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INSTITUTE OF MEDICINE

Committee on Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases

Background

Mutations in mitochondrial DNA can cause serious diseases that are in some cases fatal. Researchers have proposed transferring the nuclear genetic material from the eggs or zygotes of a woman affected with mitochondrial disease caused by mutations in mitochondrial DNA to an egg or zygote of a woman with normal mitochondria. As mitochondria are inherited solely from a mother through her eggs, this would in theory prevent maternal transmission of mitochondrial disease from the affected woman to her children. These modifications of eggs and zygotes would allow affected women to have genetically related children without passing on their mutant mitochondrial DNA. However, these children would have nuclear DNA from one man and one woman and mitochondrial DNA from another woman. Thus, any children born to women as a result of these methods would have DNA from three individuals. These procedures constitute forms of heritable genetic modification because the changes in mitochondrial DNA will affect not only these children but also may be passed on to future generations. As such they may also be considered heritable “germline” modification, although the nuclear genetic material is not altered in these procedures.

The Food and Drug Administration (FDA) regulates gene therapy products and human tissue, including reproductive tissue, intended for transfer into humans. An FDA Advisory Committee (AC) met on February 25 and 26, 2014, to discuss the science regarding assisted reproductive methods involving genetic modification of eggs and zygotes for the prevention of mitochondrial disease. Consistent with FDA’s role in human subject protection, the AC discussion also focused on issues involving potential future clinical trials and on the risks for individual study participants and for any children that are born to women as a result of such studies. Broader ethical and social policy issues were outside the scope of the discussion; however, some of the written and oral public comments at the meeting focused on these issues. FDA has requested that the Institute of Medicine produce a consensus report regarding the ethical and social policy issues related to genetic modification of eggs and zygotes to prevent transmission of mitochondrial disease.

Statement of Task

An ad hoc committee of the Institute of Medicine will conduct a study to develop a report that will inform FDA in consideration of review of applications in the area of genetic modification of eggs and zygotes for the prevention of mitochondrial disease specific to mitochondrial DNA. These

include maternal spindle transfer, pronuclear transfer, and polar body transfer but could also encompass other technologies not currently proposed.

The development of novel techniques in this area raises complex ethical and social policy issues, including:

- Whether manipulation of mitochondrial content should be considered germline modification (defined as human inheritable genetic modification) in the same way and with the same social and ethical implications as germline modification of nuclear DNA, or whether, from a social and ethical perspective, it should be viewed differently from germline modification of nuclear DNA.
- The implications of manipulating mitochondrial content both in children born to women as a result of participating in these studies and in descendants of any female children.
- Ethical issues in providing “consent” or “permission” to accept risks on behalf of a child who does not exist.
- Ethical and social issues that arise if a child is born with genetic material from three individuals.

Taking into consideration these ethical and social policy issues, the committee’s report will address the conduct of clinical investigations of these novel techniques, including the foundational question of whether safeguards such as specific measures and public oversight could adequately address the social and ethical concerns, or whether those concerns preclude clinical investigations. In addition, the report will specifically examine:

- The circumstances under which clinical investigations of the technology for the prevention of mitochondrial disease might be conducted ethically, including implications for the concept of “informed consent” and other aspects of the enrollment and tracking of participants during and after the trial.
- Whether, and how, the existence of alternative approaches to prevent the transfer of mitochondrial disease from mother to child (e.g., adoption, egg donation, or preimplantation genetic diagnosis for mitochondrial mutations for which it would be informative) should factor into the assessment of allowing these trials to proceed.
- Whether it is advisable to establish controls that would distinguish between genetic modification to prevent transmission of mitochondrial disease (therapeutic/prevention purposes) and genetic modification to enhance desired traits (enhancement purposes). What controls could be effective at maintaining this distinction, particularly for first in human clinical investigations?

COMMITTEE ROSTER

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ANTICIPATED STUDY TIMELINE - 15 Month Study (+ 4 month dissemination)

October – December 2014: Committee formation

January 2015: Committee meeting 1

March 2015: Committee meeting 2 (incl. 2-day public workshop and 1 day closed session)

May 2015: Committee meeting 3 (incl. 1-day public comment session and 2 day closed session)

July 2015: Committee meeting 4 (2-day closed session)

September 2015: Committee meeting 5 (2-day closed session)

January 2016: Delivery of prepublication copy of final report to sponsor

STUDY STAFF

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STUDY SPONSOR

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