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The clinical introduction of germline editing: what should we learn from earlier reproductive genetic technologies?

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Germline editing: fault line or continuity?



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1970s



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1970s

BRITAIN'S BIGGEST EVENING SALE

Evening News

LATE SPECIAL CITY PRICES

LONDON: THURSDAY JULY 27 1978

Meet Louise, the world's
first test-tube arrival

SUPERBABE



Wide-eyed Louise Brown pictured in hospital 18 hours after she was born. Today she's doing well. See Page Three



LOUISE BROWN

40 YEARS OF IVF



SPECIAL 40TH ANNIVERSARY EDITION OF
MY LIFE AS THE WORLD'S FIRST TEST-TUBE BABY

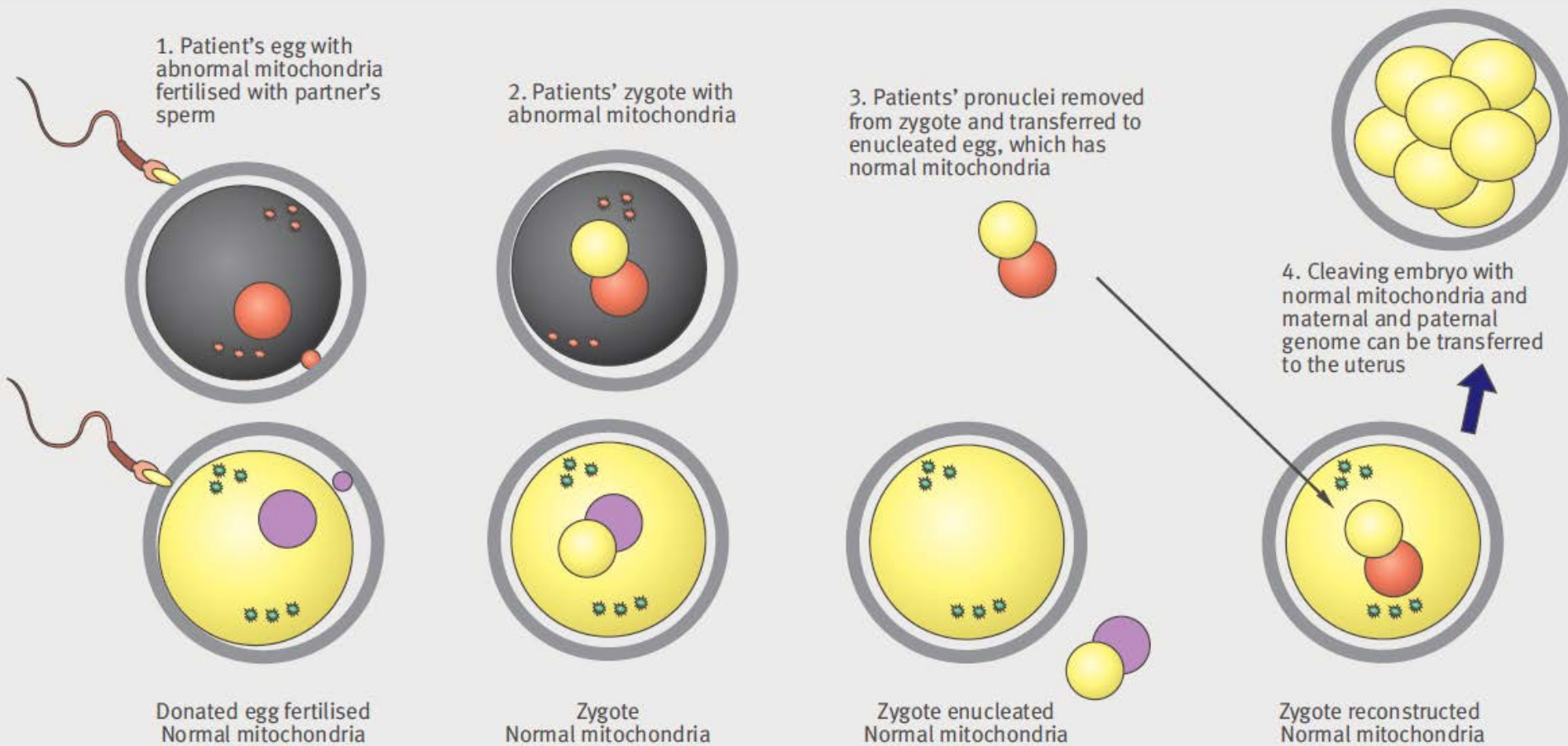
Prenatal diagnosis and screening programs



