Assisted reproductive technologies to avoid the transmission of mitochondrial disease: the UK experience of moving from research towards clinical application

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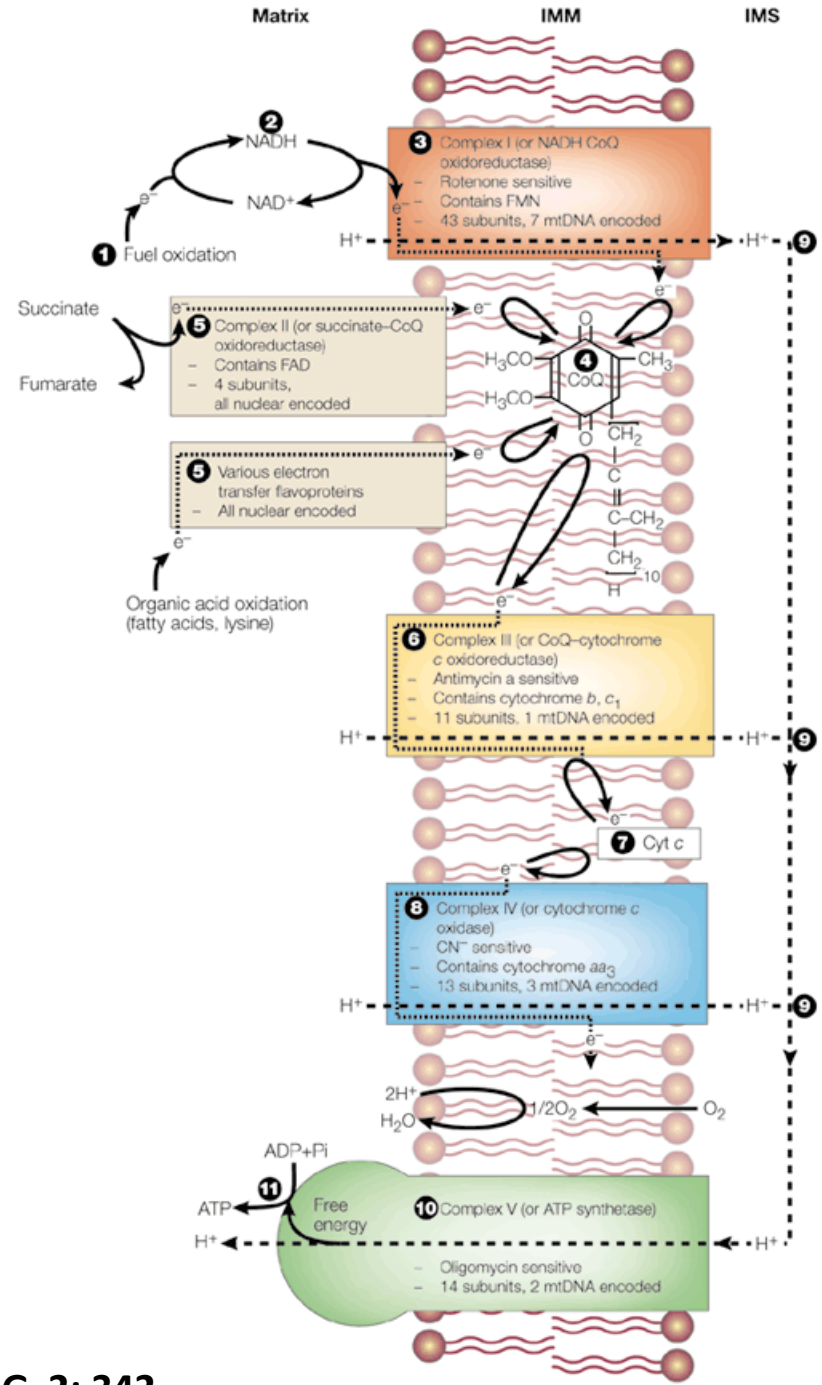
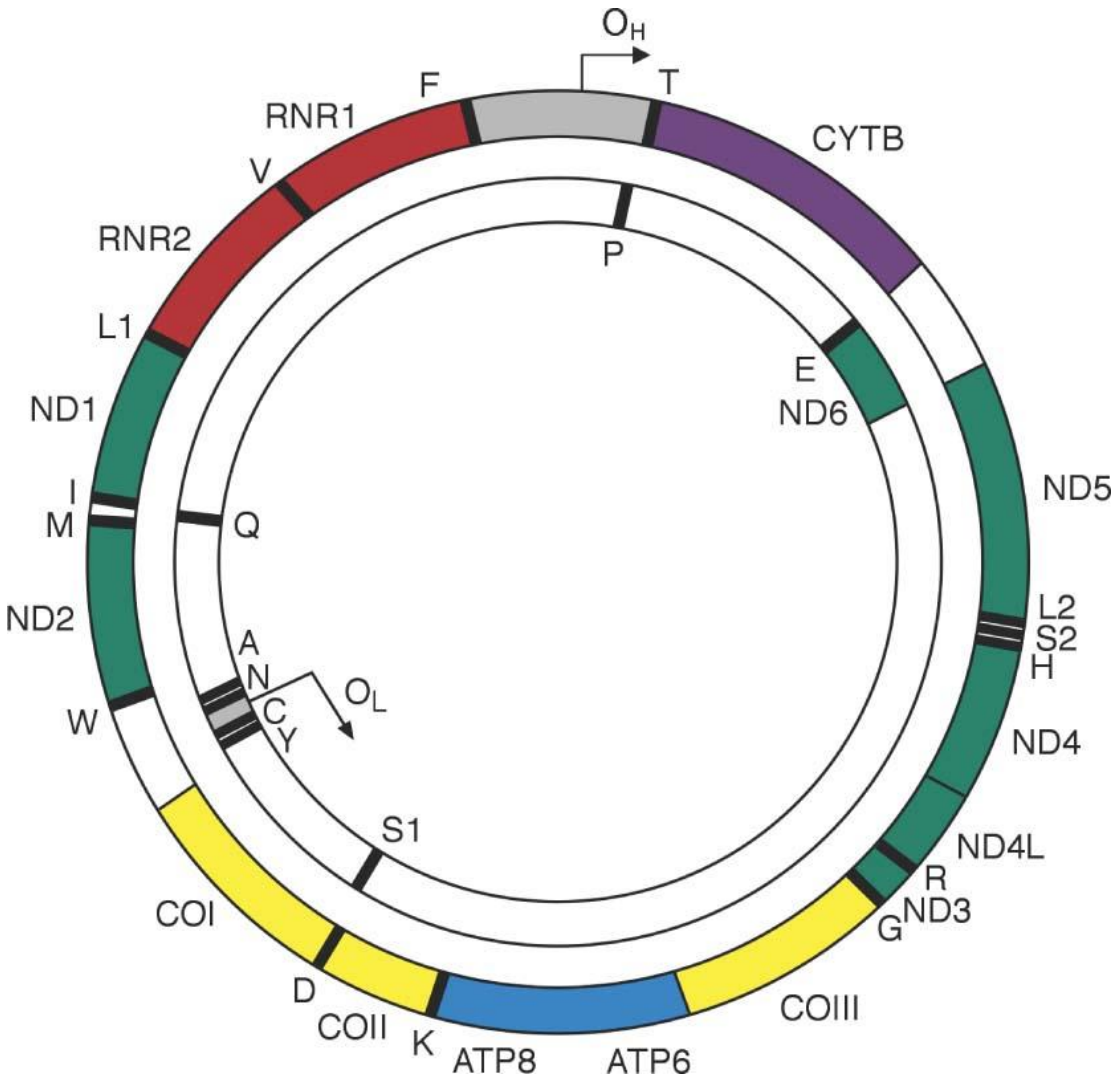
My talk

