Anti-Discrimination Working Group

Meeting #3

Wednesday, 23 June 2023

10.00, NCRR main meeting room (and online)

Agenda

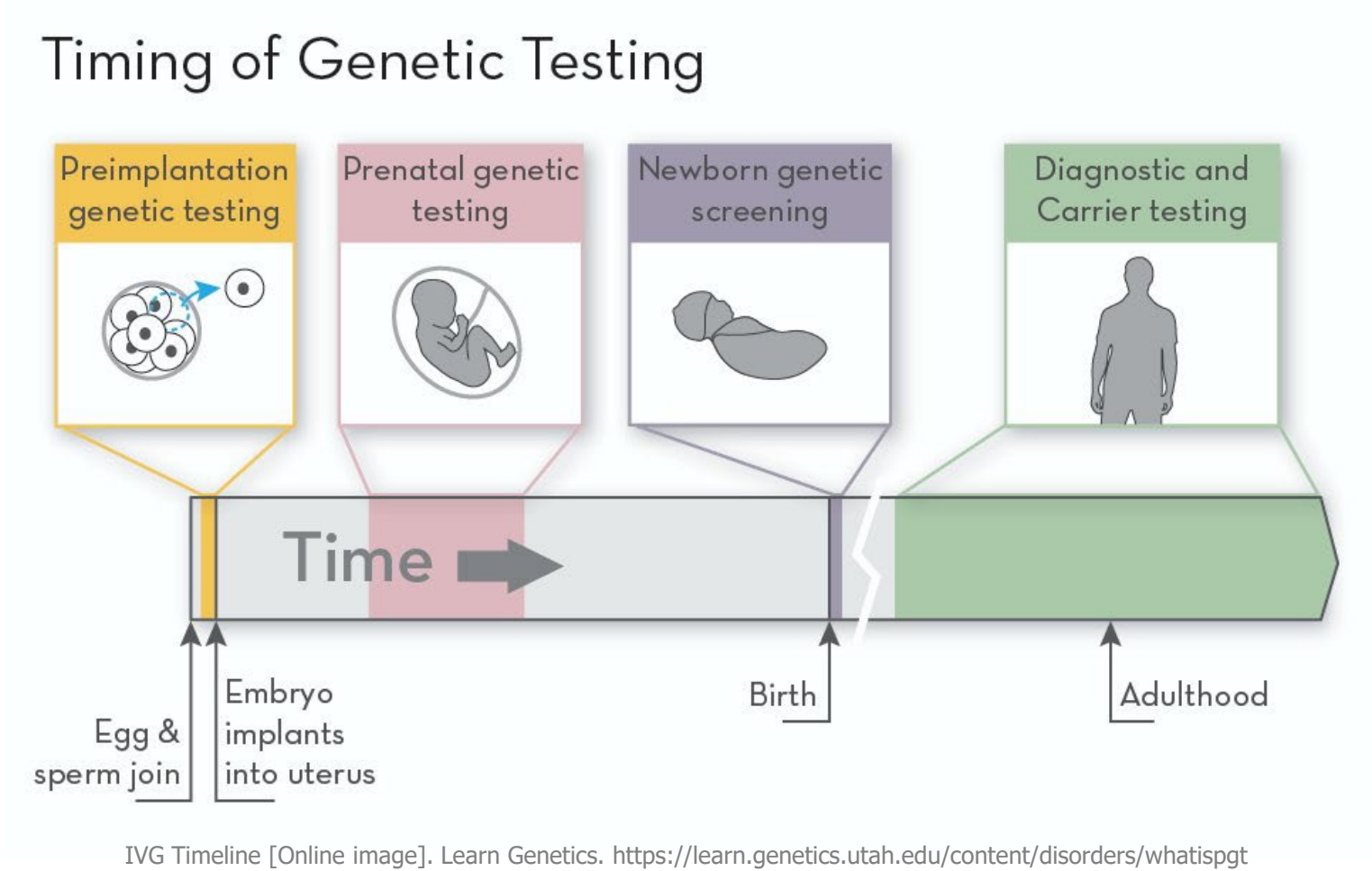
1. Introduction round
2. Aims of the group
3. Embryonic/prenatal genetic testing in Denmark
4. Polygenic embryo screening
5. Discussion
6. Ideas for next meeting