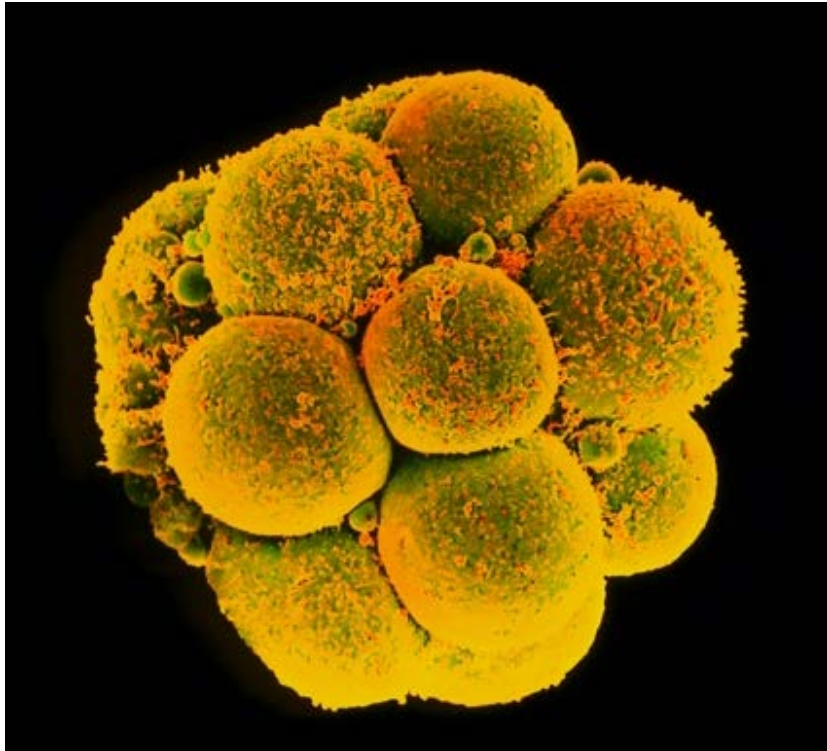
Preimplantation genetic diagnosis



Mitochondrial replacement technologies



Fault line: germline modification (?)



Human embryo day 3





Oviedo Convention (1997)



COUNCIL OF EUROPE

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Details of Treaty No.164

Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine

Title	Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine
Reference	CETS No.164
Opening of the treaty	Oviedo, 04/04/1997 - Treaty open for signature by the member States, the non-member States which have participated in its elaboration and by the European Union, and for accession by other non-member States

Article 13 – Interventions on the human genome

An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.



Morally relevant similarities and differences

PGD

- Selection on multiple traits possible, but limited amount of embryos
- Limited by the genetic material of providers gametes
- Affected embryos are discarded

MRT

- Presumed to alter only 'non-essential' DNA (mtDNA)
- Modification of the mtDNA (but still germline modification)
- Oocyte donor needed
- More risky
- More in line with goals medicine (?)

Embryo modification

- Simultaneously modify several variants: slippery slope? (particularly in combination with IVG)
- More risky
- More in line with goals of medicine (?)

Logical Fallacies: The Slippery Slope



**Aim: to have a healthy,
genetically related child**



ELSEVIER

Reproductive BioMedicine Online

Volume 39, Issue 1, July 2019, Pages 103-110



Article

The relative importance of genetic parenthood

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<https://doi.org/10.1016/j.rbmo.2019.02.008>

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Abstract

Research question

How much do patients with severe [infertility](#) and their gynaecologists value genetic parenthood relative to other key treatment characteristics?

Design

A discrete choice experiment included the following treatment characteristics: genetic parenthood, pregnancy rate, curing infertility, maternal health, child health and costs. The questionnaire was disseminated between 2015 and 2016 among Dutch and Belgian patients with severe infertility and their gynaecologists.

