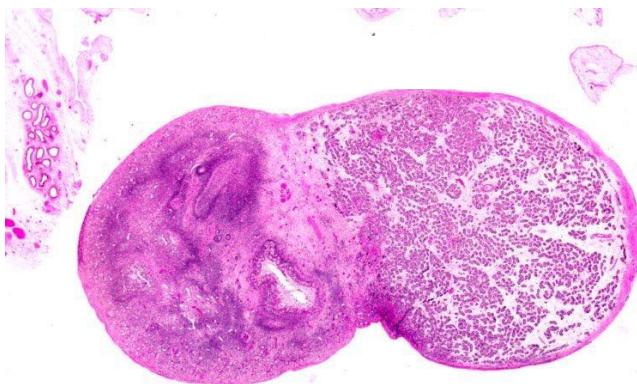


# Is sex binary?



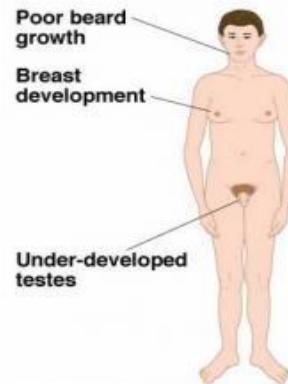
# Is sex binary?

Ovotesticular disorder of sexual development ("true hermaphroditism")



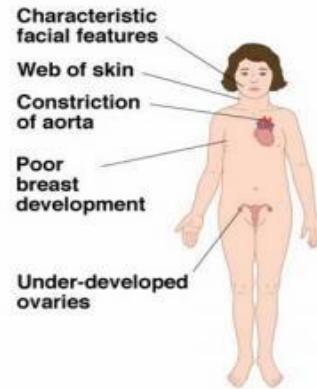
Approximate incidence of less than 1 in 20,000

## Klinefelter syndrome

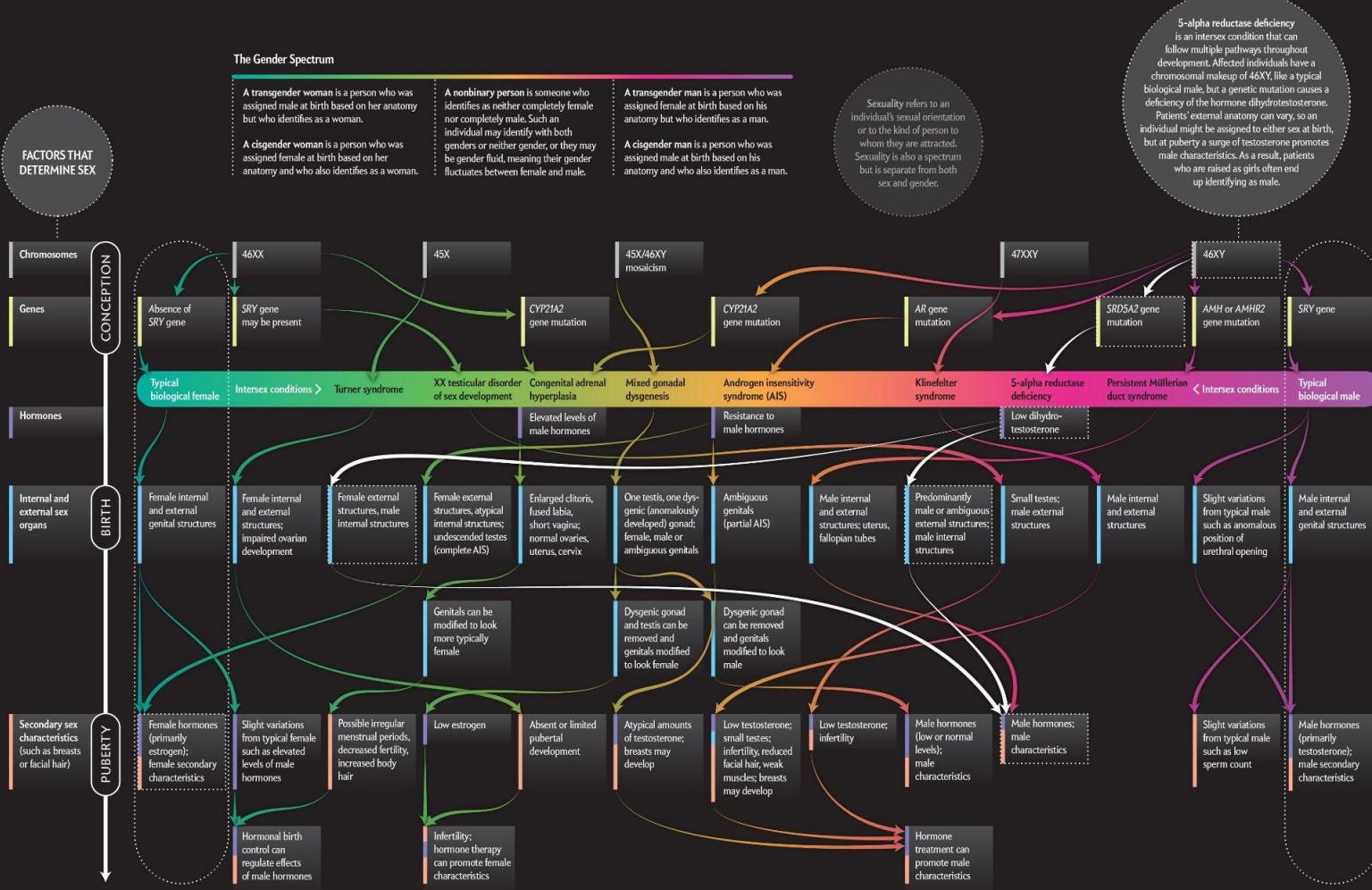


One in 500 to 1000 male births (0.1 to 0.2%)

## Turner syndrome



One in 2500 female births (0.04%)



