

Briefing Overview

- Study context
- Ethical analysis
- Recommendations
- **Webcast participants:** submit questions to the committee for the Q&A to immediately follow at mitoethics@nas.edu.

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

3

The slide features a decorative header with three colored circles (purple, green, blue) to the left of the title. The background is a light green gradient.



Study Context

- MRT could potentially prevent transmission of mtDNA diseases from mother to child
- But the techniques raise safety as well as social, ethical, and policy concerns
- Several countries considering whether to permit MRT, and how to regulate the techniques, with the UK farthest along
- FDA held Advisory Committee meeting in February, 2014 to discuss the state of the science, but was not charged with addressing ethical, social, or policy considerations



Study Context

- Requested by FDA
- Committee with diverse expertise and perspectives, balanced
- Peer review following the Academies' process



Charge to the IOM Committee

- Consider ethical, social, and policy issues raised by MRT
- Assess whether it is ethically permissible for clinical investigations of MRT to proceed
- If permissible, articulate the circumstances and conditions under which clinical investigations of MRT might be conducted ethically



IOM Committee Members

JEFFREY KAHN (Chair), Johns Hopkins Berman Institute of Bioethics
JEFFREY BOTKIN, University of Utah
DAVID CHAN, California Institute of Technology
R. ALTA CHARO, University of Wisconsin at Madison
JAMES CHILDRESS, University of Virginia
ALAN DECHERNEY, National Institute of Child Health and Human Development,
 National Institutes of Health
MARNI FALK, The Children's Hospital of Philadelphia and University of
 Pennsylvania Perelman School of Medicine
JONATHAN KIMMELMAN, McGill University
ANNA MASTROIANNI, University of Washington
VAMSI MOOTHA, Harvard Medical School and Howard Hughes Medical Institute
LAURIE STRONGIN, Hope for Henry Foundation
KEITH WAILOO, Princeton University

Mitochondrial biology and genetics

Mitochondria: subcellular, cytoplasmic organelles important for cellular energy production

- Also regulate other cellular functions, such as: calcium homeostasis, apoptosis, metabolism

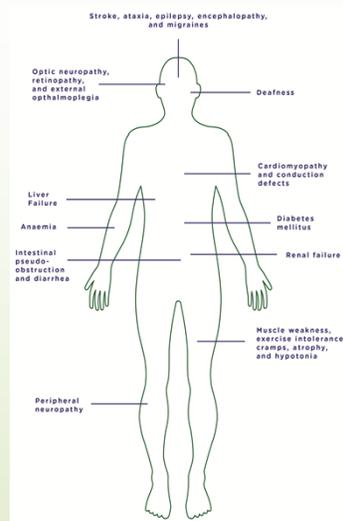
Mitochondria contain own extracellular genome (mtDNA)

- Circular chromosomes nDNA: linear
- 37 coding genes nDNA: 20-30,000
- 100-10,000 copies per cell nDNA: 2 of each chromosome
- Maternal inheritance nDNA: biparental
- Can exhibit heteroplasmy (state in which a cell, tissue, or individual contains more than one type of mtDNA genotype)