Results

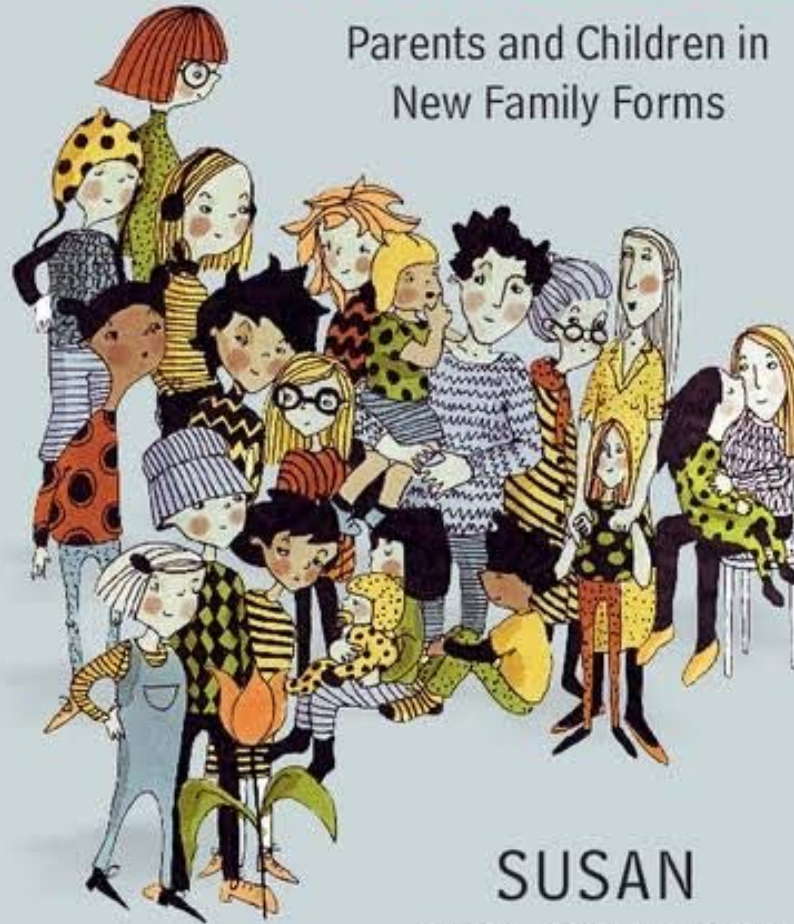
The questionnaire was completed by 173 patients and 111 gynaecologists. When choosing between treatments that varied in safety, effectiveness and costs, the treatment's ability to lead to genetic parenthood did not affect the treatment preference of patients with severe infertility ($n = 173$). Genetic parenthood affected the treatment preference of gynaecologists ($n = 111$) less than all other treatment characteristics. Patients indicated that they would switch to a treatment that did not enable genetic parenthood in return for a child health risk reduction of 3.6%, a cost reduction of €3500, an ovarian hyperstimulation risk reduction of 4.6%, a maternal cancer risk reduction of 2.7% or a pregnancy rate increase of 18%. Gynaecologists made similar trade-offs.

Conclusions

While awaiting replication of this study in larger populations, these findings challenge the presumed dominant importance of genetic parenthood. This raises questions about whether donor gametes could be presented as a worthy alternative earlier in treatment trajectories and whether investments in novel treatments enabling genetic parenthood, like in-vitro gametogenesis, are proportional to their future clinical effect.

MODERN FAMILIES

Parents and Children in
New Family Forms



SUSAN
GOLOMBOK



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Regulation of preimplantation genetic diagnosis

The Dutch situation:

- Regulation PGD 2009
- Assessment done case by case by an interdisciplinary committee
- Local (all applications) and national committee (only new indications)
- Set of criteria to assess acceptability of PGD:
 1. Seriousness and nature of the disease (high risk of serious harm)
 2. Treatment options
 3. Additional medical criteria
 4. Psychological and moral factors