*Let's have a closer look*

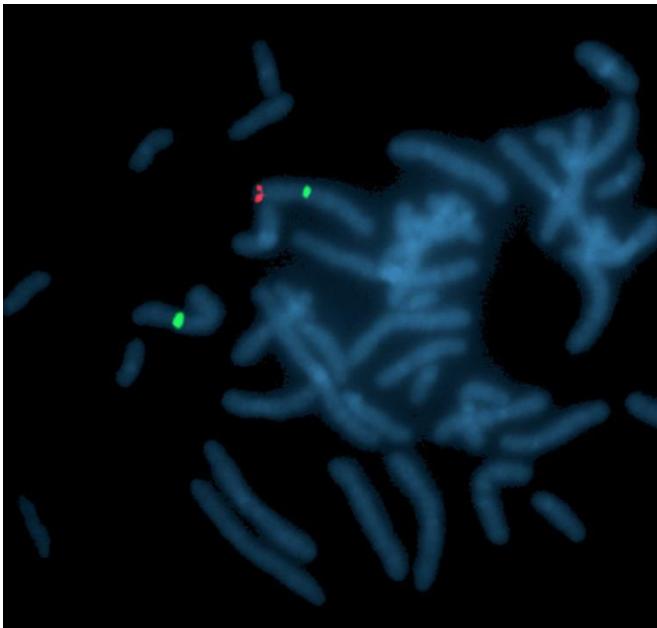


<https://bit.ly/3RAkQa0>

# Activity time!

# Can you play geneticist?

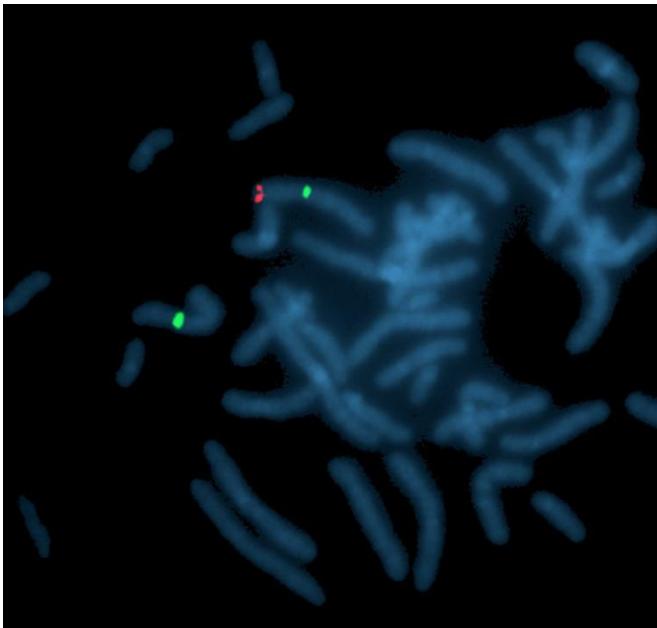
## *SRY-positive XX male*



FISH showing *SRY* gene locus (red) translocated on the short arm of chromosome X (centromeres in green), from Adrião et al. *Clin Pediatr Endocrinol*. 2020.

- **SRY gene initiates male sex determination. What do you expect in a 46,XX male?**
  - small testes
  - gynecomastia
- **Testosterone is key in the growth hormone axis. What do you expect in a 46,XX male?**
  - high height and weight
  - small height and weight
- **X inactivation balances gene dosage. What do you expect in a 46,XX male?**
  - the mutated X is preferentially activated
  - the mutated X is preferentially deactivated
- **Y-X translocation happens during the formation of the gametes. What could cause 46,XX male?**
  - A random event during sperm formation in the affected person's father
  - Exposure to environmental toxins during fetal development

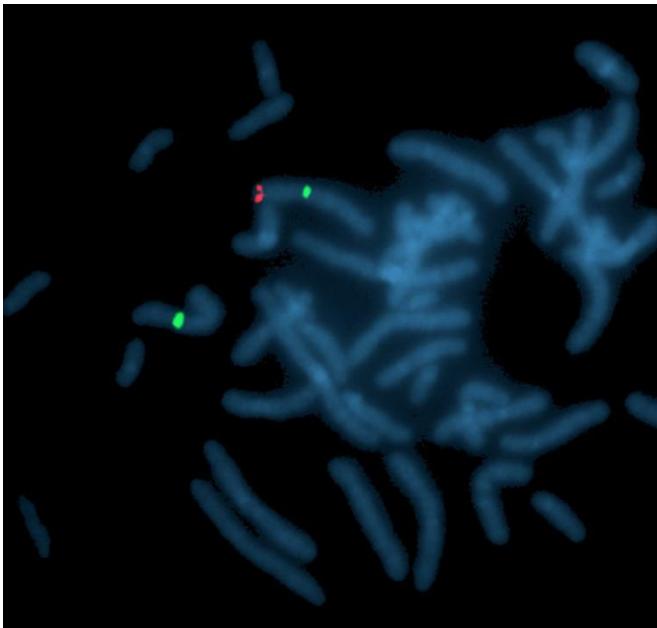
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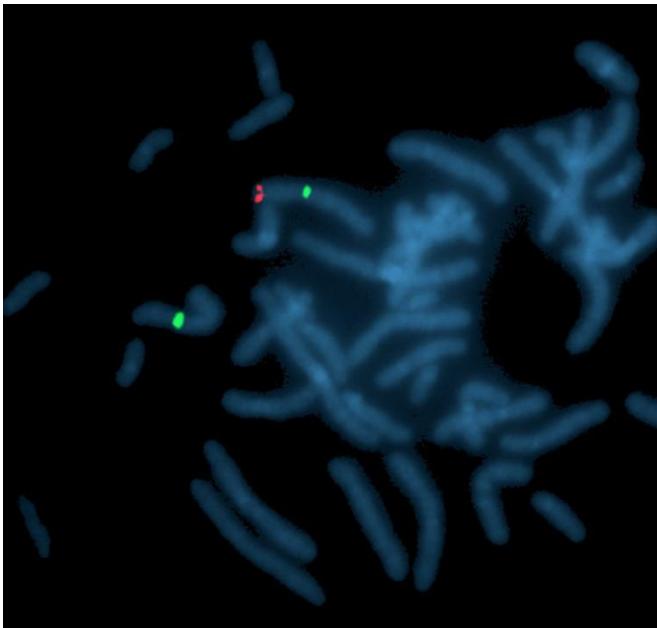
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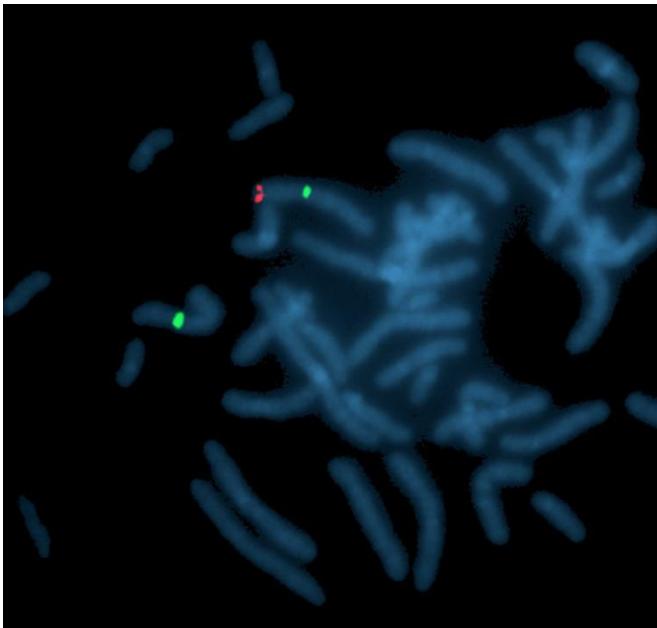
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# Gender



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# Activity time!