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

8

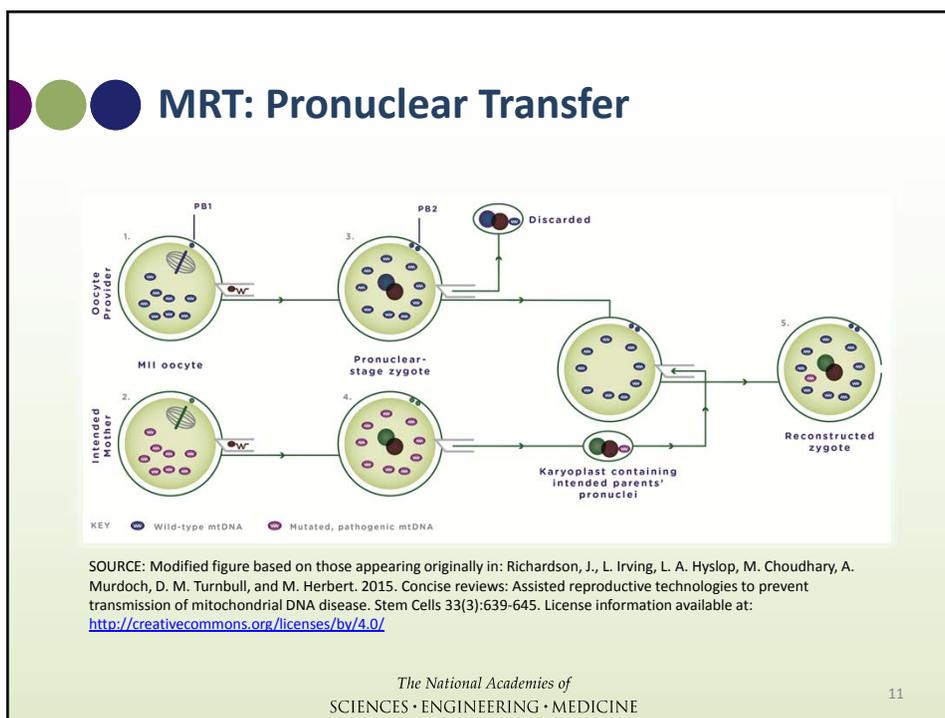
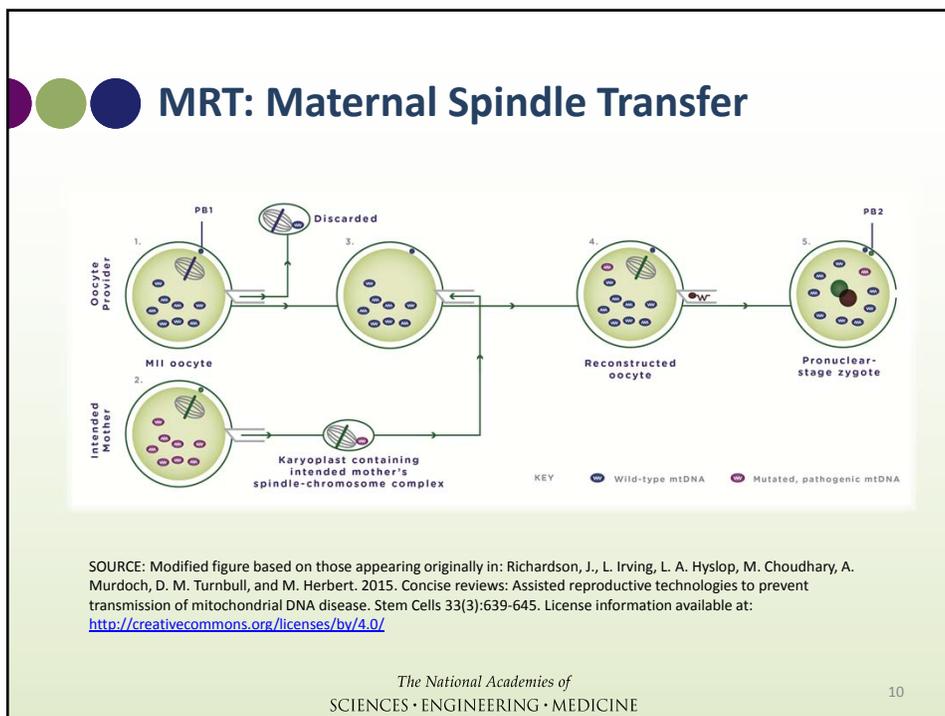
mtDNA Disease



Source: Adapted by permission from Macmillan Publishers Ltd: NATURE REVIEWS GENETICS, copyright 2005.

