Sex and gender in biomedical research: concepts and examples

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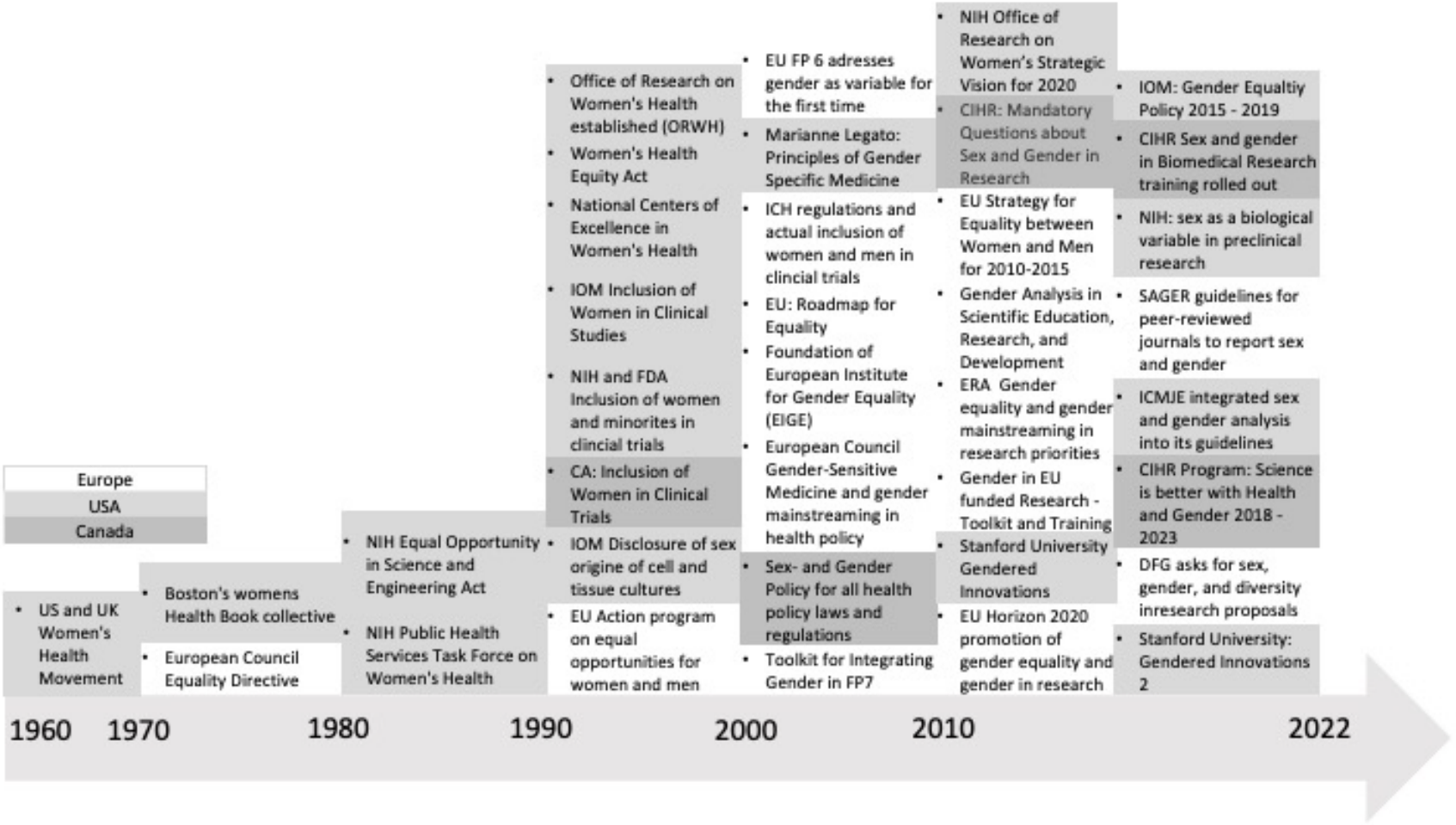
Sex and gender in research

- **What is the gender dimension**
- **Sex-specific analysis in research and innovation**
- **Gender-specific analysis in research and innovation**
- **Examples**
- **Connection between content and context**

Historical path to sex- and gender sensitive research



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Becher and Oertelt-Prigione, *Int Rev Neurobiol*, 2020

Why do we need the gender dimension?

H 2020/Europe: "…**improve the scientific quality and societal relevance** of the produced knowledge, technology and/or innovation"

IGH : „...**improving the rigor, reproducibility and generalizability** of science. It's about excellence…"

NIH : "….**enhance reproducibility through rigor and transparency** and increase the knowledge base…."

- **Reproducibility**
- **Excellence**
- **Societal value**

II. OBJECTIVES

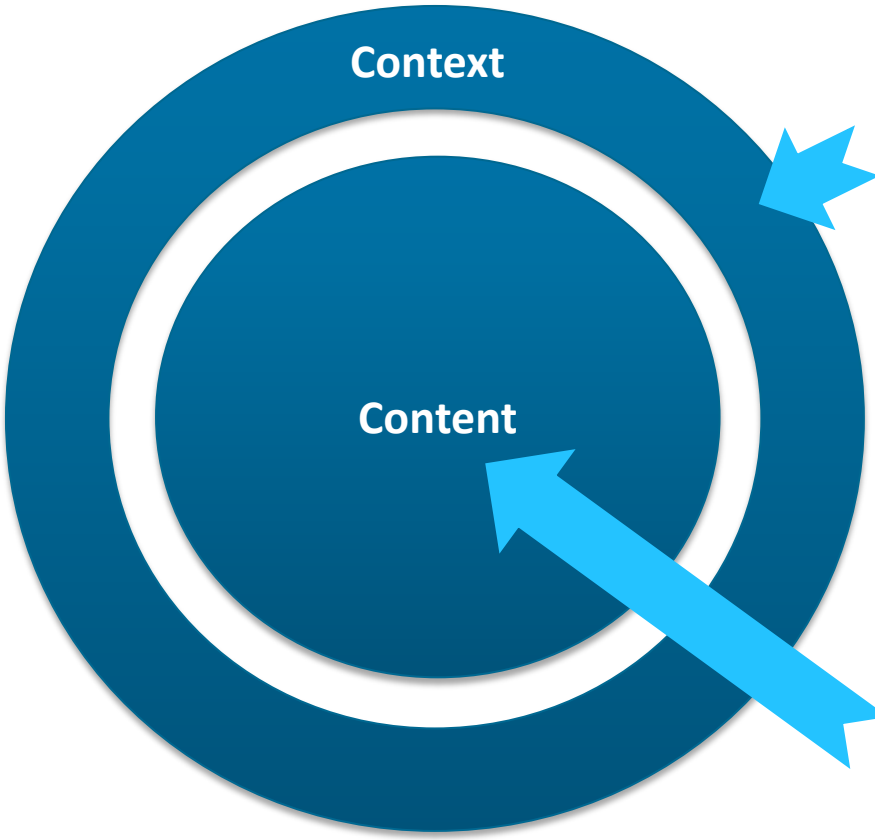
Three objectives underpin the Commission's activities on gender equality in Horizon 2020. They are in line with the RTD strategy on gender as well as with the ones set in the ERA Communication of July 2012:

- *Fostering gender balance in Horizon 2020 research teams,* in order to address the gaps in the participation of women in the Framework Programme's projects
- *Ensuring gender balance in decision-making,* in order to reach the Commission's target of 40% of the under-represented sex in panels and groups (50% for advisory Groups)
- *Integrating gender/sex analysis in research and innovation (R&I) content,* helps improve the scientific quality and societal relevance of the produced knowledge, technology and/or innovation.

These objectives are part of the Commission provisions for the implementation of Horizon 2020 and are integrated at each stage of the Research and Innovation cycle.

