

# Clinical investigations of MRT are 'ethically permissible' if conditions met

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Conducting clinical investigations of mitochondrial replacement techniques (MRT) in humans is ethically permissible as long as significant conditions and principles are met, says a new report from the National Academies of Sciences, Engineering, and Medicine. One of those conditions, among many laid out in the report, is that initial MRT clinical investigations should be limited to women who are at risk of transmitting a severe mitochondrial genetic disease that could lead to a child's early death or substantial impairment. Another is that in initial clinical investigations only male embryos created through MRT should be allowed to be placed in a woman for a possible pregnancy. The recommended restriction is predicated not on selection of one sex over another, but on the need to proceed carefully and to prevent potential adverse and uncertain consequences of MRT from being passed on to future generations. The committee that conducted the study and wrote the report stressed that when balancing the benefits and risks of MRT clinical investigations, the primary consideration is minimizing the risk of harm to the child born as a result of the techniques.

While not currently conducted in humans in the United States, mitochondrial replacement techniques hold the potential to significantly reduce the risk of transmitting serious and at times fatal mitochondrial DNA diseases from mother to child, but the techniques also raise many concerns. Mitochondria are found in almost every cell of the body and produce energy for cells. Mitochondrial disease, sometimes caused by mutations in mitochondrial DNA, occurs when the mitochondria fail to produce enough energy for cells or organs to function properly. All

people have two types of DNA - nuclear DNA that encodes our traits and is found in the nucleus of a cell and mitochondrial DNA found in mitochondria. MRT would remove nuclear DNA from the egg of a woman affected by mitochondrial DNA disease and transfer it to an egg free of nuclear DNA provided by a woman with normal mitochondria. As mitochondria are inherited solely from the mother, this would, in theory, prevent transmission of mitochondrial DNA disease from the at-risk woman to her child. Children born as a result of MRT would have genetic material from three individuals: nuclear DNA from one man and one woman and mitochondrial DNA from another woman. The committee concluded that the combination of nuclear and mitochondrial DNA created by MRT results in heritable genetic modification, often termed germline modification. However, since mitochondrial DNA is only passed from women to their offspring, the genetic modification introduced by MRT would be heritable only in female children born through the process of MRT.

"In examining the ethical, social, and policy issues associated with mitochondrial replacement techniques, we concluded that the most germane issues could be avoided if the use of these techniques were restricted by certain conditions, rather than prohibiting them altogether," said Jeffrey Kahn, chair of the committee and the Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy at The Johns Hopkins Berman Institute of Bioethics in Baltimore. "Although MRT would not treat a person with a [mitochondrial disease](#), its pursuit could satisfy prospective parents' desire to bear genetically related offspring with a significantly reduced risk of passing on mitochondrial disease. The limitations on MRT that we propose focus on protecting the health and well-being of children born as a result of the techniques."

The committee recommended that initial MRT clinical investigations should be considered by the U.S. Food and Drug Administration only if and when several conditions are met, including limiting clinical

investigations to women who are at risk of passing on a serious mitochondrial disease to her offspring, where the mitochondrial DNA's mutation is known to cause disease, and clinical presentation of the disease is predicted to be severe by causing early death or substantial impairment in the child.

Another recommended restriction is allowing only male embryos to be transferred to a woman for a possible pregnancy during initial clinical investigations. Because of the scientific uncertainties associated with these novel techniques and because MRT in female embryos would result in germline modification - meaning the changes would be heritable and thus appear in any children that resulted from the technique as well as succeeding generations - a cautious approach is required, the committee said. Preclinical research to study intergenerational effects of MRT could continue while MRT allows some families to have male children with a significantly reduced risk of being born with a mitochondrial disease.

Following successful initial investigation of MRT in male embryos, FDA could consider extending MRT research to include the transfer of female embryos if clear evidence of safety and efficacy from male cohorts using identical MRT procedures is available, even if it takes a long period of time to collect this evidence. In addition, preclinical research in animals has to show evidence of intergenerational safety and efficacy, and FDA's decision should be consistent with the outcome of public and scientific deliberations to establish a shared framework concerning the acceptability of and moral limits on heritable genetic modification.

Additional conditions for initial MRT clinical investigations are:

- initial safety is established and risks to all parties directly involved in the proposed clinical investigations are minimized, although minimizing risk to future children should be of highest

- priority;
- the likelihood of efficacy is established by preclinical research using in vitro modeling, animal testing, and testing on human embryos as necessary;
  - if the intended mother at risk of transmitting mitochondrial disease also desires to carry the pregnancy, it is determined by professional opinion that she is able to complete a pregnancy without significant risk of serious adverse consequences to her health or the health of the fetus;
  - clinical investigations are limited to investigators and centers with demonstrated expertise in and skill with the relevant techniques; and
  - FDA has reviewed the science surrounding matching the mitochondrial DNA subtype of the egg provider with that of the intended mother and if compelling, has considered such matching as a means of mitigating the possible risk of incompatibility that could arise from combining the egg provider's mitochondrial DNA with the nuclear DNA of the intended mother.

The committee also recommended that nonviable human embryos be used in preclinical research when possible. When not possible, viable human embryos, which would not be placed in a woman, should be used in preclinical research, but only when required in the interest of developing the science necessary to minimize risks to children born as a result of MRT, and even then, only in the smallest numbers and at the earliest stages of development consistent with scientific criteria for validity.

The informed consent of research participants in MRT clinical investigations should be required pursuant to federal guidelines and applicable state laws and institutional practices. Best-practice consent processes should be followed for individuals who provide reproductive

cells, and for intended parents. For children born as a result of MRT, consent processes should include assent for monitoring and research procedures to be performed after birth, when of appropriate age, and include seeking informed consent from the children upon their reaching the legal age of consent.

The committee also recommended adherence to several principles for oversight of MRT investigation and future clinical use, including transparency, public engagement, partnership, data quality maximization, circumscribed use of MRT, and long-term follow-up.

The study by the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine was sponsored by the U.S. Department of Health and Human Services' Food and Drug Administration. The Academies are private, nonprofit institutions that provide independent, objective analysis and advice to the nation to solve complex problems and inform public policy decisions related to science, technology, and medicine. They operate under an 1863 congressional charter to the National Academy of Sciences, signed by President Lincoln. For more information, visit <http://national-academies.org>.

Provided by National Academy of Sciences

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