Introductions

Aims of the group

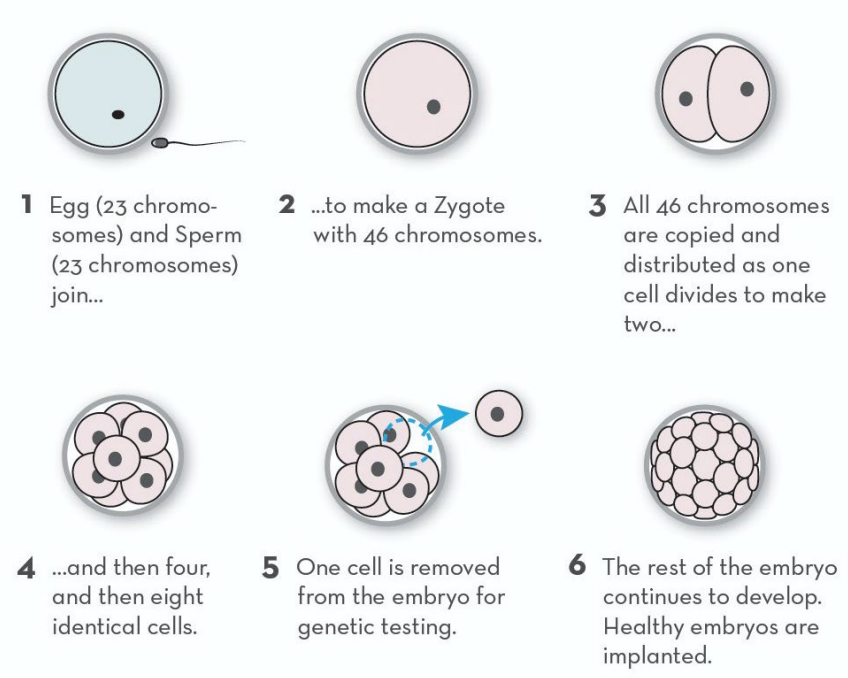
1. To strive for **equality**
2. To strive for **diversity**
3. To be **open & transparent**
4. To be mindful that **the topics we discuss may be triggering and upsetting**, impacting on people in different ways.
   - This is not a passive intellectual topic. It takes time to install the correct support and find solutions. This is a learning process.
5. To discuss ongoing issues with **discrimination in research**
6. To recognize **harmful structures and practices** of discrimination in research
7. To **advocate for changes** that promote equity in research

Genetic testing



IVG Timeline [Online image]. Learn Genetics. https://learn.genetics.utah.edu/content/disorders/whatispgt

Pre-implantation genetic testing (PGT)



PGT [Online image]. Learn Genetics. https://learn.genetics.utah.edu/content/disorders/whatispgt

- PGT for Aneuploidy **(PGT-A)**
  - Chromosomal abnormalities (e.g., Down syndrome, Turner syndrome)
  - Deselection of affected embryos to optimize pregnancy rates and reduce miscarriage rates
- PGT for Monogenic/Single Gene Disorders **(PGT-M)** and PGT for Chromosomal Structural Rearrangements **(PGT-SR)**
  - Known genetic disorders (e.g., Huntington's disease, cystic fibrosis, Tay-Sachs)
  - Reduce risk of transmitting genetic disorders

Pre-implantation genetic testing (PGT)

- Cells are biopsied from the embryo at the blastocyst stage (~5–7 days after fertilization)
- Genetic material is analyzed
- Unaffected embryos are selected for transfer
- Tests are highly sensitive and very accurate (95–99%)

