



# **Genetic testing Developments and implications for ART**

Claudia Spits

Meeting between Comission, T&C CAs and Stakeholders  
Brussels, 16th November 2017

# Topics

- Genome-wide analysis approaches and their impact on expanded carrier screening, voiding of gamete donor anonymity, preimplantation genetic testing and non-invasive prenatal testing
- Mitochondrial replacement therapy
- Germline genome editing
- All of these require guidelines at national or international level
- ESHRE provides recommendations and guidelines for best practice
- “Recent developments in genetics and medically-assisted reproduction: from research to clinical applications”. Paper soon to be published in Human Reproduction Open and in the European Journal of Human Genetics

# Expanded carrier screening

- Preconception screening for high-risk populations and gamete donors
- We moved from single-gene testing to panels >100 genes
- In many countries, available direct-to-consumer



# Expanded carrier screening

- Open issues:
  - What do we test for?
    - Need for increased understanding of genetic disease
    - Priority on severe childhood-onset disorders
    - Minimize incidental findings
  - Who do we test?
  - Who pays?
- Some societies have published recommendations, f.i. European Society of Human Genetics “Responsible implementation of expanded carrier screening”, EJHG, 2016

# Advanced genetic testing and voiding of anonymity of gamete donors

- Direct-to-consumer genetic testing allows for ancestry determination
- Registries like Donor Sibling Registry, Donor-Conceived Register and Family Tree DNA allow linking donors to children/siblings
  - This is not a problem if all parties agree, but it is for donors that wish to remain anonymous
  - It is not sufficient for a donor to avoid entering genetic data in the databank, if any family member does, they can be collaterally identified



# Advanced genetic testing and voiding of anonymity of gamete donors

- Direct-to-consumer genetic testing allows for ancestry determination
- Registries like Donor Sibling Registry, Donor-Conceived Register and Family Tree DNA allow linking donors to children/siblings
  - This is not a problem if all parties agree, but it is for donors that wish to remain anonymous
  - It is not sufficient for a donor to avoid entering genetic data in the databank, if any family member does, they can be collaterally identified
- Fertility centres must inform:
  - donors that they will strive to protect their identity, but that their anonymity cannot be guaranteed
  - couples undergoing ART with gamete donation should be aware that their children may discover their donor

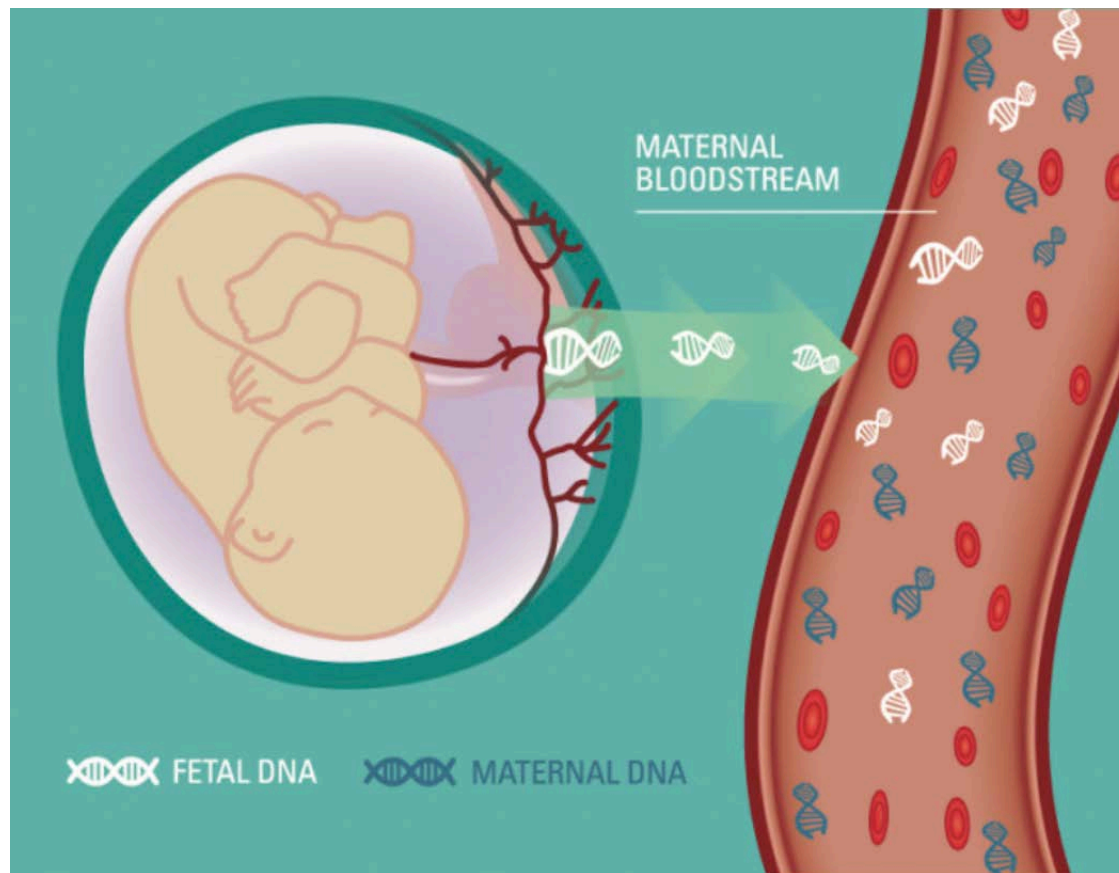
# Preimplantation genetic testing

- The difference between PGD and PGS are disappearing because of the use of genome-wide approaches
  - Monogenic disease
  - Chromosome abnormalities
  - Incidental findings
- Still controversy on whether screening for aneuploidy improves IVF outcome
  - Definition of 'improvement/success' still not standardized
- PGT could be used to 'rank' embryos for transfer
  - Who should decide on how to rank?
  - Interpretation of incidental findings
- ESHRE is working on an update on PGD/PGS guidelines