- Brief background on mtDNA and disease
- What is mitochondrial donation?
- The HFEA and licensing mitochondrial donation
- Ethical objections
- Scientific assessment – safety considerations
- Future: alternatives and the wider genetic modification debate



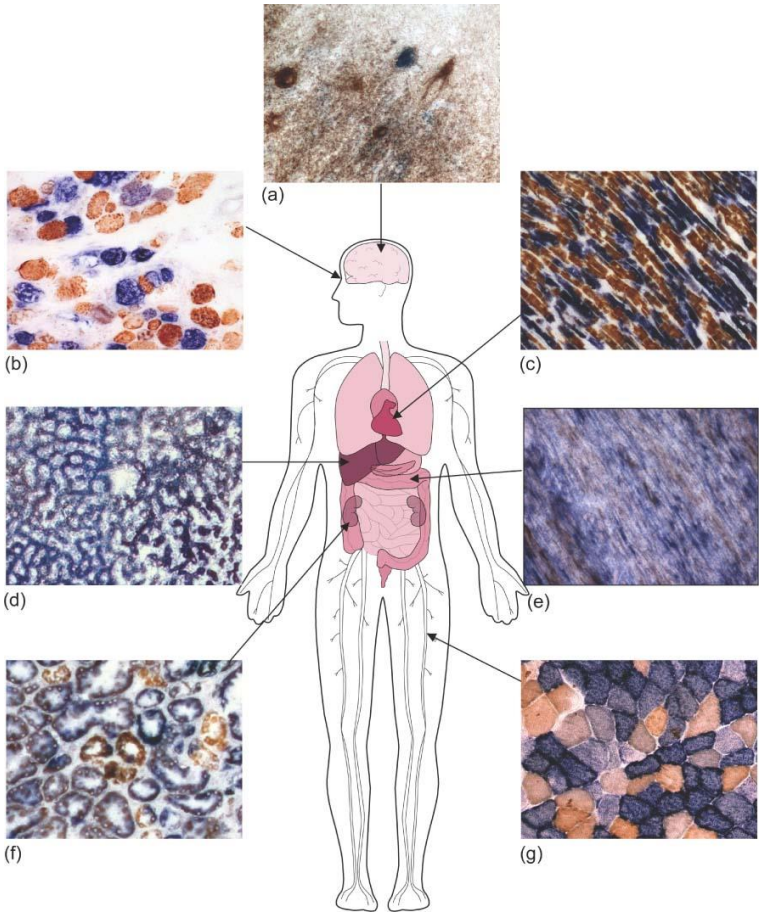
From Smeitink et al (2001) NRG 2: 342-

Mitochondrial DNA (mtDNA)



The Journal of Pathology
Volume 226, Issue 2, pages 274-286, 21 NOV 2011 DOI: 10.1002/path.3028