About sex and gender in healthcare

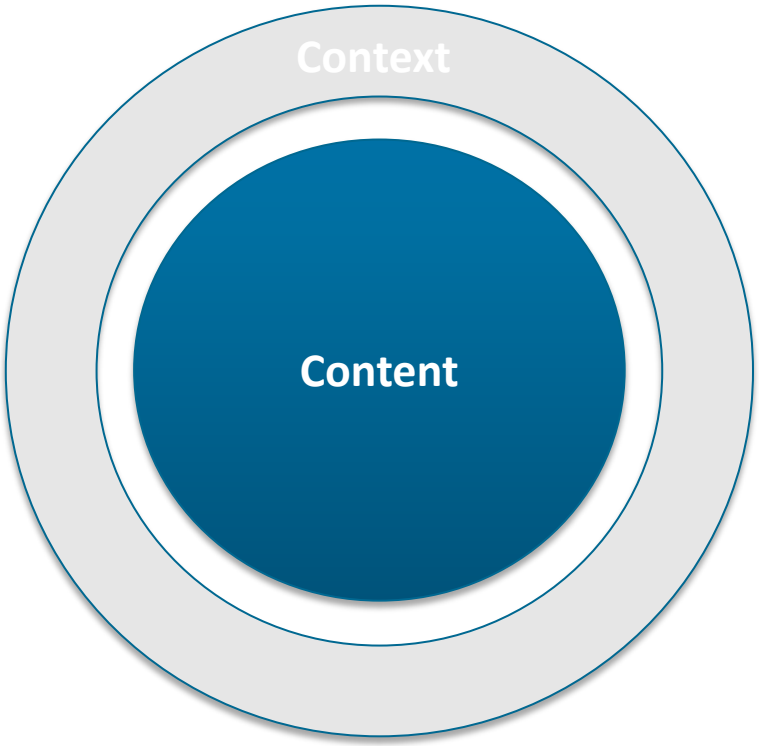
Content and context



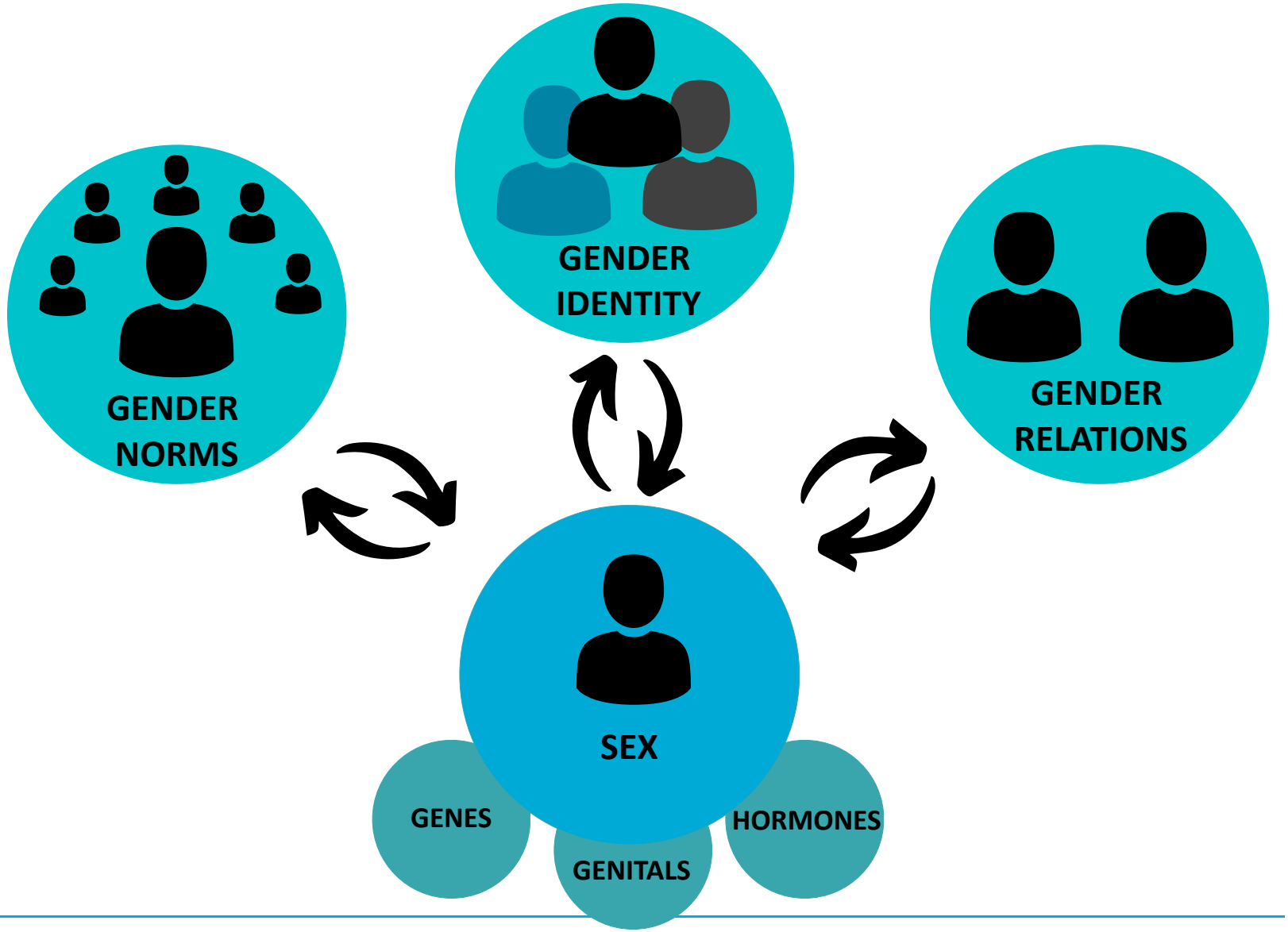
- Gender balance in research teams
- Gender balance in decision making

- Gender and sex analysis in research and innovation

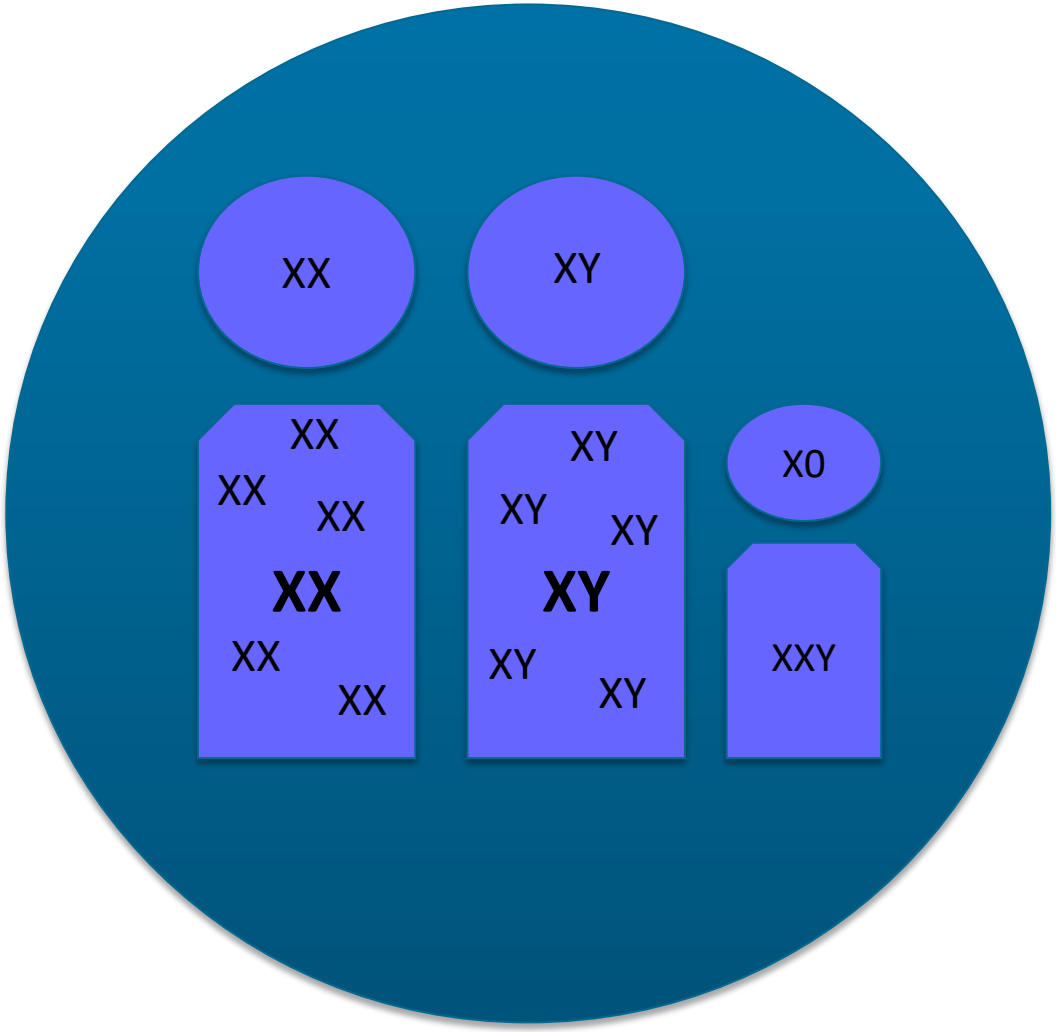
Gender and sex analysis in research and innovation



Sex and gender - terminology



Every cell has a sex

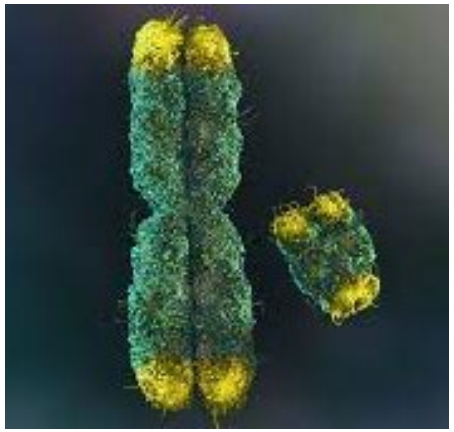


Operationalization of sex

Three levels (3Gs) have been used to define sex:

- **Genetics**
- **Hormones (Gonads)**
- **Genitalia**

Operationalization of sex - genetics



XX – 48-49% (assumptions based on the incidence of non XX/XY)
XY – 48-49% (assumptions based on the incidence of non XX/XY)

But:
X0, XXY, XXXY etc. – 0.04% (Turner), 0.1% (Klinefelter)
Age-related monosomy in peripheral cells

- **Assumption in most (bio)medical research is dichotomy XX (female) – XY (male)**

Fausto-Sterling, Sexing the Body, 2000

Operationalization of sex – hormones (gonads)

Which hormones?