What comes to  
mind first when you  
think of gender?

# Gender

Gender refers to the **socially constructed** roles, behaviours, expressions and identities **of girls, women, boys, men, and gender diverse people**. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender identity is **not confined to a binary (girl/woman, boy/man)** nor is it static; it exists along a **continuum** and can **change over time**. There is **considerable diversity** in how individuals and groups understand, experience and express gender through the roles they take on, the expectations placed on them, relations with others and the **complex ways** that gender is **institutionalised** in society.

*CIHR Institute of Gender & Health. What Is Gender? What Is Sex? 2020.*

Available online: <https://cihr-irsc.gc.ca/e/48642.html>

# Gender

Which image represents a **masculine** characteristic,  
and which represents a **feminine** characteristic?



# Gender



Amazons in battle. Greek relief  
(4th century BC. Künsthistorische Museum, Vienna)

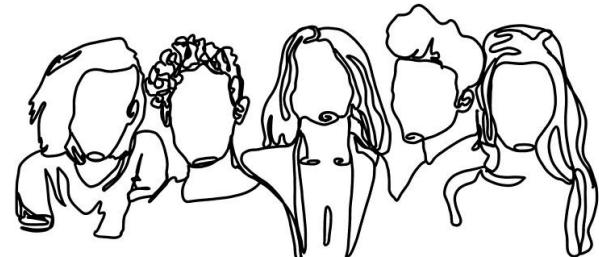


# Gender

- ▶ gender identity (302)
  - ▶ exploring gender identity
  - ▶ female gender identity
  - ▶ male gender identity
  - ▶ no gender identity
  - ▶ nonbinary gender identity (294)
    - ▶ exclusive gender identity (278)
      - ▶ culturally-specific gender identity (274)
      - ▶ intersex-specific gender identity (1)
      - ▶ neurotype-specific gender identity
    - ▶ fluctuating gender identity (2)
    - ▶ indescribable gender identity (1)
    - ▶ multiple gender identity (3)
    - ▶ non-gendered identity (2)
    - ▶ overlapping gender identity (1)
    - ▶ partial gender identity (2)
  - ▶ other gender identity
  - ▶ unknown gender identity (1)

## The Gender, Sex, and Sexual Orientation (GSSO) ontology

<https://www.ebi.ac.uk/ols4/ontologies/gss>



source: Androgyny by With-Love-AKeys

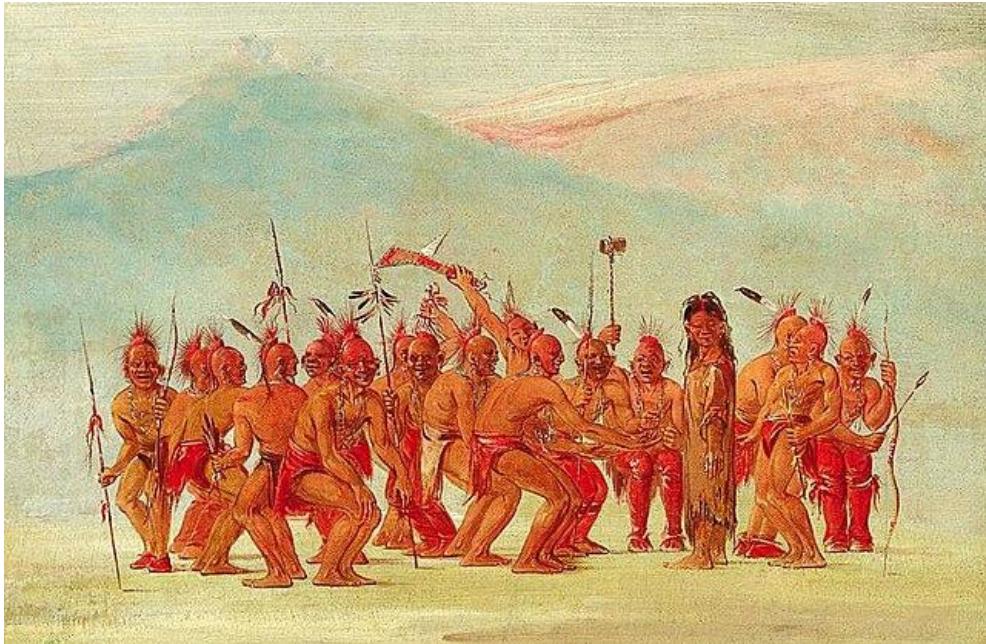
*Let's have a closer look*



<https://bit.ly/3KTZb8H>

# Gender

Two-spirit (Indigenous North Americans)



George Catlin, "*Dance to the Berdache*" (1861-1869)

Muxes (Mexico)



Cover of Vogue Mexico and the muxes  
(Vogue Mexico)