http://onlinelibrary.wiley.com/doi/10.1002/path.3028/full#fig1

Mitochondrial DNA (mtDNA) and disease



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Options for women with mitochondrial disease who want to have children

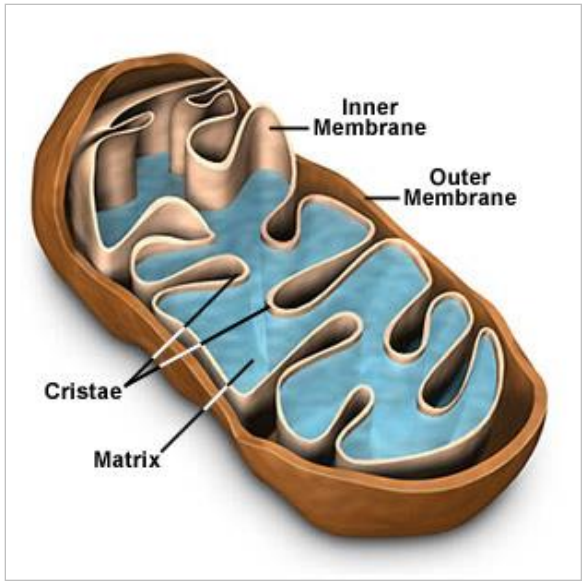
- Do not reproduce
- Adoption
- Egg donation
- Preimplantation genetic diagnosis (PGD)

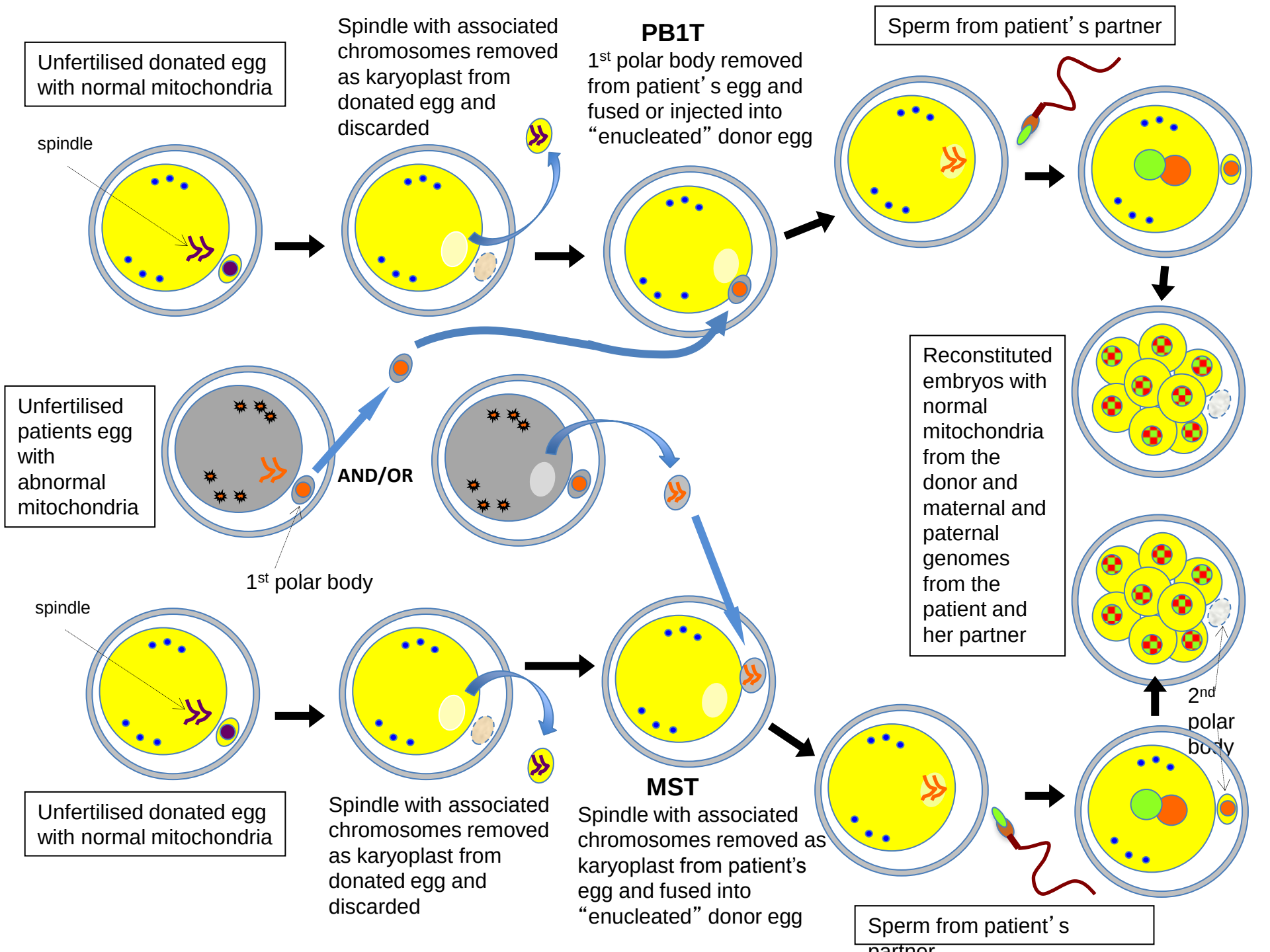
What is mitochondrial donation?

