Mitochondrial Replacement Techniques

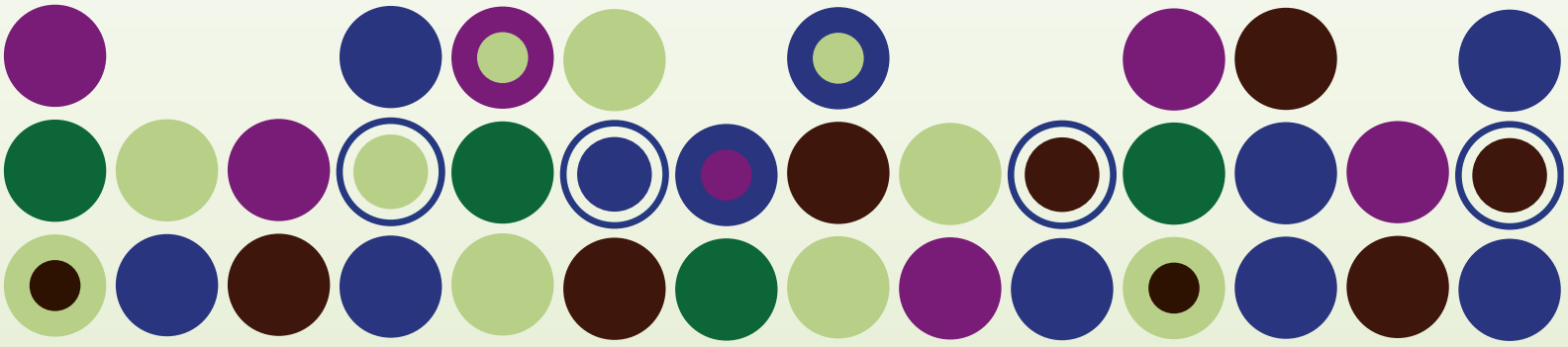
CONDITIONS AND PRINCIPLES FOR THE CONDUCT AND OVERSIGHT OF POTENTIAL MRT INVESTIGATIONS

Mitochondrial replacement techniques (MRT) are designed to prevent the transmission of mitochondrial DNA (mtDNA) diseases from mother to child, but the techniques raise ethical, social, and policy issues. In the Institute of Medicine report *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations,* an expert committee concludes that it is ethically permissible to conduct clinical investigations of MRT subject to certain conditions and principles. This action guide is intended for those who may plan to conduct or oversee potential MRT investigations and lays out the conditions and principles offered by the committee to guide the conduct and oversight of these investigations. Selected material from five of the report's recommendations is presented below. For the complete text of the recommendations, and to read the full report, please visit nas.edu/MitoDNAEthics.

Conditions for ethical MRT first-in-human clinical investigations

The committee recommends that FDA only consider initial MRT clinical investigations if and when certain conditions can be met, including:

- limiting initial investigations to women who otherwise are at risk of transmitting a serious mtDNA disease, where the mutation's pathogenicity is undisputed and the clinical presentation of the disease is predicted to be severe, as characterized by early mortality or substantial impairment of basic function;
- confirming that if the intended mother at risk of transmitting mtDNA disease is also the woman who will carry the pregnancy, professional opinion determines that she would be able to complete a pregnancy without significant risk of serious adverse consequences to her health or the health of the fetus;
- limiting intrauterine transfer for gestation to male embryos in initial clinical investigations; and
- ensuring that only investigators and centers with demonstrated expertise in and skill with relevant techniques are used in initial investigations. (See Recommendation 1 in full report for complete text.)



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Ensuring the ethical provenance of preclinical or clinical data

The committee also recommends that in light of concerns about the oocyte procurement and embryo manipulations necessary for MRT preclinical and clinical research, regulatory authorities should ensure the ethical provenance of preclinical or clinical data submitted to FDA in support of an Investigational New Drug (IND) application. To the extent possible, regulatory authorities should ensure that sponsors adhere to ethical standards comparable to those developed by the U.S. National Academies of Sciences, Engineering, and Medicine (the Academies), the U.S. National Institutes of Health (NIH), and the International Society for Stem Cell Research (ISSCR). In preclinical research, nonviable human embryos should be used when possible. When use of nonviable embryos is not possible, viable human embryos should be used 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. (See Recommendation 2 in full report for complete text.)

Principles for a cautious approach

If the conditions for ethical MRT first-in-human clinical investigations are met, FDA should ensure that the design and conduct of initial and subsequent clinical investigations of MRT adhere to the following principles and practices:

- the health and well-being of any future children born as a result of MRT protocols should have priority in the balancing of benefits and risks in clinical investigations;
- study designs of MRT protocols should be standardized to the extent possible to enable valid comparisons and pooling of outcomes across groups;
- data from research or clinical practices outside FDA jurisdiction should be incorporated into FDA's analysis; and
- clinical investigations should collect long-term information regarding psychological and social effects on children born as a result of MRT, including their perceptions about their identity, ancestry, and kinship. (See Recommendation 3 in full report for complete text.)

Informed consent

The informed consent of those deemed research participants in MRT clinical investigations would be required pursuant to federal guidelines and applicable state laws and institutional practices. The committee concludes that the nature of the MRT consent process for intended parents would need to reflect a research protocol that had been crafted with the health and well-being of future children in mind. In addition, best-practice consent processes should be followed for individuals who provide gametes, and the informed consent process for MRT should reflect the novel aspects of the technique to be employed. (See Recommendation 5 in the full report for complete text.)

Long-term follow-up and monitoring

The committee recommends that FDA's overall plan for review and possible approval and subsequent marketing of MRT should include a requirement that sponsors design, fund, and commit to long-term monitoring of children born as a result of MRT, with a plan for periodic review of the long-term follow-up data. (See Recommendation 6 in the full report for complete text.)

To read the full report and to view related resources, please visit nas.edu/MitoDNAEthics.

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