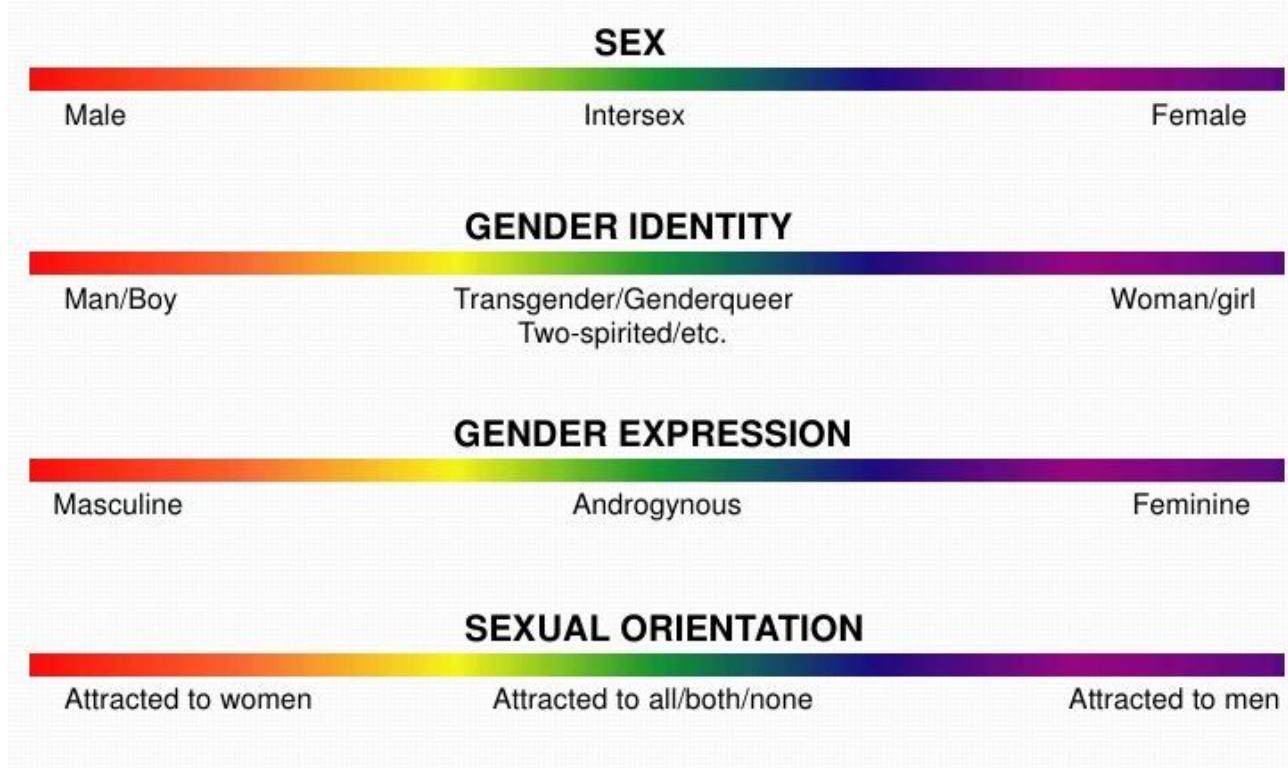
# Gender

## A map of gender-diverse cultures

[https://www.pbs.org/independentlens/content/two-spirits\\_map-html/](https://www.pbs.org/independentlens/content/two-spirits_map-html/)



*It's all on a spectrum*



# Why it matters in science and technology



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Complete this sentence: "The child was not feeling well and the mother called the doctor, but when"



The child was not feeling well and the mother called the doctor, but when the doctor arrived,  
**he** was surprised to find the child already feeling much better.

# The importance of intersectionality



MIT Media Lab researcher  
Joy Buolamwini

# Generative AI bias

<https://www.bloomberg.com/graphics/2023-generative-ai-bias/>



## MACHINE TRANSLATION

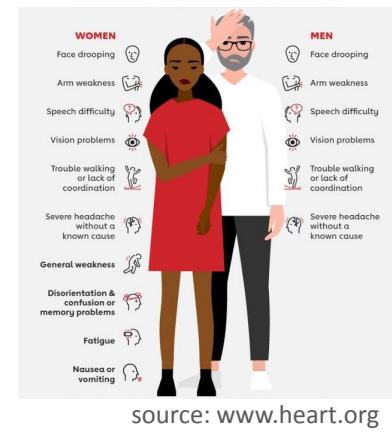
Before

After

Translations are gender-specific. [LEARN MORE](#)

source: <https://blog.google>

## DISEASE DIAGNOSIS



## IMAGE GENERATION



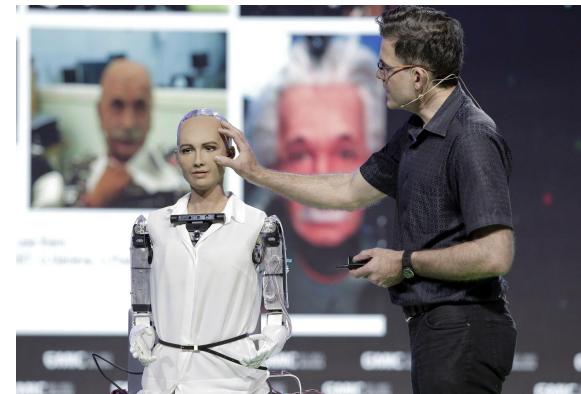
source: <https://theconversation.com>

## AUTOMOBILE ENGINEERING



source: [www.ilmessaggero.it](http://www.ilmessaggero.it)

## ROBOTICS

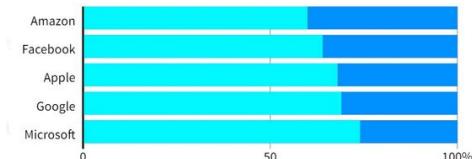


source: <https://www.racked.com>

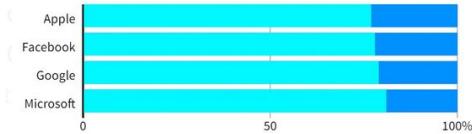
## CURRICULUM SELECTION

### GLOBAL HEADCOUNT

■ Male ■ Female



### EMPLOYEES IN TECHNICAL ROLES



Note: Amazon does not disclose the gender breakdown of its technical workforce.  
Source: Latest data available from the companies, since 2017.