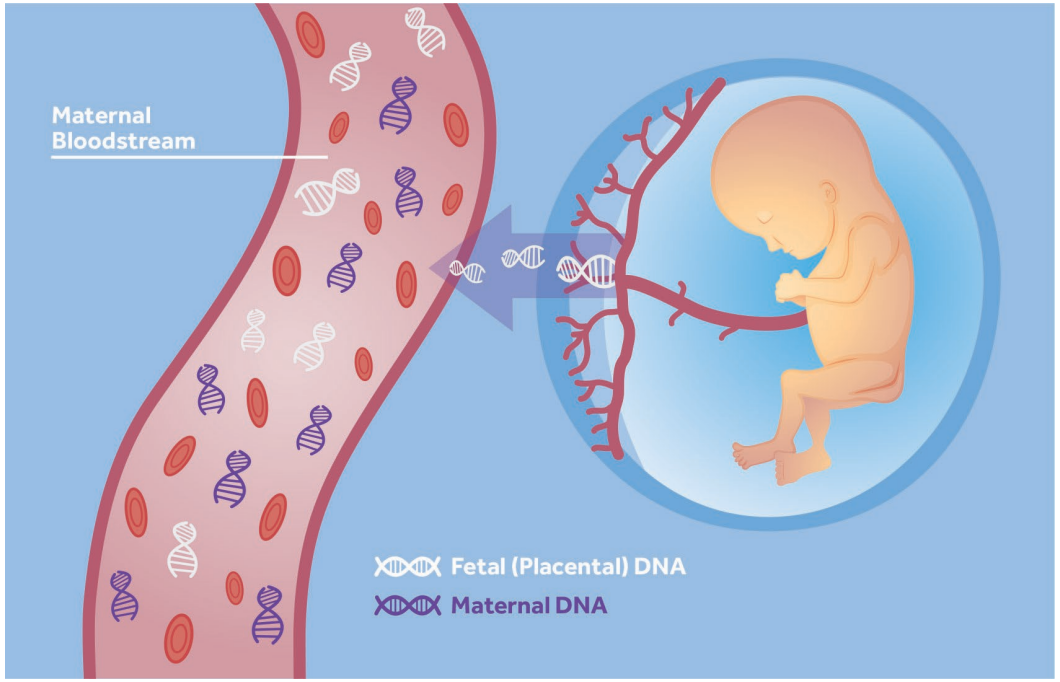
"Discarding embryos five days after fertilization in PGT appears – in all aspects – to be ethically acceptable and in harmony with a traditional Nordic principle of ethical gradualism." *(Ingerslev et al., 2020)*

PGT in Denmark

- Publicly funded
- Rigshospitalet Copenhagen and Aalborg University Hospital
- ~10x more PGT per million inhabitants than Norway, 3x more than Finland, and 2x more than Sweden/Iceland *(Hreinsson et al., 2020)*
- **PGT-M/PGT-SR:** Parent(s) with a high risk of transmitting a severe genetic disorder
- **PGT-A:** Allowed within an approved research protocol

Non-invasive prenatal screening (NIPT)

- Chromosomal abnormalities:
  - Down syndrome (trisomy 21)
  - Patau syndrome (trisomy 13)
  - Edwards syndrome (trisomy 18)
- After the first-trimester scan (week 11–13)
- Measures the amount of fetal DNA corresponding to chromosomes 13, 18, and 21
- Estimate whether risk is increased or decreased
- High sensitivity and specificity (90–99%)



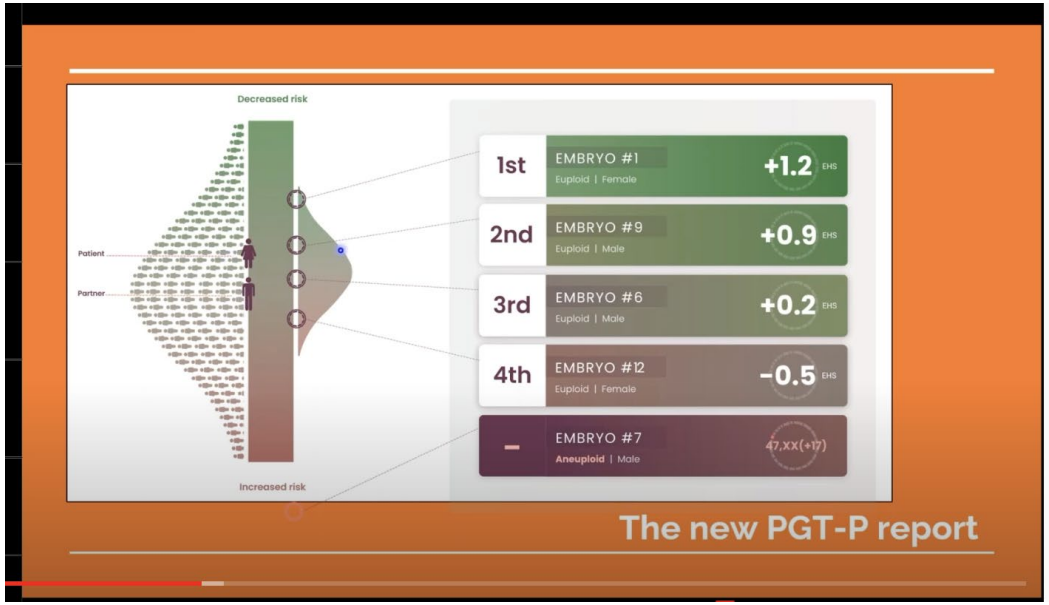
Fetal placental DNA image [Online image]. St George's University Hospitals. https://www.stgeorges.nhs.uk/service/maternity-services/your-pregnancy/fetal-medicine-unit/the-safe-test/