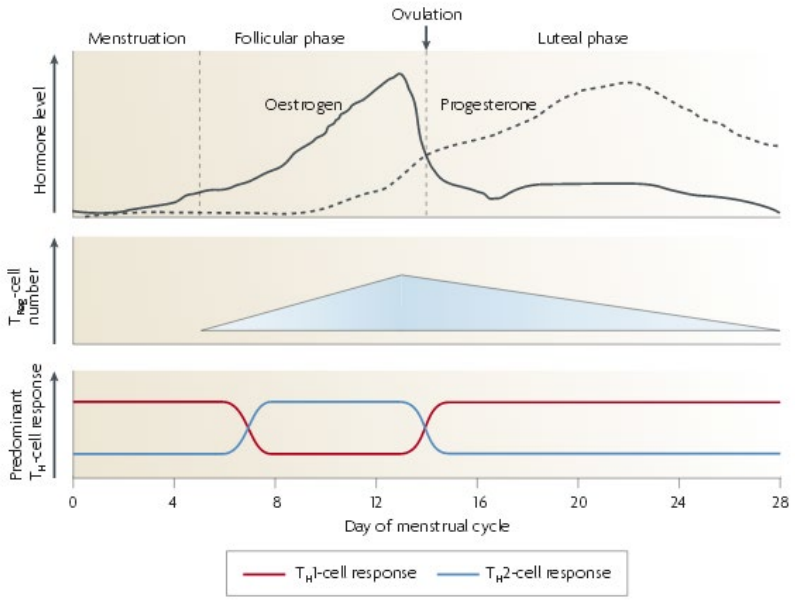
Estradiol (E2 – most bioactive)
Estriol (E3 – most abundant)
Progesterone

DHEA (dehydroepiandrosterone)
Testosterone

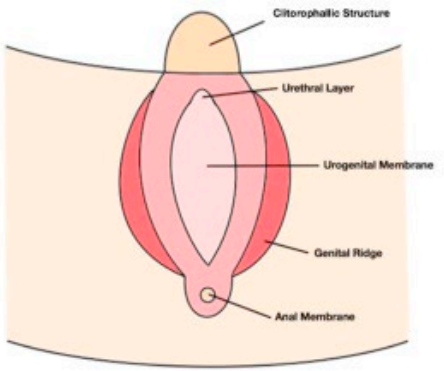
SHBG (sex-hormone binding globulin)

Collection: blood, saliva

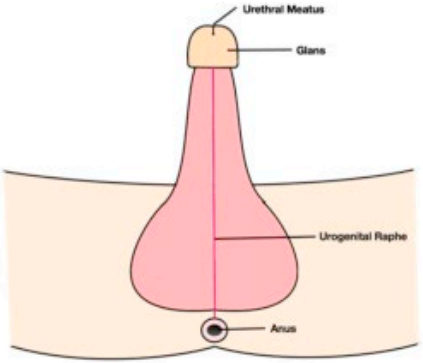
When to measure hormones?



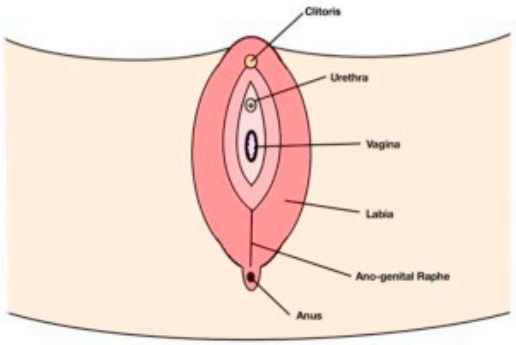
Operationalization of sex - genitalia



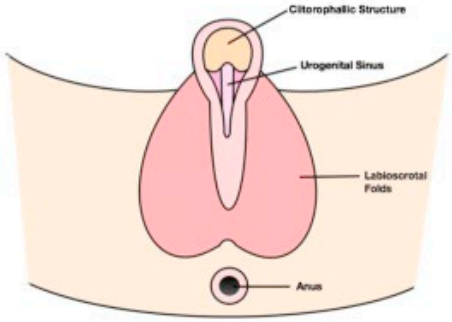
Undifferentiated External Genitalia



Differentiated Male External Genitalia



Differentiated Female External Genitalia



External Genitalia of a Patient with DSD

Intersex / DSD (differences of sex development) – 0.07 – 1.7%

Examples of medical basis for DSD: (partial) androgen insensitivity syndrome, congenital adrenal hyperplasia, vaginal atresia, Müllerian agenesis, gonadal dysgenesis

Hughes, I. A. et al. 2006. *Journal of Pediatric Urology,*

Potential confounders – cell cultures

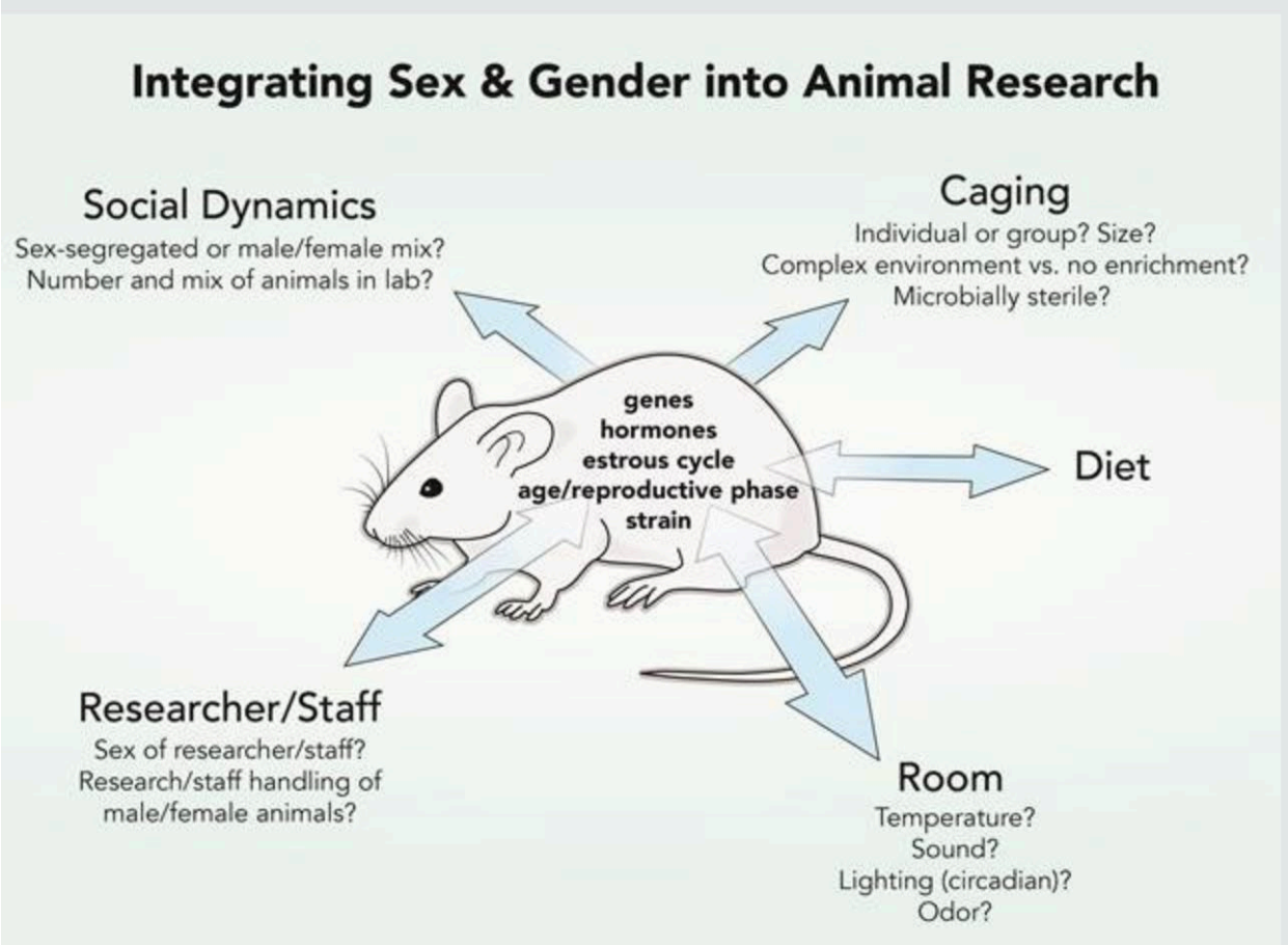
General questions:

- Sex of the cell culture?
- Stability of the karyotype
- X inactivation patterns (role of e.g. reprogramming)
- Type of media
- Changes in methylation profiles according to origin

Open questions:

- Effect of hormonal addition to media (synthetic, uptake differences etc.)
- Sex differences in intrinsic effects of media (on e.g. growth)

Potential confounders – animal models



http://genderedinnovations.stanford.edu/case-studies/animals2

Examiner´s sex

We found that exposure of mice and rats to male but not female experimenters produces pain inhibition. Male-related stimuli induced a robust physiological stress response that results in stress-induced analgesia. This effect could be replicated with T-shirts worn by men, bedding material from gonadally intact and unfamiliar male mammals, and presentation of compounds secreted from the human axilla.