source: <https://medium.datadriveninvestor.com>

$$\text{Bias}(\hat{\theta}, \theta) = E[\hat{\theta} - \theta]$$

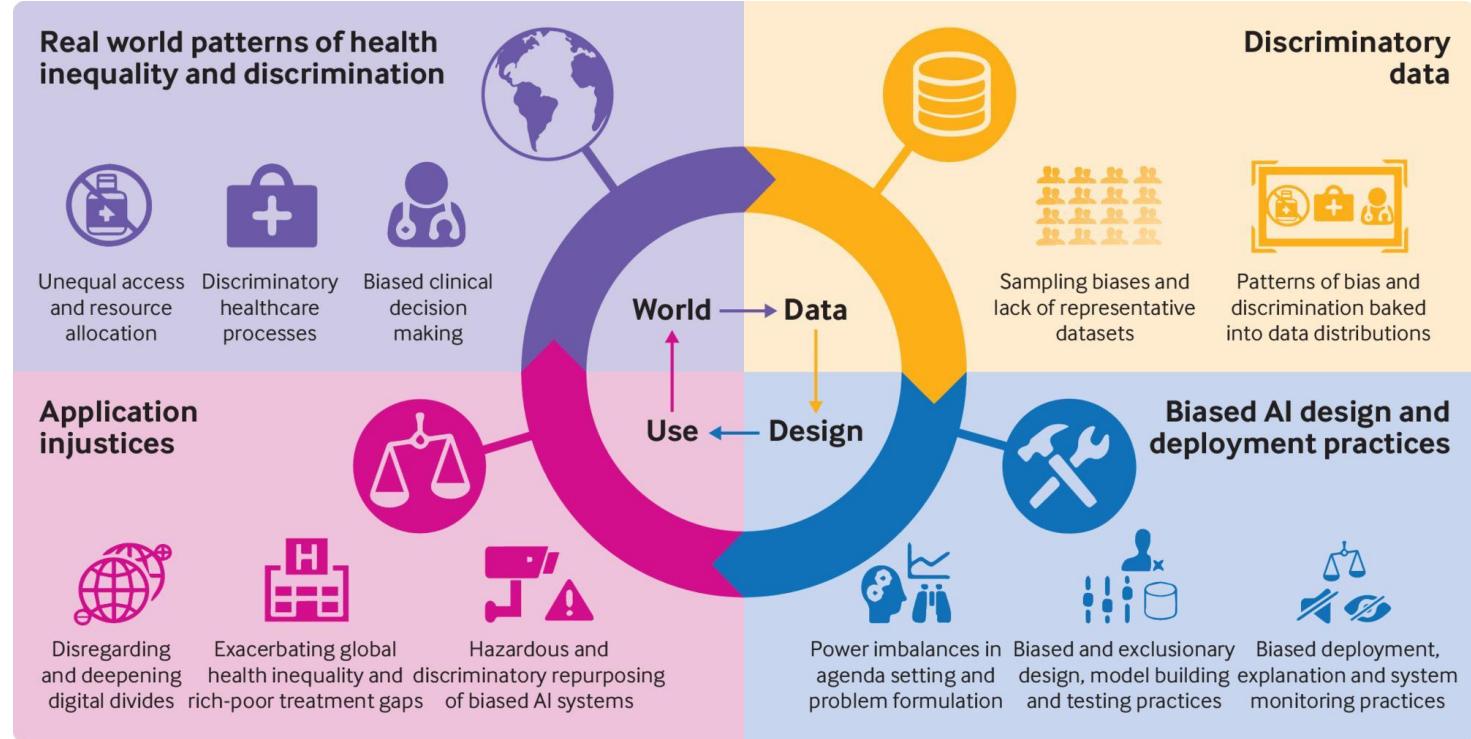
**Bias** in statistics is the **average difference** between the thing you are trying to estimate and your actual estimate.



A **BIAS** is

a **systematic error** made by a human (cognitive bias) or  
a machine (algorithmic bias)

that leads to a **disadvantage** for an individual or a group  
of people identified by **personal attributes** (sex, gender,  
age, race, ethnicity, etc.)



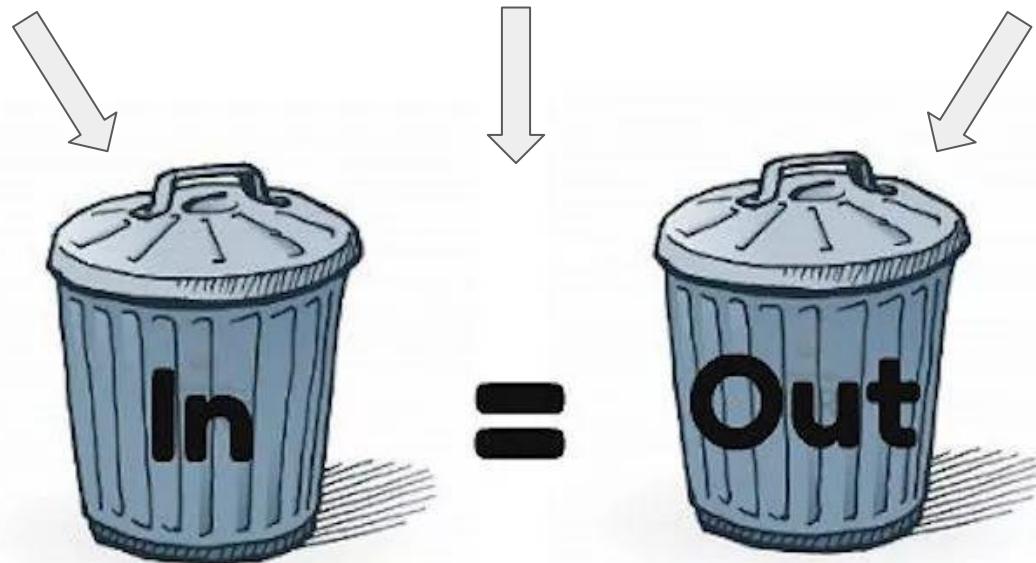
BMJ 2021;372:n304

# "Garbage in, garbage out"

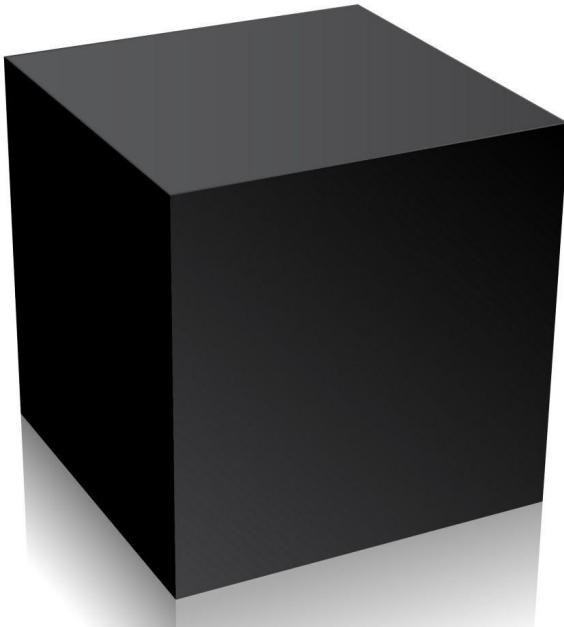
How the data has been generated, collected, processed?