NIPT in Denmark

- **1973-2004:** Invasive prenatal screening (Down syndrome) in high-risk pregnancies only
- **2004:** National combined first-trimester screening **(cFTS)** program
- High uptake (>96%) of **cFTS** *(Lund et al., 2021)*
- **2013:** NIPT introduced as an alternative in high-risk pregnancies
- **2017:** National **NIPT** program

Polygenic embryo screening (PES)

- The application of polygenic risk scores in the context of PGT, in order to determine each embryo's liability for one or more diseases/traits, and to guide selection of an embryo for implantation *(Lencz et al., 2022)*



Screenshot from Genomic Prediction presentation [Online image]. (2021). Center for Genetics and Society. https://www.geneticsandsociety.org/biopolitical-times/first-polygenic-risk-score-baby

Embryonic screening and eugenics

Genetic Screening Now Lets Parents Pick the Healthiest Embryos

People using IVF can see which embryo is least likely to develop cancer and other diseases. But can protecting your child slip into playing God?

PHOTOGRAPH: ALBERT MARTINE/GETTY IMAGES

At 18 months old, Aurea Yenmai Smigrodzki is inquisitive like any other toddler. She likes peanut butter, the beach, and mobile phones—or any toys that look like phones. She likes to copy her mum and dad, Thuy and Rafal, when they are using theirs. Aurea doesn't know it yet, but her birth was very special: She is the world's first PGT-P baby, meaning she is statistically less likely than the rest of us to develop a genetic disease or disorder throughout her life.

https://www.wired.co.uk/article/genetic-screening-ivf-healthiest-embryos

Polygenic embryo screening (PES)

Concerns about the use of polygenic embryo screening for psychiatric and cognitive traits

Todd Lencz, Maya Sabatello, Anna Docherty*, Roseann E Peterson*, Takahiro Soda*, Jehannine Austin, Laura Bierut, David Crepaz-Keay, David Curtis, Franziska Degenhardt, Laura Huckins, Gabriel Lazaro-Munoz, Manuel Mattheisen, Bettina Meiser, Holly Peay, Marcella Rietschel, Consuelo Walss-Bass, Lea K Davis*

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- For thirty years, preimplantation genetic testing has been a routine part of IVF.
  - Identification of embryos with monogenic disease-causing alleles (e.g., CF, Tay-Sachs disease).
- PES is a new technique.
  - Commercially available from at least one provider.

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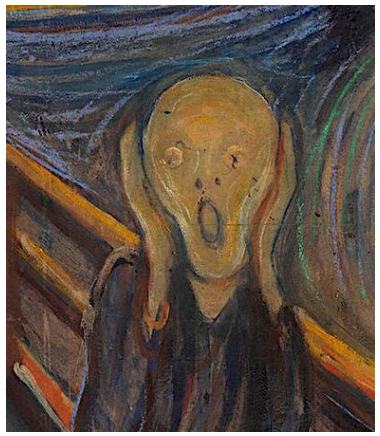

Why should we be concerned about PES?

I don’t see the problem with PES. Surely we want to try and improve the health of the population? If PES is trying to achieve this, what is the problem? How is this any different to PGT and NIPT?