Experimenter sex can thus affect apparent baseline responses in behavioral testing.

Sorge RE, Nat Methods, 2014

Reporting of sex

1. Rationale of the study – potential effects of sex on performed experiments

2. Experimental set up , total # of subjects, cells, animals – breakdown by sex (table 1)

3. Ideally describe potential confounders (housing conditions, soy-based chow, light and dark, temperature etc.) – EXPERIMENTER DATA?

4. Analyze by sex (potentially with interactions, e.g. sex*age)

5. Report analysis in **sex-disaggregated** manner

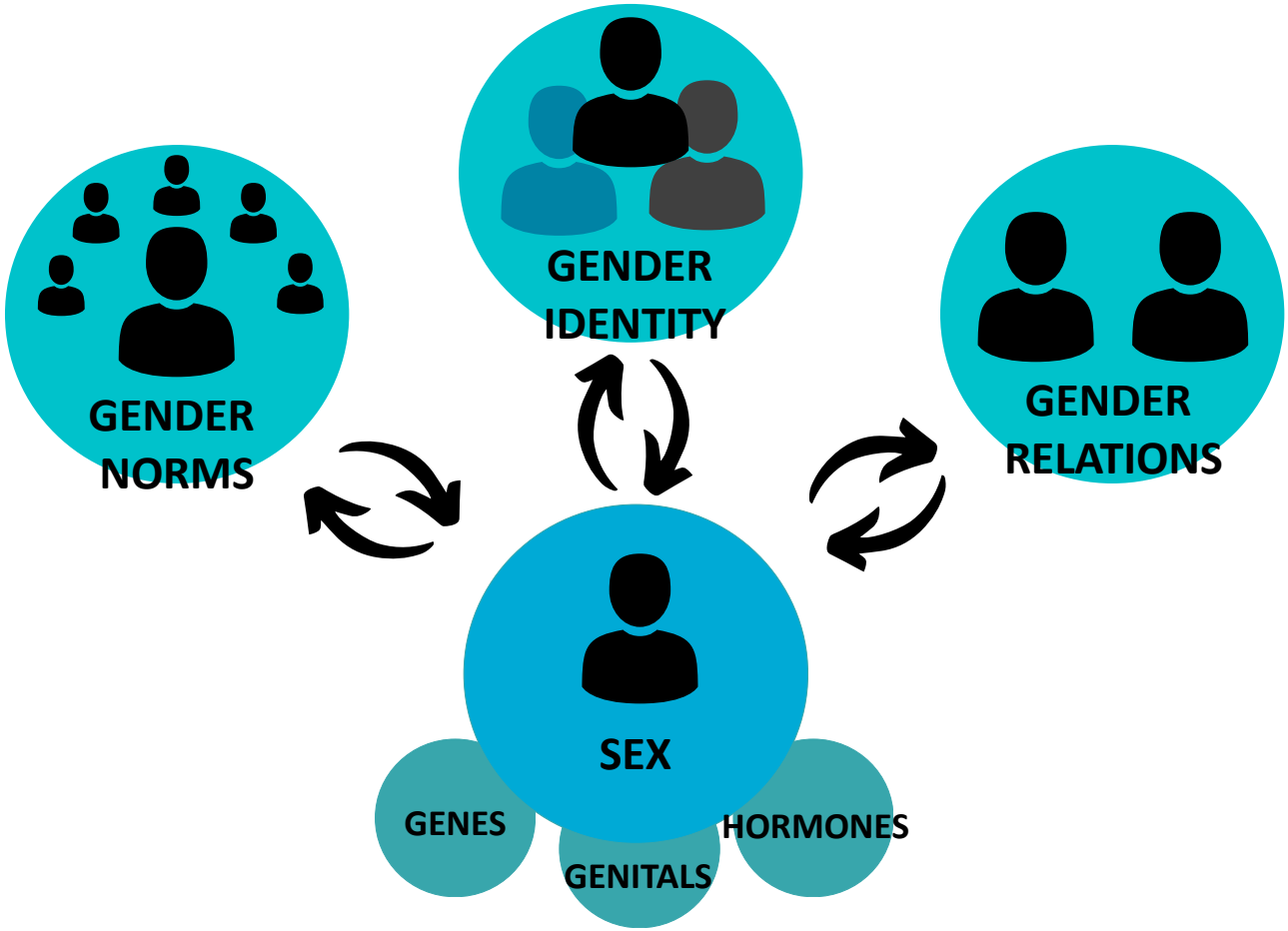
6. Discuss implications

Mesuring gender:

a concept from the social sciences in medicine

Four dimensions:
- Identity
- Role
- Relationships

Being vs Doing



Gender identity – two steps approach

What sex were you assigned at birth?
Female – male – intersex – a sex not listed here (please specify) – prefer not to respond

Current gender identity?
Woman – Man – Non-binary – Genderqueer – a gender not listed here (please specify) – prefer not to respnd

Magliozzi, D., Saperstein, A., & Westbrook, L. (2016). *Socius*

Gender roles – Bem SRI

TABLE 1

ITEMS ON THE MASCULINITY, FEMININITY, AND SOCIAL DESIRABILITY SCALES OF THE BSRI

Masculine items	Feminine items	Neutral items
49. Acts as a leader	11. Affectionate	51. Adaptable
46. Aggressive	5. Cheerful	36. Conceited
58. Ambitious	50. Childlike	9. Conscientious
22. Analytical	32. Compassionate	60. Conventional
13. Assertive	53. Does not use harsh language	45. Friendly
10. Athletic	35. Eager to soothe hurt feelings	15. Happy
55. Competitive	20. Feminine	3. Helpful
4. Defends own beliefs	14. Flatterable	48. Inefficient
37. Dominant	59. Gentle	24. Jealous
19. Forceful	47. Gullible	39. Likable
25. Has leadership abilities	56. Loves children	6. Moody
7. Independent	17. Loyal	21. Reliable
52. Individualistic	26. Sensitive to the needs of others	30. Secretive
31. Makes decisions easily	8. Shy	33. Sincere
40. Masculine	38. Soft spoken	42. Solemn
1. Self-reliant	23. Sympathetic	57. Tactful
34. Self-sufficient	44. Tender	12. Theatrical
16. Strong personality	29. Understanding	27. Truthful
43. Willing to take a stand	41. Warm	18. Unpredictable
28. Willing to take risks	2. Yielding	54. Unsystematic

Note. The number preceding each item reflects the position of each adjective as it actually appears on the Inventory.

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Bem SL, J Consult Clin Psych, 1974

Gender relations - the self-perceived and self-reported gender equality scale

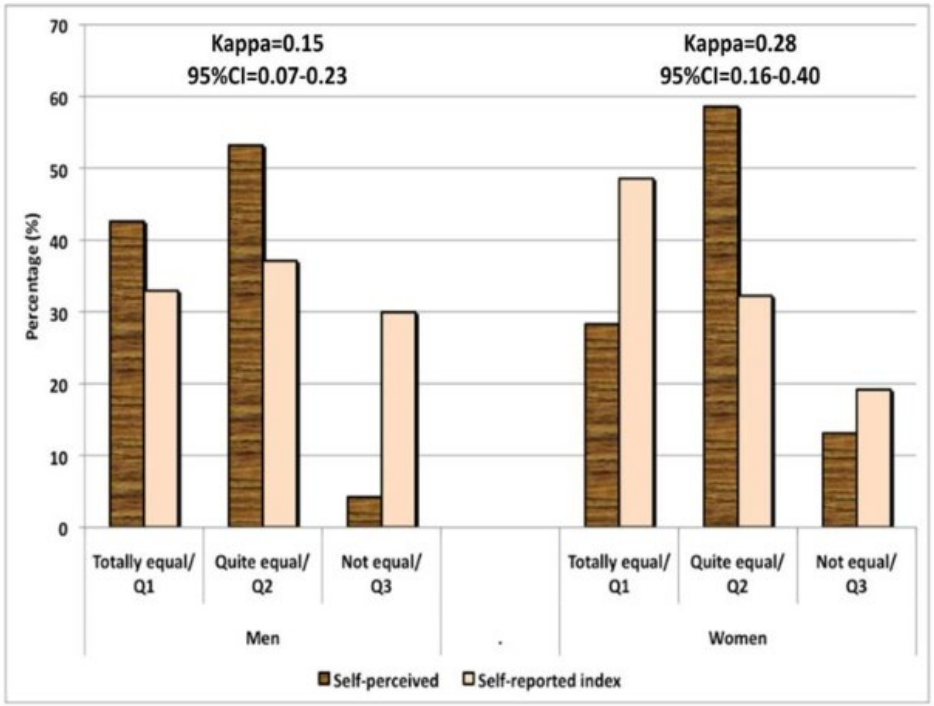

Figure 1
Agreement between self-perceived gender equality and self-reported gender equality index.