What is the model actually learning?

How will the output be used in the real-world?



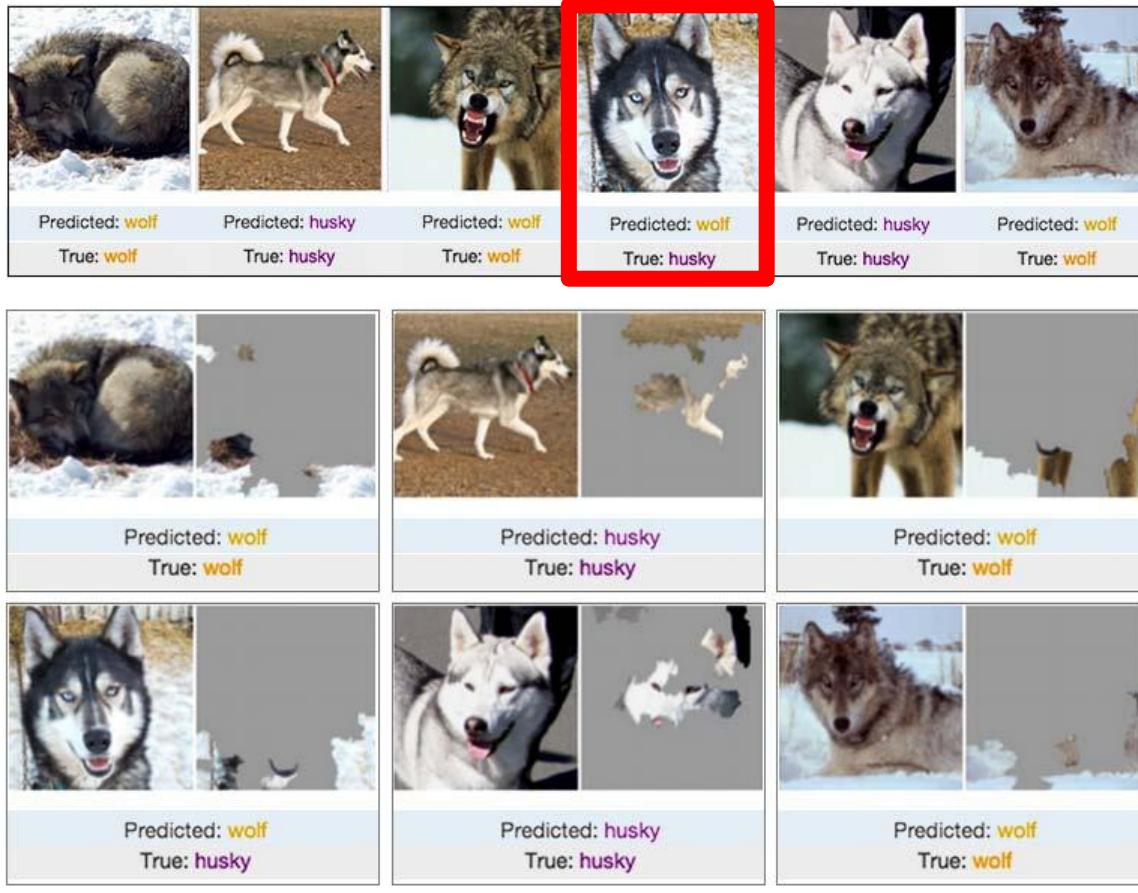
# Black boxes



## **Post-hoc explainability techniques** (model-agnostic or model-specific)

- text explanations
- visual explanations
- local explanations
- explanations by example
- explanations by simplification
- feature relevance explanations

# Why are AI explanations important?



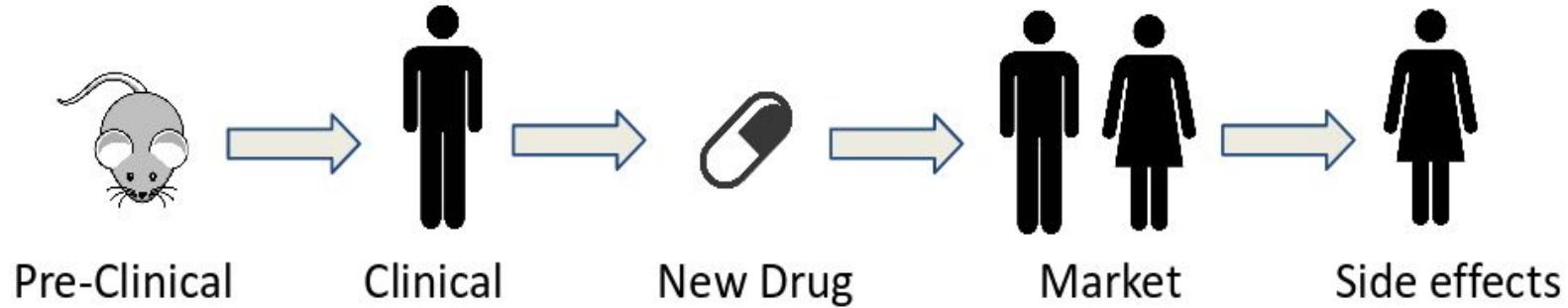
source: Explaining Black-Box  
Machine Learning Predictions  
– Sameer Singh

# Sex and gender bias in experimental data

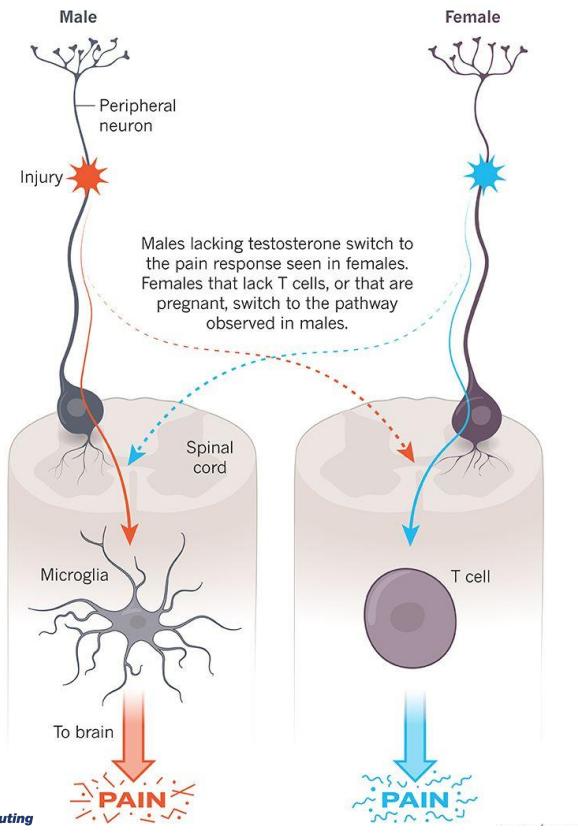


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# Experimental design and bias propagation