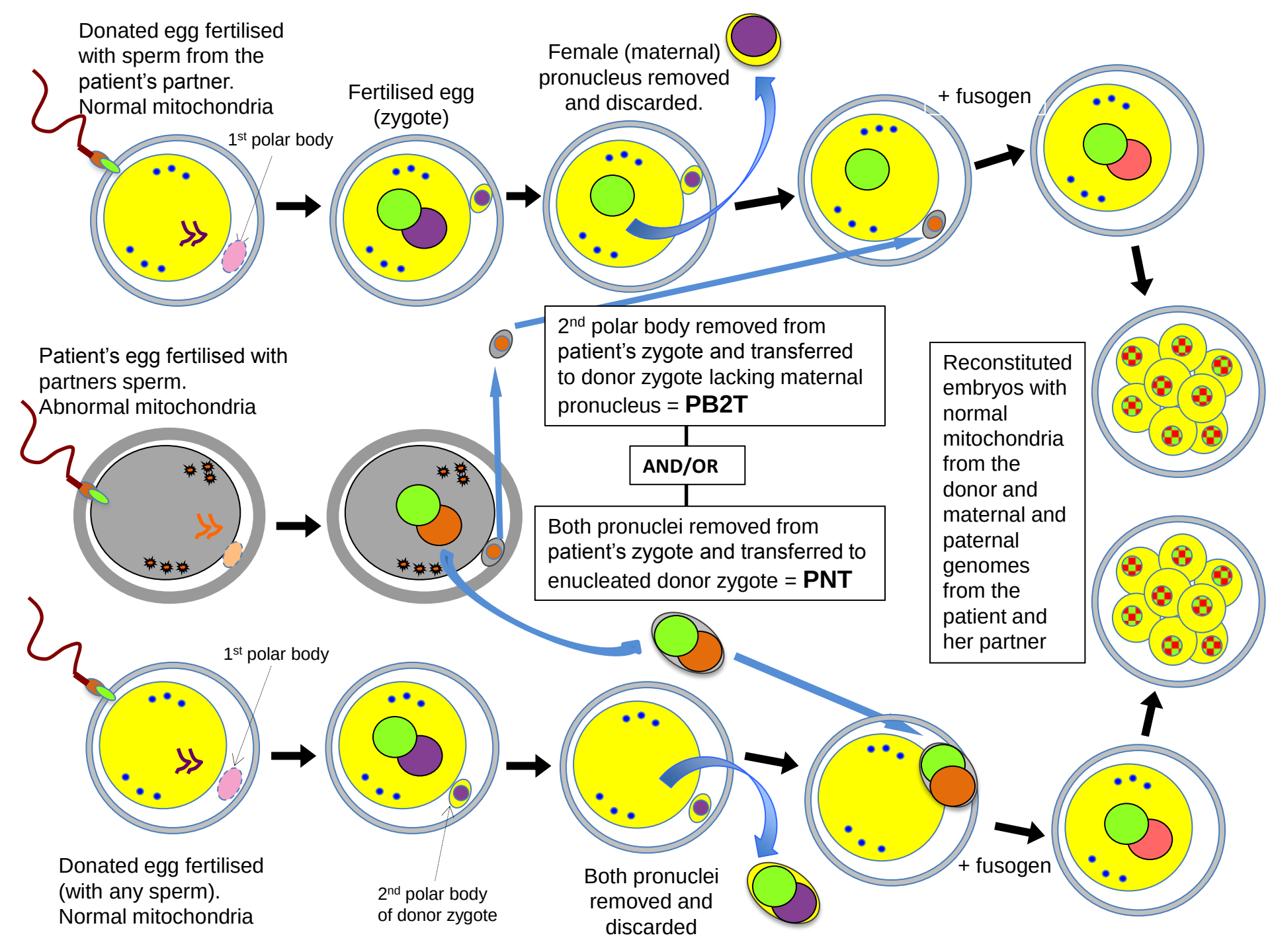
- Mitochondrial disease caused by faults in the small amount of DNA in the mitochondria, inherited from the mother