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Sörlin A, Intl J Equity Health, 2011

Gender index (CVD recurrence) – role + relationships

(1) primary earner in the household,
(2) personal income,
(3) numbers of hours per week spent doing housework,
(4) status of primary person responsible for doing housework,
(5) level of stress at home,
(6) Bem Sex Role Inventory masculinity score, and
(7) Bem Sex Role Inventory femininity score.

The gender-related score represents the probability (between 0% and 100%) for each patient to be a “woman”. The lower the reported score, the more the patient reported characteristics traditionally ascribed to men and the higher the score, the more the patient reported characteristics ascribed to being a woman. Intermediate scores represent patients with an equivalent level of characteristics traditionally ascribed to women and men.

Norris CM, J Womens Health, 2017

Gender as a sociocultural variable (GASV – EFA/CFA, no predefined outcome)

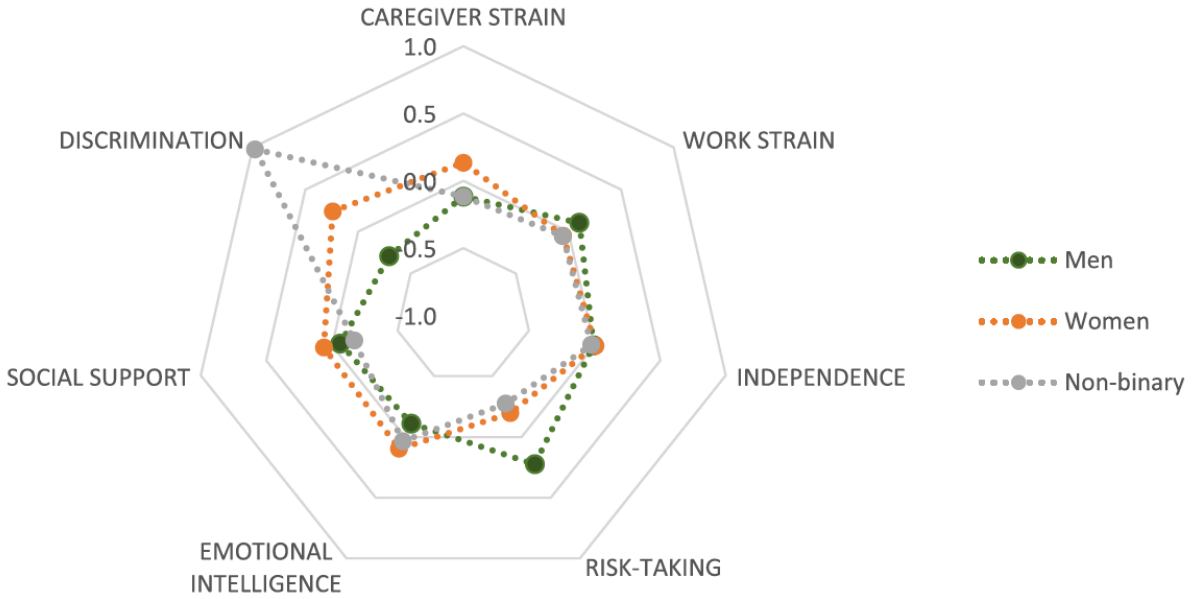

Fig. 1 Gender-related variables capturing specific behaviors and attitudes. The figure displays the z-scores for the seven gender-related variables for respondents seeing themselves as men (green), women (orange) and gender fluid/Non-binary (grey) in sample 1 (*N* = 1893)

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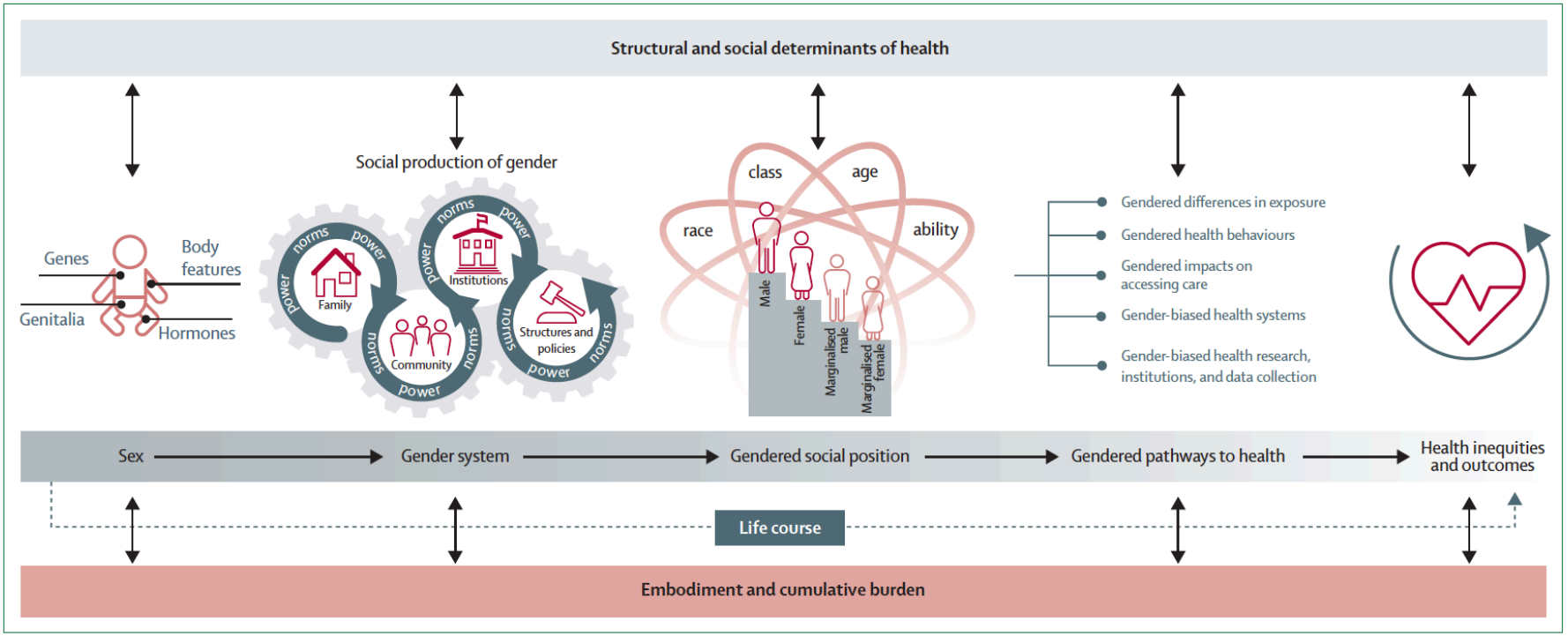
Nielsen MW et al., *Biol Sex Diff*, 2021

Sex and gender are intertwined



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Heise L. et al., The Lancet, 2019

Potential consequences

Consequences of ignoring sex differences I: Reduced reproducibility

We found that exposure of mice and rats to male but not female experimenters produces pain inhibition. Male-related stimuli induced a robust physiological stress response that results in stress-induced analgesia. This effect could be replicated with T-shirts worn by men, bedding material from gonadally intact and unfamiliar male mammals, and presentation of compounds secreted from the human axilla.

Experimenter sex can thus affect apparent baseline responses in behavioral testing.

Sorge RE, Nat Methods, 2014

Consequences of ignoring sex/gender differences II: Delayed diagnosis

Diagnosis in women with bladder cancer and haematuria is more likely delayed because attributed to cystitis

Although women refer more symptoms of asthma, they are less likely diagnosed. In girls wheezing is less common than in boys

Men are diagnosed later with osteoporosis and autoimmune diseases, because these are perceived as „female“

If not diagnosed correctly, men with MS are more likely referred to an orthopedic surgeon, women to a psychiatrist.