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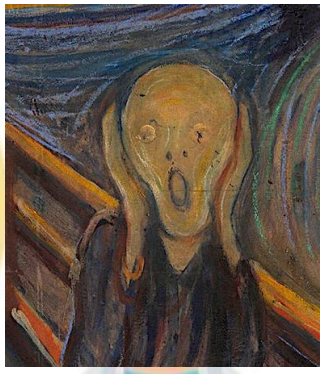

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PES

Practical/scientific issues about efficacy

Ethical issues

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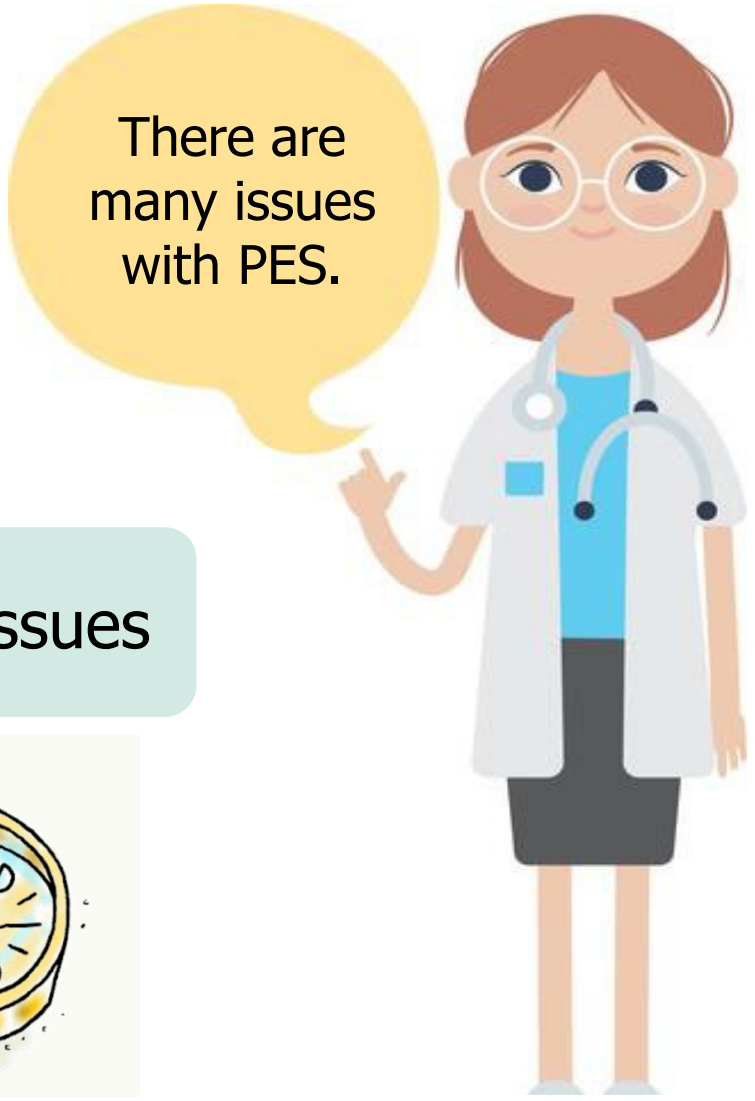


Practical/scientific issues with PES

Issues with accuracy

1. PES depends on accuracy of polygenic scores (sample size and trait heritability).

2. Variance explained by a polygenic score is much lower than SNP-based h2 (which, in turn, is much lower than broad-sense H2).

3. Polygenic scores are based on GWAS results which may also capture genetic nurture.

4. Polygenic scores are inherently probabilstic and capture risk for multiple phenotypes.

Health disparities*

Regulatory issues

5. Polygenic scores are not transferrable across genetic ancestries.

6. The goals of PES are not clearly defined. What do parents want?

7. No established guidelines on communication of results of polygenic scores, what they mean, and what parents can expect from PES.

8. Regulations differ across countries. This could lead to reproductive tourism.

*Practical and ethical

Ethical issues with PES

Costs to society

1. Encouragement of eugenicist beliefs.

2. Encouragement of genetic essentialism.

3. Encouragement of fatalism.

4. Increased stigma around certain disorders/traits.

Costs to research

5. Need to take into account views of research participants (e.g., in GWASs).

6. Researchers feeling that their contributions have been misused.

7. Distrust of genetics research community.

Statement issued by the International Society of Psychiatric Genetics (ISPG)

ADVISORY ON THE USE OF POLYGENIC RISK SCORES TO SCREEN EMBROS FOR ADULT MENTAL HEALTH CONDITIONS.