- Estimated 1 in 5,000 people affected by mitochondrial disease, around 1 in 6,500 children thought to develop serious mitochondrial disorder

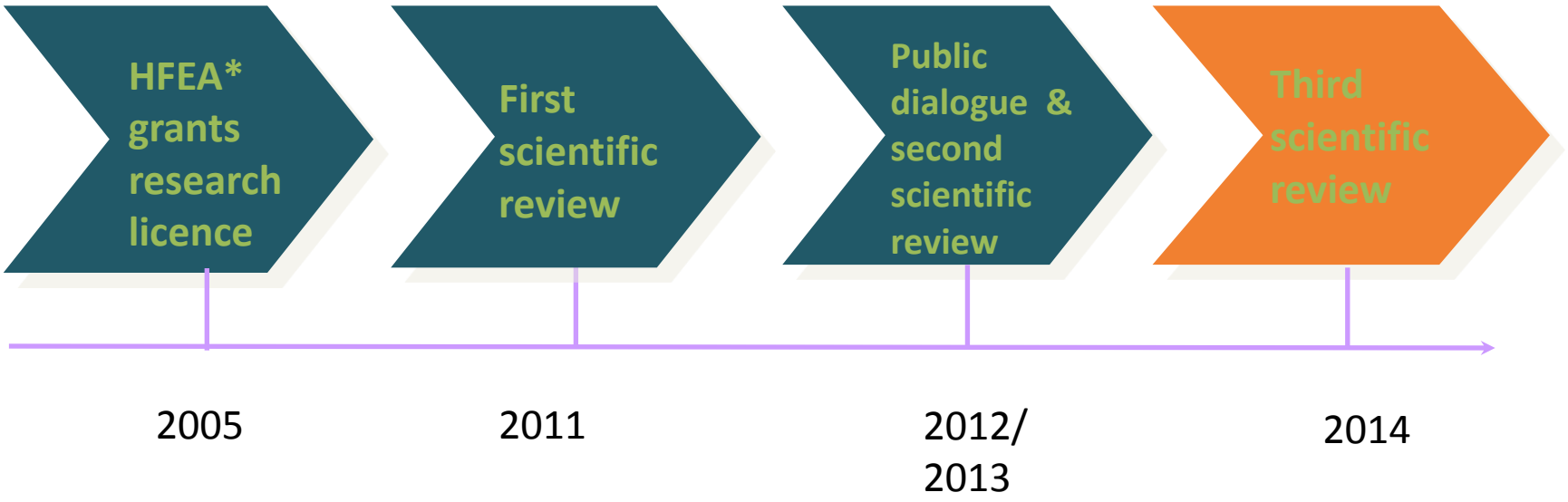
- **Maternal spindle transfer (MST) & pronuclear transfer (PNT)**: techniques to avoid inheritance of affected mitochondria by transferring nuclear material from eggs or early embryos




Unfertilised donated egg with normal mitochondria
spindle
Spindle with associated chromosomes removed as karyoplast from donated egg and discarded
PB1T
1st polar body removed from patient's egg and fused or injected into "enucleated" donor egg
Sperm from patient's partner
Unfertilised patients egg with abnormal mitochondria
AND/OR
1st polar body
Reconstituted embryos with normal mitochondria from the donor and maternal and paternal genomes from the patient and her partner
spindle
2nd polar body
Unfertilised donated egg with normal mitochondria
Spindle with associated chromosomes removed as karyoplast from donated egg and discarded
MST
Spindle with associated chromosomes removed as karyoplast from patient's egg and fused into "enucleated" donor egg
Sperm from patient's partner


Donated egg fertilised with sperm from the patient's partner.
Normal mitochondria
1st polar body
Fertilised egg (zygote)
Female (maternal) pronucleus removed and discarded.
+ fusogen
Patient's egg fertilised with partners sperm.
Abnormal mitochondria
2nd polar body removed from patient's zygote and transferred to donor zygote lacking maternal pronucleus = PB2T
AND/OR
Both pronuclei removed from patient's zygote and transferred to enucleated donor zygote = PNT
Reconstituted embryos with normal mitochondria from the donor and maternal and paternal genomes from the patient and her partner
1st polar body
Donated egg fertilised (with any sperm).
Normal mitochondria
2nd polar body of donor zygote
Both pronuclei removed and discarded
+ fusogen

Timeline



***Human Fertilisation & Embryology Authority (HFEA)**

What did the government ask HFEA to do?