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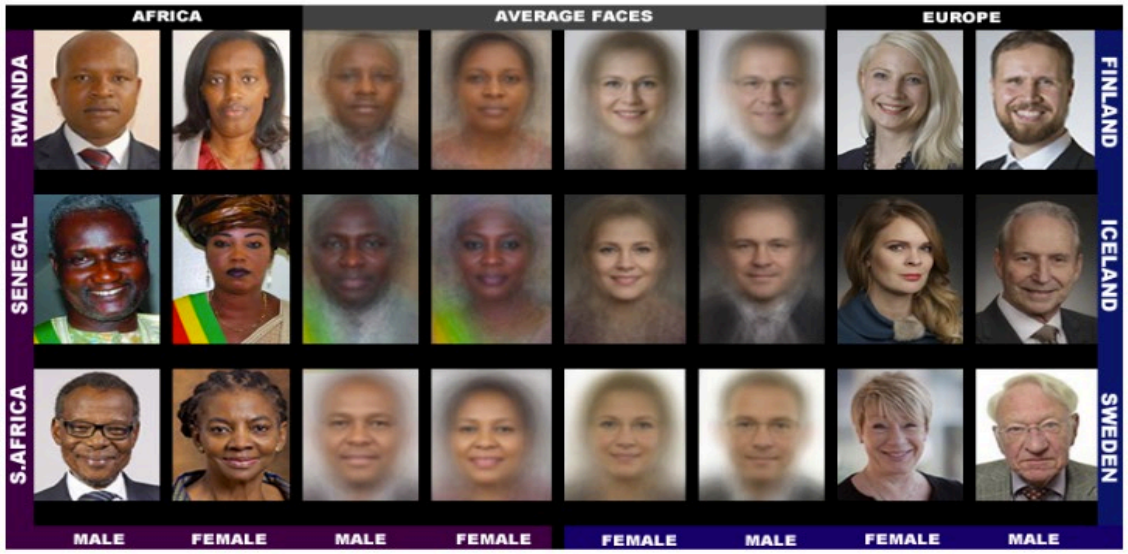
Oertelt-Prigione S and Regitz-Zagrosek, „Sex and Gender Aspects in Clinical Medicine, Springer (London), 2012

Consequences of ignoring sex/gender differences III:

Algorithm bias

Likelihood of being misclassified or not recognized by commercial algorithms according to gender and skin color



	All	Female	Male	Darker	Lighter	DF	DM	LF	LM
MSFT									
Error Proportion	-	76.9%	23.1%	93.6%	6.4%	70.5%	23.1%	6.4%	0.0%
Error Count	78	60	18	73	5	55	18	5	0
FACE++									
Error Proportion	-	95.9%	4.1%	74.0%	26.0%	72.4%	1.6%	23.6%	2.4%
Error Count	123	118	5	91	32	89	2	29	3
IBM									
Error Proportion	-	74.7%	25.3%	85.7%	14.3%	61.0%	24.7%	13.6%	0.6%
Error Count	154	115	39	132	22	94	38	21	1

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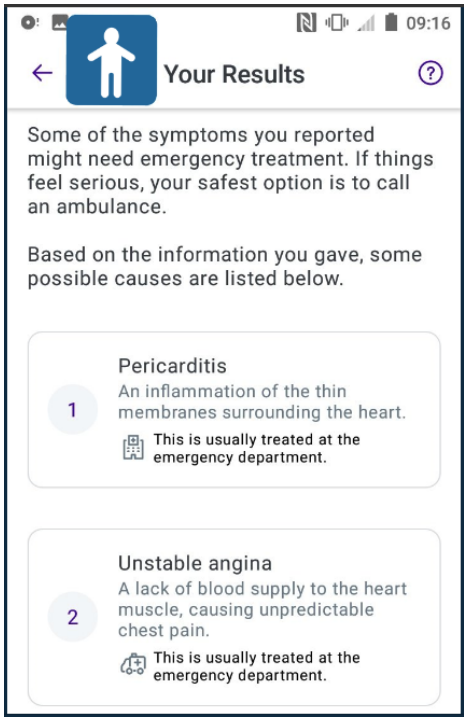
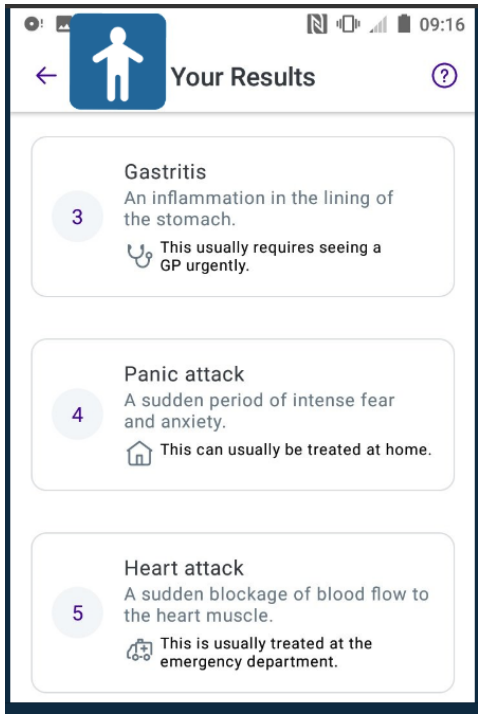
Buolamwini J, Proc Mach Learn Res, 2018

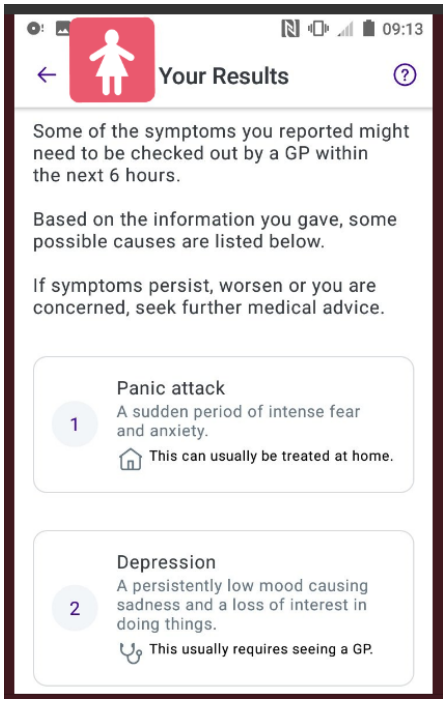
Consequences of ignoring sex/gender differences III:

Algorithm bias

A 56yr old 10/day smoker, has had a painful left arm for the last hour & now feels a sweaty & sick….







#deathbychatbot

Consequences of ignoring sex/gender and ethnic differences IV: Device malfunctioning

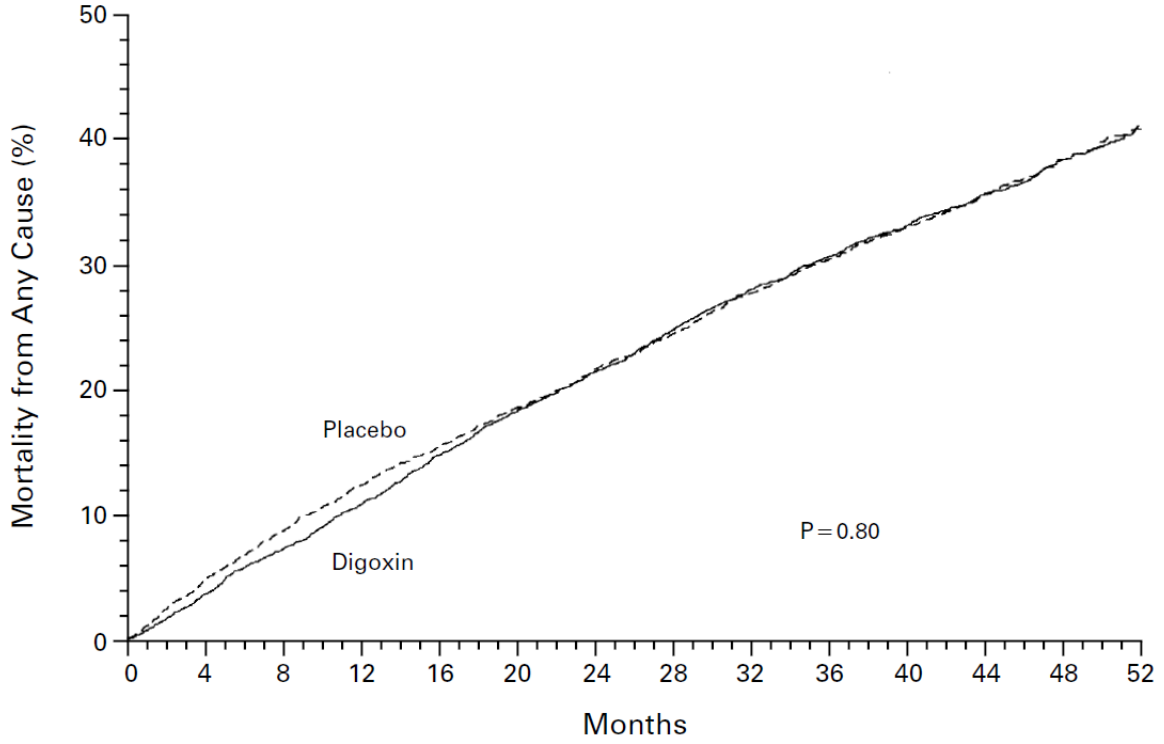
Pulse oximeters don't accurately report oxygen saturation levels in patients with darker skin.