Approved by the ISPG Board May, 2021

- Several private companies are using polygenic risk scores to screen embryos for adult mental health conditions. The screening is done as part of *in-vitro* fertilization. A polygenic risk score is a single number that measures part of a person's genetic predisposition for a condition[1]. These genetic scores are built by adding up the small effects from many hundreds or thousands of genes. Although in general higher scores mean you are more likely to have a condition, many healthy people will have high scores; others might develop the condition even with a low score. The accuracy with which a polygenic score can predict psychiatric illnesses, such as schizophrenia, bipolar disorder and major depression, is currently not sufficient for clinical use. Furthermore, the unintended consequences of its use for embryo selection need to be considered. While polygenic risk scores are used in research, there are currently no clinical uses in psychiatry.
- The ISPG views with concern the offering of polygenic embryo screening services for psychiatric conditions, for both scientific and ethical reasons. First, polygenic risk scores do not determine whether a person will develop a condition. They measure just one of many possible risk factors. Second, polygenic risk scores are not specific to a single condition. This means that selection for one condition can affect other genetic traits. Third, it is not known how to accurately communicate the level of risk to prospective parents. Fourth, in many countries, there is no regulation or oversight of polygenic embryo screening to protect against misuse, like there is for other kinds of genetic testing. Fifth, screening embryos for psychiatric conditions may increase stigma surrounding these diagnoses. Finally, psychiatric genetics has a history of misuse for eugenics[2-4], and polygenic embryo screening raises many ethical, legal, and social issues that can potentially lead to harm and have not yet been studied or addressed[5].
- While scientific and ethical issues have been widely studied for single-gene embryo testing[6], the issues listed above have not been explored for polygenic embryo screening. The few published polygenic embryo screening studies have been mostly led by a private company selling these services[7–11]. Public discussion and debate including all potential stakeholders is urgently needed on a national and international scale. Given these considerations, the ISPG urges caution and calls for additional research and oversight on the use of polygenic embryo screening.

Discussion

1. Does PES perpetuate societal biases and reinforce notions of genetic superiority/inferiority? Discrimination/stigmatization of individuals with certain traits?

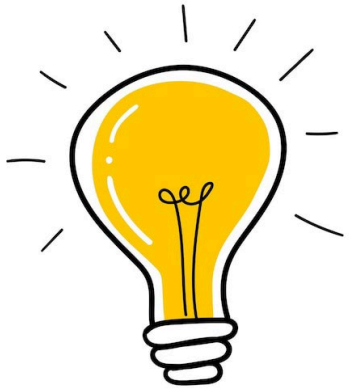
2. Potential loss of genetic diversity and impact on the wider population due to the selective avoidance of certain disorders/traits?

3. Impact on genetics research: Will this discourage participation from diverse, under-represented communities and increase the health disparities that already exist?

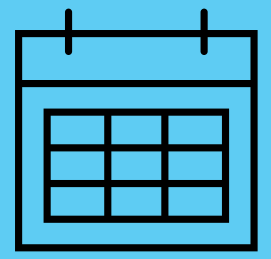
4. Research contributions being misused or applied in a way that we find problematic?

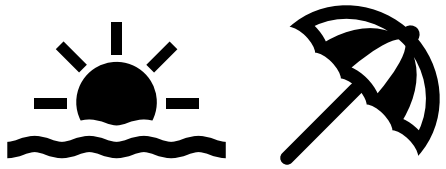
Ideas for next meeting

- Genetic counselling?
- Bioethics?
- Discrimination at the workplace (academia/research)?



Next meeting:
August?





Thanks – Have a great summer!

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Jette Steinbach ✉ jst.ncrr@au.dk

References & further resources

- Hreinsson, J, Iwarsson, E, Hanson, C, et al. (2020). Preimplantation genetic testing legislation and accessibility in the Nordic countries. Acta Obstetricia et Gynecologica Scandinavica, 99, 716-721.
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- Toft, C. L., Diemer, T., Ingerslev, H. J., Pedersen, I. S., Adrian, S. W., & Kesmodel, U. S. (2022). Patients' choices and opinions on chorionic villous sampling and non-invasive alternatives for prenatal testing following preimplantation genetic testing for hereditary disorders: A cross-sectional questionnaire study. Prenatal Diagnosis, 42(2), 212-225.