Conduct a **public dialogue exercise** to explore:

- The **ethical aspects** and issues involved in techniques to avoid mitochondrial disease; and

- The **practical implications** of allowing such techniques within regulation

Three reviews on the safety and efficacy of methods to avoid mitochondrial disease (plus addendum on polar body transfer)

An **introductory briefing note** to inform Parliamentary debate

Objections

- **Ethical**

  Women could have children without mitochondrial donation (egg donation, adoption)

  Identity concerns (what does mtDNA contribute?)

  We are effectively experimenting on humans

  We are altering the human germ line – inter-generational justice

  It makes nuclear DNA editing more likely (GM babies)

  Designer babies (slippery slope etc.)

  We are 'playing God'

Nuffield Council on Bioethics - *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review (2012)*

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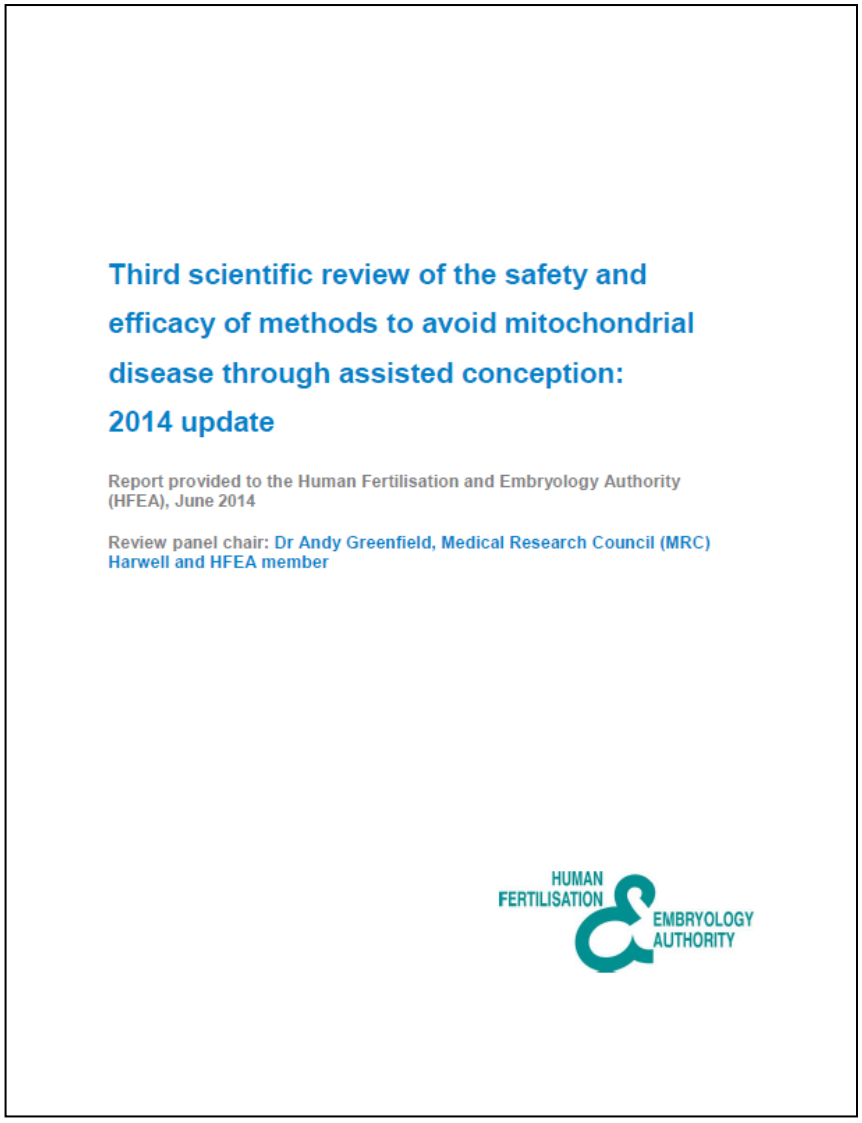
Safety and efficacy

Three reports from the **expert scientific panel**, over three years

The panel concluded that:

- There is **no evidence to demonstrate that mitochondrial donation is unsafe**
- Research is progressing well and the recommended further experiments are expected to confirm this view

http://www.hfea.gov.uk/8807.html



What research has been carried out?