Analysis of over 47,000 readings found that oximeters misread blood gases 12 % of the time in patients with darker skin compared to 4 % of the time in patients with lighter skin.

Feiner, J. R. et al., *Anesthesia & Analgesia*, 2007
Sjoding, M. W et al. *New England Journal of Medicine*, 2020

Consequences of ignoring sex differences V:

Lack of detection of differences in effectiveness



No. of Patients at Risk

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Figure 1. Mortality in the Digoxin and Placebo Groups.
The number of patients at risk at each four-month interval is shown below the figure.

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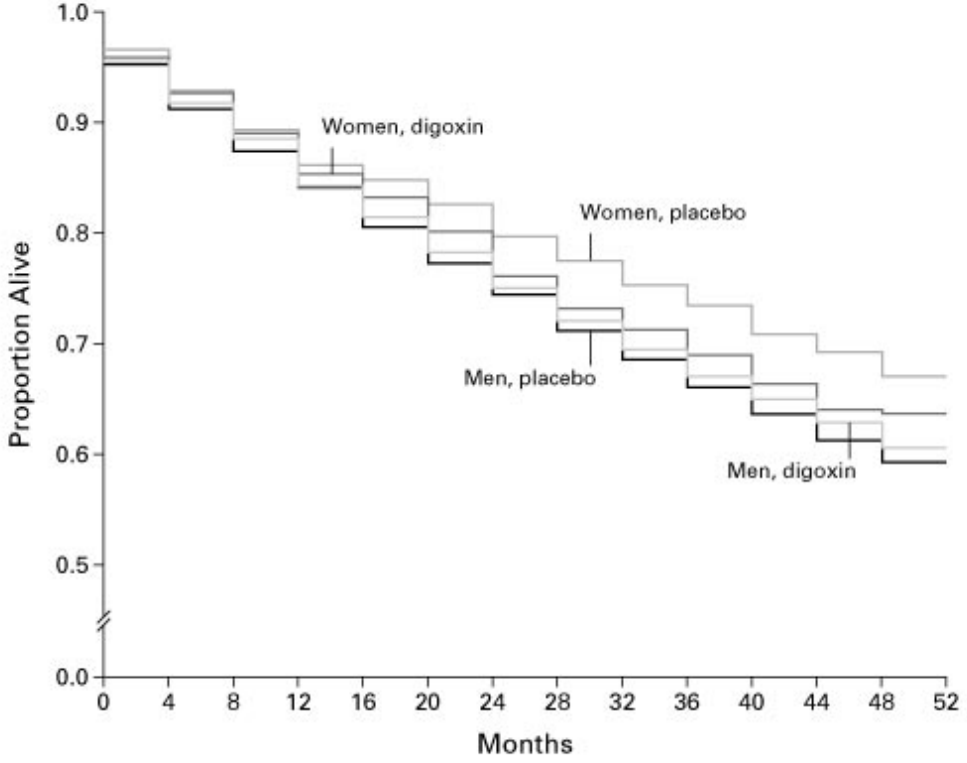
The Digitalis Investigation group, N Engl J Med, 1997

Consequences of ignoring sex differences V:

Lack of detection of differences in effectiveness



No. at Risk

Men, placebo	2639	2510	2401	2301	2210	2111	2022	1944	1686	1438	1152	886	568	255
Men, digoxin	2642	2549	2449	2353	2243	2135	2047	1962	1685	1420	1129	870	572	249
Women, placebo	764	729	701	675	657	645	626	603	511	440	347	266	163	73
Women, digoxin	755	720	693	665	638	621	596	564	488	414	338	261	164	79

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Rathore SS, N Engl J Med, 2002

Consequences of ignoring sex differences V:

Mortality due to increase of unexpected side effects

TABLE 1. PRESCRIPTION DRUGS WITHDRAWN FROM UNITED STATES MARKET, JANUARY 1, 1997–DECEMBER 31, 2000

Drug	*Type of drug*	*Date approved*	*Date withdrawn*	*Primary health risk*
Pondimin (fenfluramine hydrochloride)	Appetite suppressant	6/14/1973	9/15/1997	Valvular heart disease
Redux (dexfenfluramine hydrochloride)	Appetite suppressant	4/29/1996	9/15/1997	Valvular heart disease
Seldane (terfenadine)	Antihistamine	5/8/1985	2/27/1998	Torsades de pointes
Posicor (mibefradil dihydrochloride)	Cardiovascular	6/20/1997	6/8/1998	Bradycardia in elderly and adverse drug interaction
Hismanal (astemizole)	Antihistamine	12/19/1988	6/18/1999	Torsades de pointes
Rezulin (troglitazone)	Diabetic	1/29/1997	3/21/2000	Liver failure
Propulsid (cisapride monohydrate)	Gastrointestinal	7/29/1993	7/14/2000	Torsades de pointes
Lotronex (alosetron hydrochloride)	Gastrointestinal	2/9/2000	11/28/2000	Ischemic colitis
Raxar (grepafloxacin hydrochloride)	Antibiotic	11/6/1997	11/1/1999	Torsades de pointes
Durac (bromfenac sodium)	Analgesic and anesthetic	7/15/1997	6/22/1998	Liver failure

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Obias-Manno, *J Women's Health*, 2007

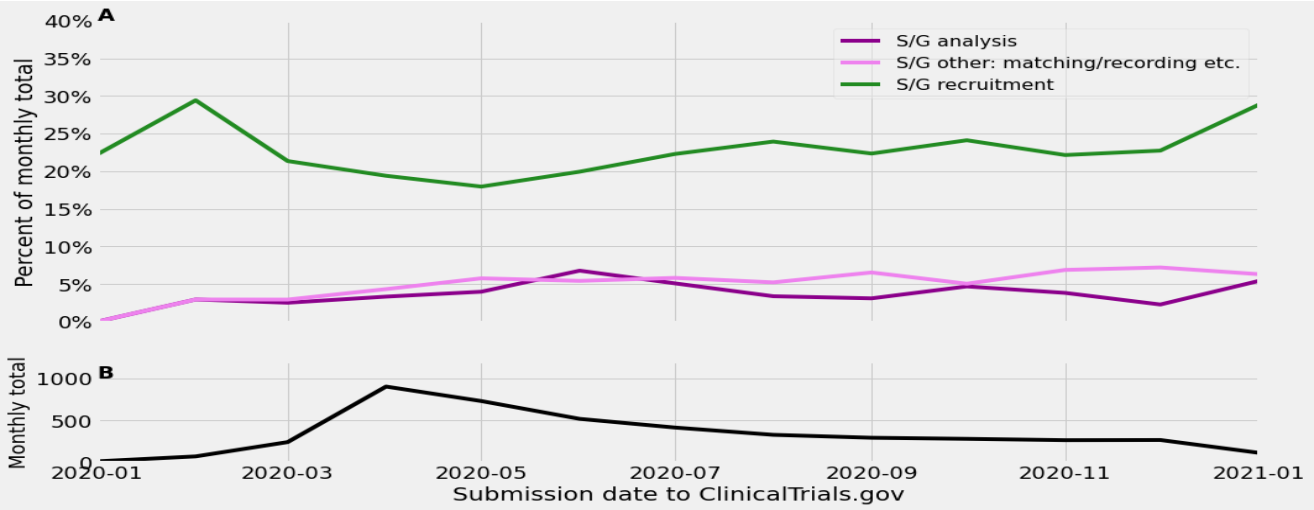
...even in 2021....even for COVID-19

Of the 4420 COVID-19 trials registered in clinicaltrials.gov between January 2020 and January 2021

- 21.2 % reported sex/gender as a recruitment criterion
- 4% reported intention to consider sex/gender upon analysis