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

9





MRT vs. “Gene Editing”

- MRT involves replacement of whole, intact, naturally occurring mtDNA within mitochondria rather than targeted genomic editing
- MRT replaces mtDNA by replacing entire mitochondria organelles. In contrast, gene editing technologies such as CRISPR-Cas9 edit genes within either nDNA or mtDNA
- MRT manipulates germ cells (oocytes or zygotes). In contrast, CRISPR-Cas9 could be employed in either germ cells or somatic cells



Ethical Analysis

Demand for MRT

- Parental desire for offspring sharing a nuclear DNA connection with both parents is widely held (but not universal)
- Not all goals of prospective parents are met by present alternatives
 - Unassisted sexual reproduction, PGD
 - Oocyte and embryo donation, adoption, childlessness
- Desire to access MRT can justify proceeding with clinical trials, subject to limits focused on protecting the health and well-being of the future children



Ethical Analysis

Identity, Kinship, and Ancestry

- Genetic contributions from two women of different maternal lineage would introduce complexities that might affect the child's experiences of identity, kinship, or ancestry
- A matter for reflection by families undertaking MRT and societal discussions
- The complexities alone are not sufficient to justify prohibiting initiating MRT clinical investigations



Ethical Analysis

Genetic modification of germ cells and the germline

- MRT results in genetic modification of germ cells
 - MRT producing female offspring would constitute heritable genetic modification (germline modification)
 - MRT producing male offspring would not constitute heritable genetic modification because the modifications would not be passed down



Ethical Analysis

Genetic modification of germ cells and the germline

- Some cite concerns about genetic modification of germ cells
 - Safety
 - Interference with nature/“playing God”
 - Eugenics/attitudes towards disability
 - Crossing the germline
- Concerns about human genetic modification or germline modification warrant significant caution and the imposition of restrictions rather than a blanket prohibition on MRT to prevent transmission of serious mtDNA disease



Ethical Analysis

Distinctions – modification of mtDNA vs nDNA

- Replacement of whole, intact, and naturally occurring mitochondrial genome
- Traits carried in nDNA are those that in the public understanding constitute the “core” of genetic relatedness
- While energetic “enhancement” to improve the function of mtDNA with regard to increased cell energy might hypothetically be possible through MRT, this appears to be far more speculative relative to modification of nDNA
- These distinctions do not imply that mtDNA is unimportant but that its modification is meaningfully different from that of nDNA



Ethical Analysis

Other Considerations

- Manipulation of embryos: Useful ethical frameworks exist that could inform appropriate boundaries of embryo manipulation in MRT investigations
- Equitable access: Potential for differential access by high-SES individuals is not a reason to abandon MRT development, but important to pay attention to the challenge of reaching individuals who might benefit, regardless of SES



Ethical Analysis

Other Considerations, cont'd

- Expanded applications:
 - Differences between mtDNA and nDNA, and the nature of the replacement techniques, help circumscribe applications and provide natural limits on the potential for misuse.
 - Regulations and guidelines are needed to limit the use of MRT to the prevention of transmission of serious, life-threatening mtDNA diseases and to prevent slippage into applications that raise other serious and unresolved ethical issues



Ethical Analysis

Conclusion

- Ethical, social, and policy issues can be avoided through limitations on the use of MRT or are blunted by the significant and important distinctions between genetic modification through MRT and modification of nDNA
- It is ethically permissible to conduct MRT clinical investigations
- Conditions and principles are needed



Laws and Regulation

Limitations on funding for research

- Dickey-Wicker
- NIH policy limits

Restrictions on whether it can be done in research or practice

- State laws
- FDA regulations

Quality control

- FDA regulations
- State level control
- Professional society guidelines



Initiating human clinical investigations

Conditions for initial MRT clinical investigations:

- Initial safety is established; risks to all parties are minimized with consideration of minimizing risk to future children of highest priority
- Likelihood of efficacy is established by preclinical research
- Limited to women at risk of transmitting serious mtDNA disease; mutation's pathogenicity is undisputed; and disease is predicted to be severe
- Initially, to reduce the risk of adverse effects being realized by multiple generations, uterine transfer is limited to male embryos



Additional conditions for investigations

- If the intended mother will carry the pregnancy, medical determination that she would be able to complete a pregnancy without significant risk of serious adverse health consequences
- Clinical investigations limited to investigators and centers with demonstrated expertise and skill
- FDA reviews rationale and plan for mtDNA haplogroup matching, and if compelling, considers it as a means of mitigating possible risk of mtDNA–nDNA incompatibilities