## Example: pain mechanisms

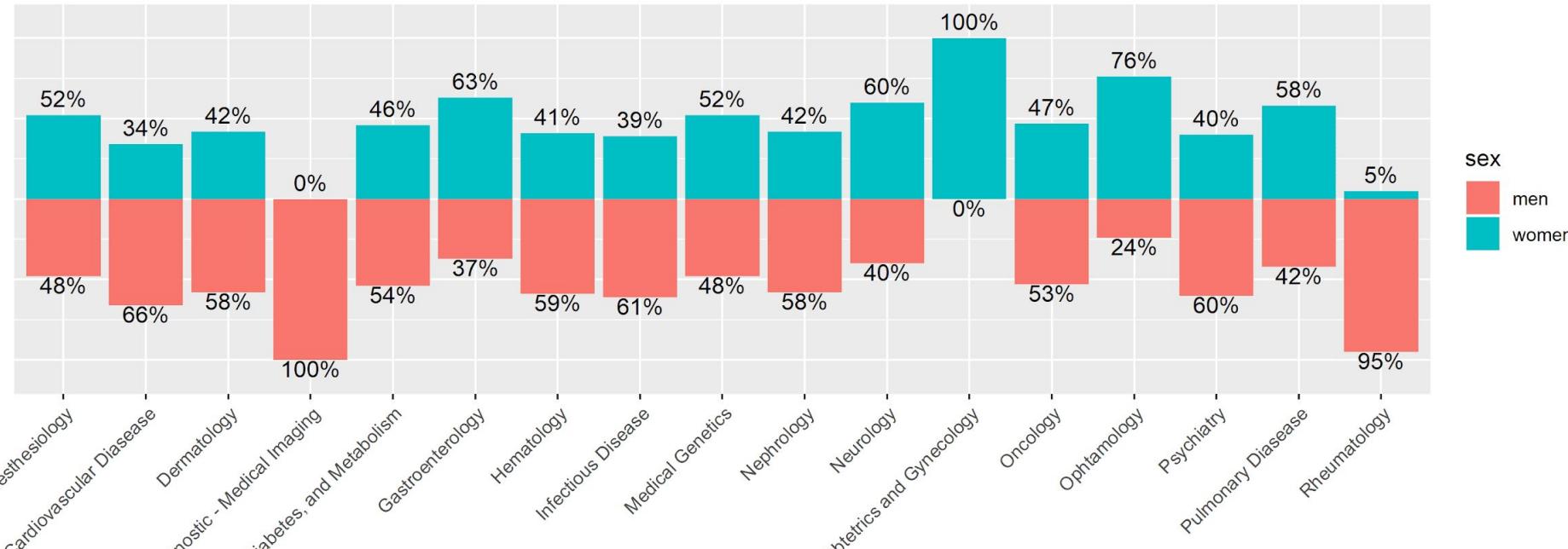


- Different immune cells—microglia in males and T cells in females—mediate **mechanical pain hypersensitivity** in mice.
- Deletion of the gene Arg1 in microglia reduced mechanical pain hypersensitivity in females but not males, indicating a crucial role for ARG1+ microglia in female pain processing.
- These results reveal significant sex differences in immune mechanisms involved in pain processing, emphasizing the **need to include sex as a biological variable in pain studies**, with implications for understanding sex-specific chronic pain conditions.

## Clinical trials participation by therapeutic area

Trials for New Molecular Entities (NMEs) approved in 2015–2016

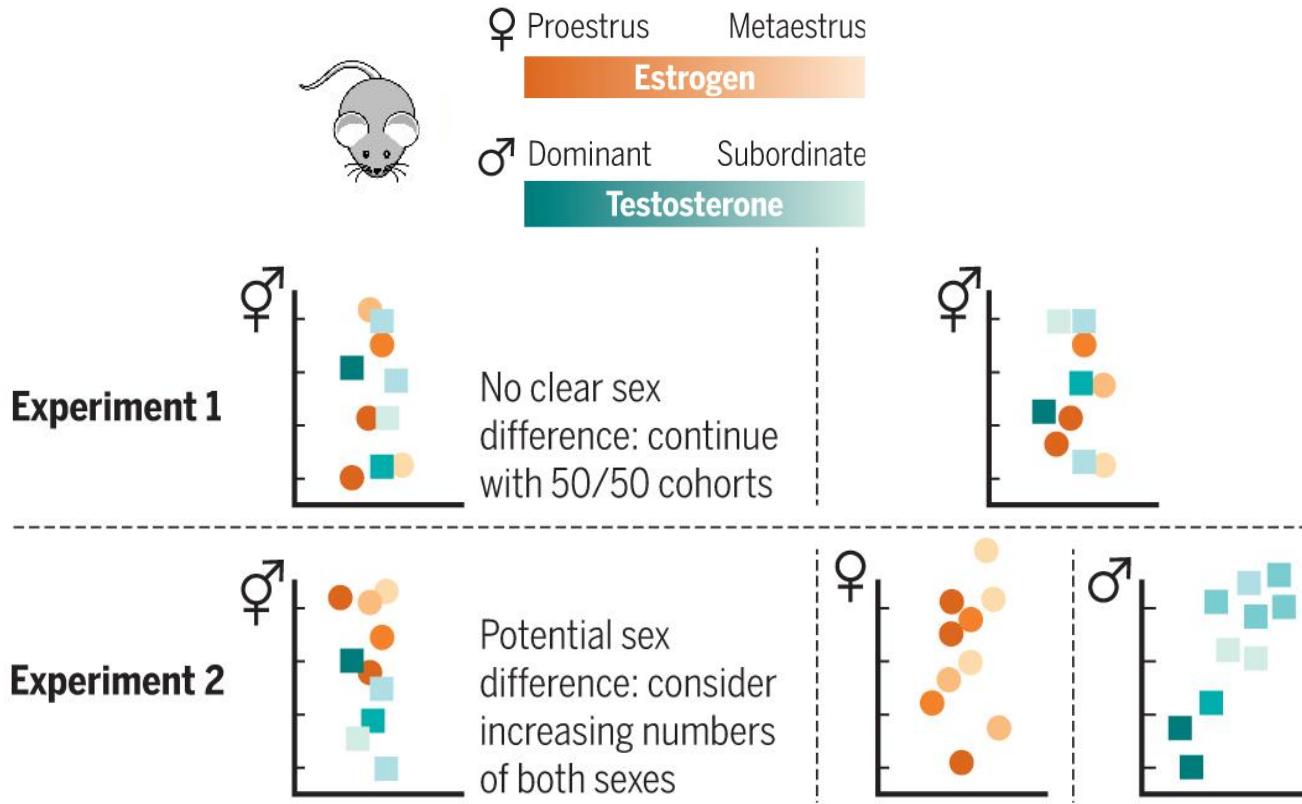
source: FDA & Office of Women's Health (OWH)