# Non-invasive prenatal testing/screening

- Isolation of fetal DNA from maternal blood, testing for viable trisomies



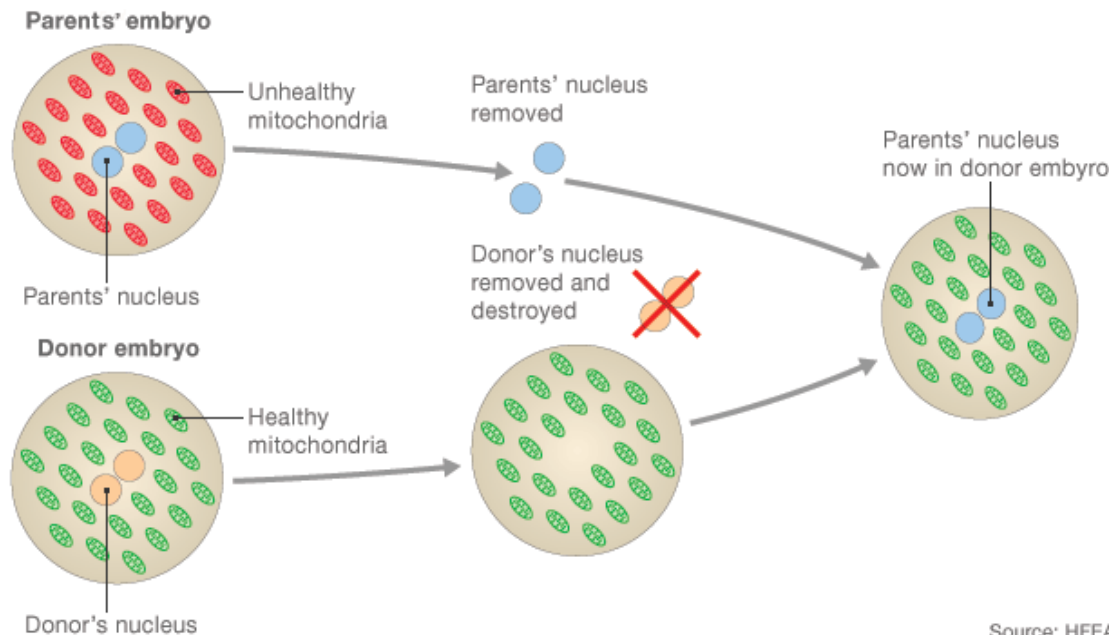


# Non-invasive prenatal testing/screening

- Open issues:
  - NIPT/S is not a diagnostic test, but screening, and may be affected by placental mosaicism or unexpected maternal abnormalities
  - There are discussions on how NIPT/S fits within a comprehensive prenatal screening policy, taking into account cost-effectiveness
  - Should NIPT/S be offered for abnormalities beyond viable aneuploidy, including X-chromosome abnormalities and microdeletion syndromes
  - It could be used for sex-selection (both for monogenic disease as for 'family balancing')
  - Incidental findings
- Individuals need to be made aware of the risk of misdiagnosis and incidental findings

# Mitochondrial replacement therapy

- PGD for mitochondrial disease remains technically challenging
  - Variation in load amongst biopsies, difficult to set a 'threshold'
- Mitochondrial replacement therapy as an alternative
  - Transplantation of pronuclei, meiotic spindle or polar bodies to donor enucleated oocytes



Source: HFEA

# Mitochondrial replacement therapy

- PGD for mitochondrial disease remains technically challenging
  - Variation in load amongst biopsies, difficult to set a 'threshold'
- Mitochondrial replacement therapy as an alternative
  - Transplantation of pronuclei, meiotic spindle or polar bodies to donor enucleated oocytes
  - Pronuclear transfer
    - in mouse: results in some mtDNA carryover
    - In human: one birth (few data, published 13 years after birth)
  - Spindle transfer
    - in Rhesus: efficient and safe
    - in human: one birth (with low mtDNA carry over, follow-up still needed)
  - Polar body transfer
    - In mouse and human, technically difficult

# Mitochondrial replacement therapy

- Virtually no knowledge on safety
- Ethical issues
  - 'Three parent families': the role of the mitochondrial donor, implications for offspring identity
  - Proportionality of developing MRT as based on a view of the importance of genetic parenthood
  - Appropriate precautions and hampering innovation

# Germline genome editing

- There are still technical difficulties, but these are expected to be overcome
- Clinical indications are limited
  - PGD/PGT are existing and safe methods to prevent transmission of genetic disease
  - It could be envisioned for
    - very high-risk couples (both affected by the same autosomal recessive disorder, one partner homozygous for autosomal dominant)
    - Cases where few embryos are expected transferrable after testing: f.i. poor responders to fertility treatment, HLA-matching + monogenic disease
- The ESHG and ESHRE are working on recommendations
- Ethical debate, mostly related to the slippery slope argument

- Questions?