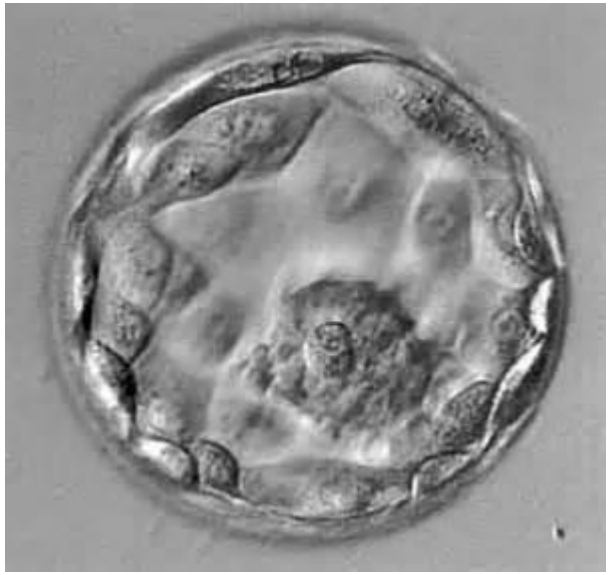
- Many experiments conducted using maternal spindle transfer (MST) and pronuclear transfer (PNT) in animals
- PNT has been carried out since the mid-1980s in mice
- MST has been carried out in a wide range of animals. More recently mice, monkeys and human embryos
- The expert panel concluded that these studies have shown that the techniques are effective and ‘not unsafe’

Mito-nuclear incompatibilities

- Experiments in different model organisms have tested compatibility of mtDNA and nuclear DNA
- Panel felt that these experiments were not an adequate reflection of human mitochondrial donation – risks are theoretical – more research required
- However, they recommended consideration of haplogroup matching as a precautionary measure

  - research at time of potential treatment crucial

What further research is needed?



- Panel has recommended further experiments: necessary to the consideration of the safety and efficacy of the technique before treatment is offered. Expects such research to support the conclusions is has reached so far.

- Main research: observe embryonic stem (ES) cells derived from embryos created by MST and PNT, to examine how mitochondria behave after cell divisions.

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DNA from second mothers to help combat 'cruel' health risks

3-parent babies 'safe' to be born

by **NICOLE LE MARIE**

THREE-PARENT babies could be born within two years after watchdogs gave the go-ahead for the controversial IVF method yesterday.

The techniques used in the procedure were 'not unsafe' and 'potentially useful', the Human Fertilisation and Embryology Authority confirmed

But further research, including experiments on human embryos, was needed, it said. So far, only mice and monkeys have been tested.

country to allow it. It is believed only genetic traits, such as eye and hair colour, from the two original parents would be passed on to the baby.

The HFEA's panel concluded that two techniques it reviewed 'had the potential to be useful for all patients with disorders caused by mutated mitochondrial DNA.'

The panel said a 'waiting list' of

Mitochondrial Donation Regulations 2015

- House of Commons debated & approved: 3 February
- House of Lords debated & approved : 24 February
- Regulations officially signed into UK law: 4 March
- Regulations come into force: 29 October

Draft Regulations laid before Parliament under section 45(4) of the Human Fertilisation and Embryology Act 1990, for approval by resolution of each House of Parliament.

DRAFT STATUTORY INSTRUMENTS

2015 No. 0000

HUMAN FERTILISATION AND EMBRYOLOGY

The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015

Made - - - - - ***

Coming into force - - 29th October 2015

These Regulations are made by the Secretary of State in exercise of the powers conferred by sections 3ZA(5) and (6), 31ZA(2)(a), 35A and 45(1) and (3A) of the Human Fertilisation and Embryology Act 1990(a).

A draft of this instrument has been approved by resolution of each House of Parliament pursuant to section 45(4) of that Act.

PART 1

Introductory Provisions

Citation and commencement

1. These Regulations may be cited as the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 and shall come into force on 29th October 2015.

Interpretation

2.—(1) In these Regulations "the Act" means the Human Fertilisation and Embryology Act 1990.

(2) In these Regulations "polar body nuclear DNA" means any nuclear DNA located in a polar body.

(3) In these Regulations a reference to the removal of any nuclear DNA (including polar body nuclear DNA) includes a reference to the removal of any material which is necessarily removed along with that DNA, and such material may include any associated organelles.