Of the 45 clinial trials published in January 2021

- Merely 18% reported sex-disaggregated analyses



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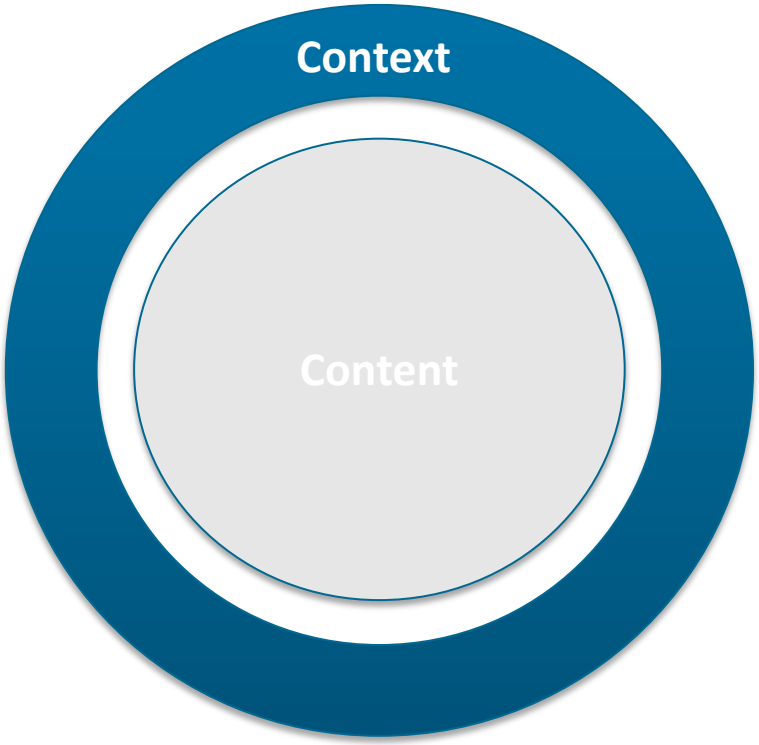
Brady E et al. S. *Nat Commun,* 2021

Essential steps towards mitigation

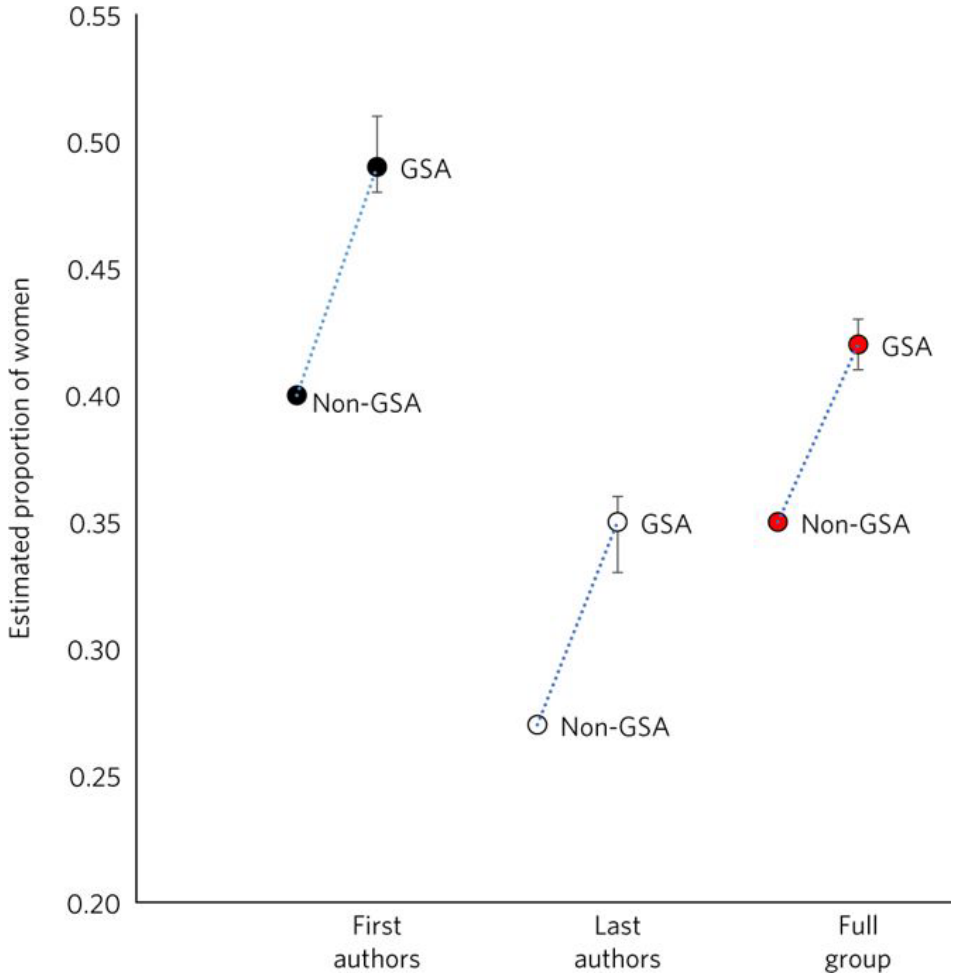
1. **Obtain information about your samples**
2. **Include (at least) both sexes / think about the conceptualization of gender**
3. **Consult an expert**
4. **Disaggregate data**
5. **Stratify analysis by sex / gender**
6. **Report data in disaggregated format**
7. **Spread the word**

Gender balance in research teams

Gender balance in decision making



Influence of the researcher on the researched topic



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Nielsen MW, Nature Hum Comm, 2017

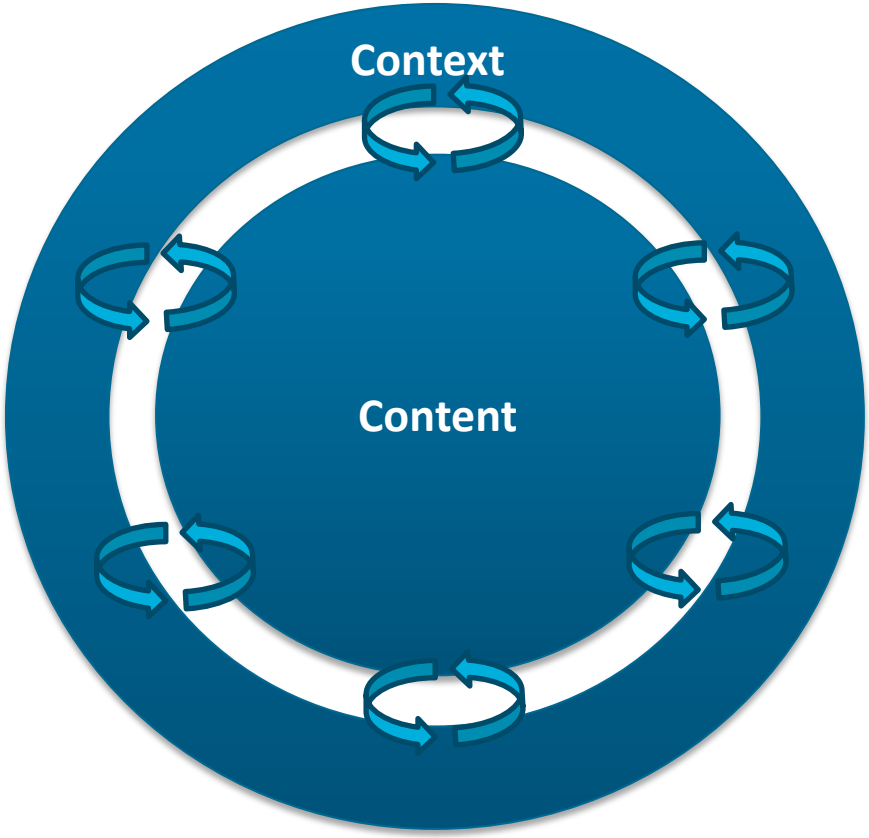
Three levels:

- Gender Equality Plan: **Eligibility Criterion**
- Integration of the gender dimension: **Award Criterion**
- Gender balance: **Ranking Criterion**

Gender Equality Plans
Five recommended areas

1. **Work-life balance and organizational culture**
2. **Gender balance in leadership and decision-making**
3. **Gender equality in recruitment and career progression**
4. **Integrating the gender dimension into research and teaching content**
5. **Measures against gender-based violence, including sexual harassment**

The gender dimension
Content and context



Thank you for your attention!

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Sabine Oertelt-Prigione

Gendered Innovations

in Science, Health & Medicine, Engineering, and Environment

FEATURED CASE STUDIES

Why Gendered Innovations?

Gendered Innovations employs methods of sex, gender, and intersectional analysis to create new knowledge.

Resources for sex- and gender-sensitive research

Websites:

https://genderedinnovations.stanford.edu/
https://orwh.od.nih.gov
https://cihr-irsc.gc.ca/e/8673.html

Papers:

- Clayton, J. A. Studying both sexes: a guiding principle for biomedicine. *FASEB J* **30**, 519-524, (2016)
- Miller L.R. et al. Considering sex as a biological variable in preclinical research. *FASEB J* **31**, 29-34 (2017)
- Tannenbaum, C., Ellis, R. P., Eyssel, F., Zou, J. & Schiebinger, L. Sex and gender analysis improves science and engineering. *Nature* **575**, 137-146 (2019)
- Zucker, I. & Prendergast, B. J. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ* **11**, 32 (2020)
- Mauvais-Jarvis F. et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet* **396**, 565-582 (2020)

Literature search – four search algorithm options

1. Montgomery and Sharif – women´s health
2. Moerman – women/men, female/male
3. Stewart – men´s health
4. Oertelt-Prigione – sex and gender differences, sex/gender-specific, dimorphic

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