**Table 3. Prescription drugs withdrawn from the US market (1997–2000).**

Drug	Type of drug	Patient population	Primary health risk
<b>Prescription drugs with evidence of greater health risks in women</b>			
Pondimin®	Appetite suppressant	Women	Valvular heart disease
Redux®	Appetite suppressant	Women	Valvular heart disease
Rezulin®	Diabetic	Women	Liver failure
Lotronex®	Gastrointestinal	Women	Ischemic colitis
Seldane®	Antihistamine	Women and men	Torsades de Pointes
Posicor®	Cardiovascular	Women and men	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal®	Antihistamine	Women and men	Torsades de Pointes
Propulsid®	Gastrointestinal	Women and men	Torsades de Pointes
<b>Prescription drugs without evidence of greater health risks in women</b>			
Raxar®	Antibiotic	Women and men	Torsades de Pointes
Duract®	Analgesic and anesthetic	Women and men	Liver failure

# General recommendations for experimental design

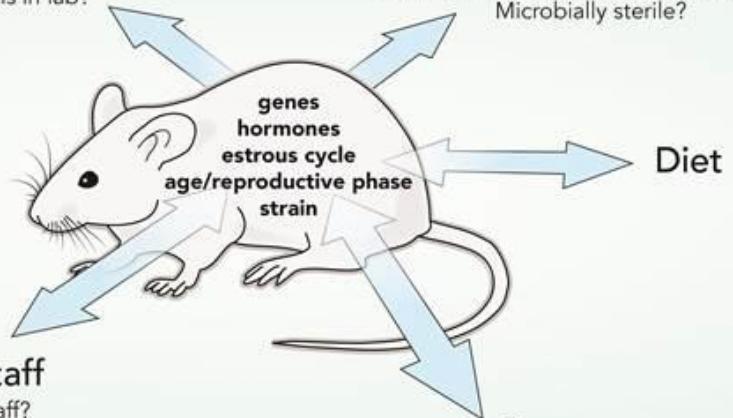


# Interaction between sex, gender and environmental conditions

## Sex and Lab Environment Interact

### Social Dynamics

Sex-segregated or male/female mix?  
Number and mix of animals in lab?



- **Experimenters** can be a confounding variable in rodent research where stress is an important factor.
- Environmental processes, such as caging practices or differential handling, may affect females and males differently.
- **Researchers should not identify an effect as dependent on sex (or a biological trait) when, in fact, it is dependent on an environmental condition.**

# The case studies of Gendered Innovations

# Gendered Innovations

in Science,  
Health & Medicine,  
Engineering, and  
Environment

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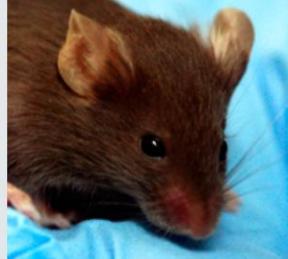
What is Gendered Innovations?

SEX & GENDER ANALYSIS

- General Methods
- Specific Methods
- Terms
- Checklists

CASE STUDIES

- Science
- Health & Medicine
- Engineering
- Environment



## Animal Research: Designing Health & Biomedical Research

ABSTRACT | FULL CASE STUDY

### The Challenge

Most basic research with animal models focuses on males and excludes females (Zucker et al., 2010; Marts et al., 2004). This creates three problems:

1. Less knowledge about disease processes in females due to underutilization of female animals. Results of studies in males are often generalized to females without justification, and even some conditions that occur more often in women are studied in mostly male animals. A gap exists between the proportion of women in patient populations and the proportion of female animals

## Main takeaways

- **Females are underrepresented in most subfields of animal studies**, except reproductive biology and immunology. The sex of the animal is not reported in 22-42% of articles in neuroscience, physiology, and interdisciplinary biology journals, which can lead to wasted research money and inability to include data in meta-analyses.

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- Methodological innovations in rodent research to better account for sex and gender interactions include:
  - **Investigating Sex Differences**: Sex differences must be investigated before they can be ruled out.
  - **Reporting Sex**: The sex of the animal test subjects should be noted in the article and reported in the methods section to ensure reproducibility and avoid over-generalization of findings to the other sex.

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- The NIH, the Canadian Institutes for Health and the European Commission have been implementing **guidelines for considering sex as a variable** in vertebrate animal and human research in recent years
- **Extrapolating outcome data from one sex to another can lead to erroneous conclusions.**

# Activity time!

Can you  
recognize  
the red flags?



source: [www.malagahoy.es](http://www.malagahoy.es)

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**Dr. Smith:** "The means aren't statistically different. Must be the hormones. Sarah, set up the next batch with the same diet."

**John:** "Seems we could've saved money on fewer animals!"

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Neglecting the effect of environmental factors on sex-related variation

## To learn more:

[https://github.com/julien-roux/SIB\\_days\\_2024\\_workshop\\_NEI/blob/main/papers/1-s2.0-S0092867424001740-main.pdf](https://github.com/julien-roux/SIB_days_2024_workshop_NEI/blob/main/papers/1-s2.0-S0092867424001740-main.pdf)



Cell

Leading Edge

### Perspective

## Sex contextualism in laboratory research: Enhancing rigor and precision in the study of sex-related variables

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*QR code for hands-on tutorial instructions*



<https://shorturl.at/LV9i3>



**Barcelona  
Supercomputing  
Center**  
*Centro Nacional de Supercomputación*



EXCELENCIA  
SEVERO  
OCHOA

# Thanks!

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