STAATSCOURANT

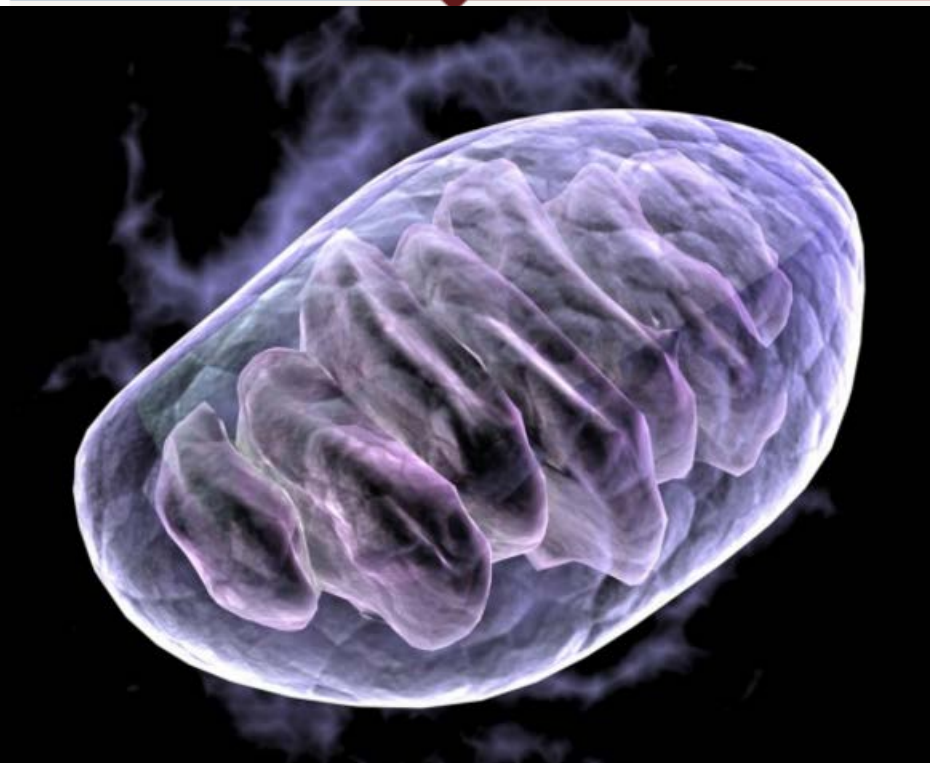
Officiële uitgave van het Koninkrijk der Nederlanden sinds 1814.

Nr. 42

3 maart

2009

Regeling van de staatssecretaris van Volksgezondheid, Welzijn en Sport van 16 februari 2009, nr. CZ-TSZ-2912089, houdende houdende regels ten aanzien van preïmplantatie genetische diagnostiek (PGD) (Regeling preïmplantatie genetische diagnostiek)



U.K. Parliament approves controversial three-parent mitochondrial gene therapy

February, 2015

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Health

MPs say yes to three-person babies

By James Gallagher
Health editor, BBC News website

3 February 2015 | Health |



Public Health Minister Jane Ellison: "This is a bold step"

World's first baby born with controversial new 'three-parent' technique

September 2016

'Hopefully, this will tame the more zealous critics ... and we will witness soon a birth of the first mitochondrial donation baby in the UK'

Ian Johnston Science Correspondent | @montaukian | Tuesday 27 September 2016 14:30 BST | 144 comments



Mitochondrial Replacement Techniques: Remaining Ethical Challenges

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Recent developments in the field of mitochondrial replacement technique (MRT) research and clinical practice have raised ethical concerns worldwide. We argue that the future use of MRTs requires a concerted effort among the global research and clinical community to implement and enforce responsible innovation and governance.



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After the fact—the case of CRISPR babies

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Abstract

The world has been startled by the irresponsible experiment of He Jiankui, who used CRISPR to genetically modify human embryos. In this viewpoint, we explore the phenomenon of moral luck in medicine and its bearing on the limits of simple judgements of the kind “everything that ends well is well” or “someone broke the rules, and is therefore blameworthy”. The risks involved in scientific and medical experiments are often brushed aside, when they turn out well. The clinical application of CRISPR in the human germline is presently too risky to be used without more preclinical research and unacceptable without broader societal support, which justifies the call for a moratorium by the scientific community. However, such policies do not determine how to assess cases, where someone was willing to take such risks beyond all rules, guidelines and regulation and succeeds. The policies including the proposed moratorium are as unanimous about the undesirability of current applications of clinical germline editing as they are about the potential importance of this research. What if this potential is achieved by breaking the rules? The paradox of moral luck impinges on this debate. In our analysis, we rebut simplified judgments and advocate a more balanced view on the relation between moral responsibility and the societal consequences of medicine.

Conclusions: what should we learn from earlier reproductive genetic technologies?

- Germline editing as a next step in line, not a complete fault line
- Many similarities in the ethics debate regarding reproductive genetic technologies
- Germline modification in combination with IVG: slippery slope?
- Genetic parenthood is not a necessary condition for happy parenthood
- Regulatory framework for PGD as an example
- Countries with prudent policies towards MRT are not the countries that pioneered
- First applications of MRT are example how NOT to innovate
- No slippery slope in embryo legislation: countries with most permissive policies are not the countries where MRT and germline editing is pioneered
- International guidelines for clinical translation of reproductive genetic technologies needed (similar to WMA Declaration of Helsinki)

Thank you!



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