Principles for a cautious approach

FDA should ensure that design and conduct of all MRT clinical investigations adhere to the following:

- Health and well-being of any future children born as a result of MRT protocols have priority in the balancing of benefits and risks
- Study designs should be standardized to the extent possible to enable comparisons and pooling
- Data from research or clinical practices outside FDA jurisdiction should be incorporated into FDA's analysis



Principles for a cautious approach, cont'd

- Clinical investigations should also collect long-term information regarding health, psychological, and social effects on children conceived as a result of MRT, including their perceptions about their identity, ancestry, and kinship



Ethical provenance of data

- Regulatory authorities should ensure the ethical provenance of preclinical or clinical data submitted to FDA in support of an IND
- Nonviable human embryos should be used when possible for preclinical research
- When not possible, viable human embryos should be used only when required in the interest of developing science to minimize risks to children
 - Even then, embryos should be used only in the smallest numbers and at the earliest stages of development consistent with scientific criteria for validity



Ethically permissible expansion of MRT clinical research to female embryos

FDA could consider extending clinical research to include transfer of female embryos if:

- Clear evidence of safety and efficacy from male cohorts, using identical MRT procedures, were available
- Preclinical animal research shows evidence of intergenerational safety and efficacy
- Decision is consistent with outcomes of other deliberations to establish a shared framework concerning heritable genetic alterations, such as the use of gene editing



Informed consent

Need for special attention to communicating the novel aspects of MRT research to potential research participants

Consent for:

- Gamete providers should reflect:
 - range of contemplated MRT procedures and ethical, social, and policy considerations
 - management of incidental findings
 - appropriate compensation
 - prospect of future contact with children
 - management of residual eggs and embryos



Informed consent, cont'd

Consent for:

- Intended parents should reflect:
 - information on the research protocol
 - focus on implications for children's health and well-being
 - alternative ways of becoming parents that can avoid maternal transmission of mtDNA disease
 - management of and potential restrictions on access to embryos created through MRT
 - preimplantation and prenatal genetic diagnostic tests
 - importance of long-term follow-up
 - potential challenges of maintaining patient privacy



Informed consent, cont'd

Consent process for:

- Children conceived as a result of MRT should reflect assent (and eventual consent) for monitoring and research procedures to be performed after birth, up to and including seeking informed consent from the children for continued research study follow-up upon their reaching the legal age of consent



Guiding principles for oversight

- Transparency
 - Timely public sharing of information
 - Encourage sponsors to commit to depositing protocols and deidentified results in public databases
- Public engagement – Exploration of stakeholder views including public meetings
- Partnership – Collaborate with other regulatory authorities
- Maximizing data quality – Enable cross-referencing and pooling of data

Guiding principles for oversight, cont'd

- Circumscribed use
 - FDA should use the means at its disposal to limit the use of MRT to the indications, individuals, and settings for which it is approved
 - Engage the public in a fresh ethical analysis of any decision to broaden the use of MRT
- Long-term follow-up – Require that sponsors design, fund, and commit to long-term monitoring of children

Resources

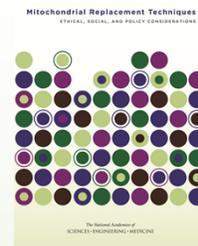
Report and Additional Resources are available for download:

www.nas.edu/mitoDNAethics

Email: mitoethics@nas.edu

Twitter: #mitoethics #mitochondrialreplacement

Note: A public meeting will be held **March 21, 2016** to discuss the report's findings, conclusions, and recommendations with stakeholders. Public registration will be available at the above link.





Resources

IOM staff:

Anne Claiborne, J.D., M.P.H. (Study Director)
Senior Program Officer
Board on Health Sciences Policy
Institute of Medicine
aclaiborne@nas.edu
(202) 334-2715

Rebecca English, Program Officer
Morgan Stathem, Associate Program Officer
Michael Berrios, Senior Program Assistant
Andrew Pope, Director, Board on Health Sciences Policy

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

34



Thank You

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

35