(4) For the purposes of these Regulations, the following are to be treated as removed from an egg—

(a) 1990 c. 37. Sections 3ZA(5) and (6), 31ZA(2)(a), 35A and 45(3A) were inserted by sections 3(5), 24, 26 and 30 of the Human Fertilisation and Embryology Act 2008 (c. 22) ("the 2008 Act"). Section 3ZA(6) is cited for the meaning of "prescribed".

Next steps

- Parliament approved Regulations in February 2015 but it will take some time before a clinic can be licensed to offer mitochondrial donation in treatment

- HFEA is designing a licensing process: **safety and efficacy** considerations, **clinic competency** and **case-by-case** approval of patients – ready for Oct 29th and a subsequent license application

- Alternative techniques: Polar Body Transfer (PBT)? Genome editing?

Acknowledgments

Expert Panel

Robin Lovell-Badge

Peter Braude

Paul de Sousa

Anneke Lucassen

Caroline Ogilvie

HFEA

Hannah Verdin

Joanne Anton

Juliet Tizzard

Peter Thompson

Nuffield Council on Bioethics

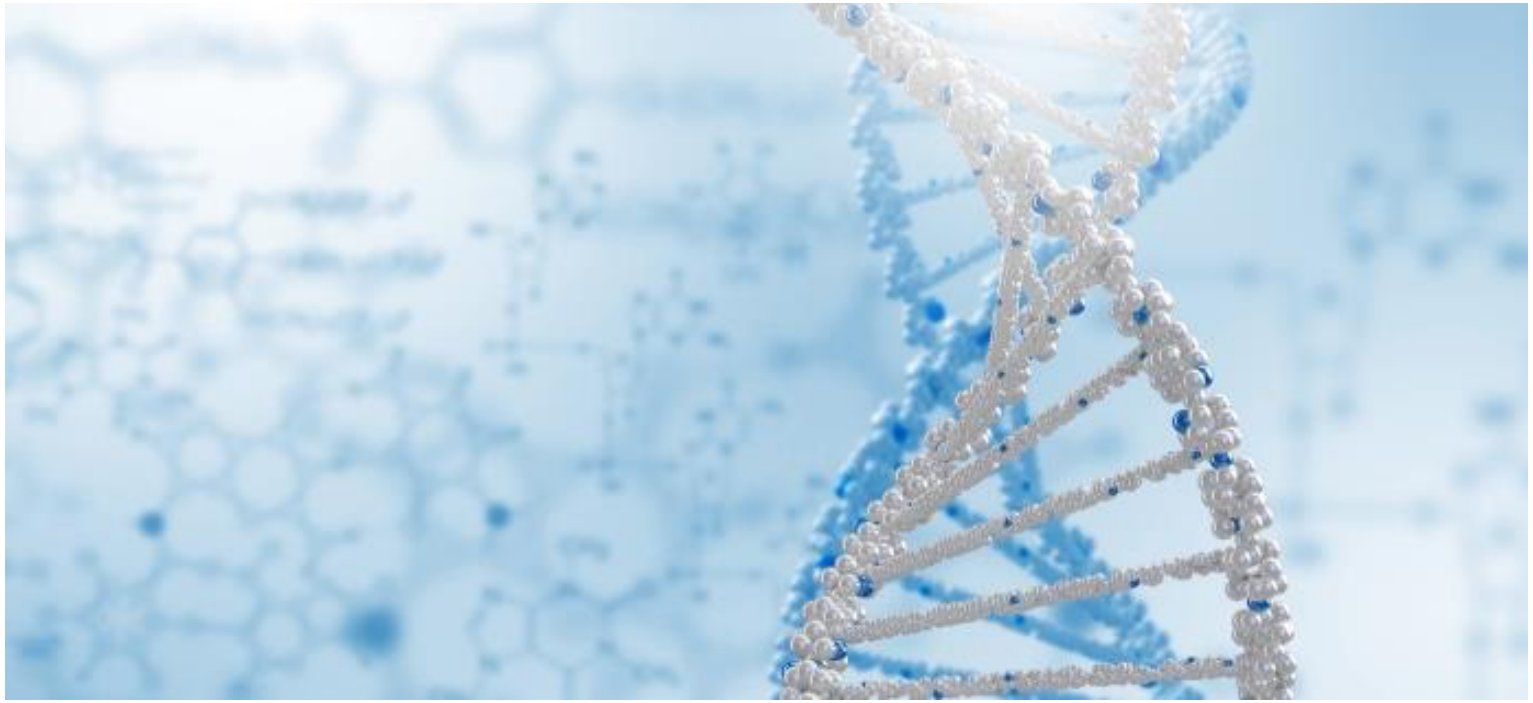
Peter Mills

Bettina Schmietow

Hugh Whittall

Jonathan Montgomery

Nuffield Council on Bioethics: Working Group on Ethical Issues Arising From Genome Editing



http://nuffieldbioethics.org/project/genome-editing/