NEBRASKA COALITION FOR ETHICAL RESEARCH

Position Paper

The summary report of the Institute of Medicine's Ad hoc committee, tasked with developing a consensus report regarding ethical, social, and policy considerations related to mitochondrial replacement techniques [MRT], concludes:

IT IS ETHICALLY PERMISSABLE TO CONDUCT HUMAN CLINICAL INVESTIGATIONS OF MITOCHONDRIAL REPLACEMENT TECHNIQUES SUBJECT TO CERTAIN CONDITIONS AND PRINCIPLES:

- **(1) Limiting clinical investigations to women who are otherwise 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; and**
- **(2) Transferring only male embryos for gestation to avoid introducing heritable genetic modification during initial clinical investigations.**

The Institute of Medicine Committee (IOMC) also recommends that the Food & Drug Administration (FDA) "consider extending research in mitochondrial replacement techniques to include the transfer of female embryos if clear evidence of safety and efficacy from male cohorts, using identical MR procedures, were available, regardless of how long it took to collect this evidence; preclinical research in animals had shown evidence of intergenerational safety and efficacy; and FDA's decisions were consistent with the outcomes of public and scientific deliberations to establish a shared framework concerning the acceptability of and moral limits on heritable genetic modification."

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Preliminary remarks:

- It should be pointed out that only the FDA has the proper authority to regulate MRT in the U.S. Only after the FDA takes the IOMC recommendations under consideration, will it, with an eye to the safety and efficacy of MRT, either endorse, modify or reject the Committee's consensus conclusion.

- We encourage our readers to keep an eye on this website for NCER's response to the upcoming FDA decision on clinical use of MRT in the U.S. If the FDA's position deviates from that of the IOM consensus statement, we will alert our readers and comment accordingly.

- You can review the position of Nebraska Coalition for Ethical Research (NCER) on the clinical use of MRT by reviewing the letter which NCER submitted to the IOMC during its 2015 public hearings on the matter. You can review the biology and science behind MRT by viewing this powerpoint presentation or by reviewing the following.

- The science of mitochondria and MRT:

    - Mitochondria are organelles—tiny "powerhouses" in our cells—that convert food into energy. These energy-generating structures are necessary to sustain life and support growth and, literally, make it possible for us to move and think.
    - Mitochondrial DNA (mtDNA) is the only DNA that we inherit exclusively from our mothers. Each mitochondrion contains 37 genes of its own DNA which are separate from the 20,000-25,000 genes found in the nucleus of our cells.
    - In a person with mitochondrial disease, the mitochondria are failing and cannot convert food and oxygen into life-sustaining energy. A subset of mitochondrial diseases is caused by mutations in mitochondrial genes, and women who carry such faulty mitochondria will transmit them to all of their children, male or female. Female offspring of each generation who conceive their children will, in turn, transmit the faulty mitochondrial genes to their children. Because nearly all cells of the body have mitochondria, mitochondrial diseases are usually complex,

serious conditions that affect multiple organs of the body. Inheriting faulty mitochondria deleteriously affects organs of our body that need high levels of energy—brain, heart, kidneys, muscles, and liver. A mitochondrial disease, once expressed, is inevitably progressive. In a pregnant woman it can cause miscarriage, stillbirth, or infant death and, in later life, it can trigger seizures, strokes, blindness, deafness, or heart and liver failure.

- It is estimated that one in 5,000 to 10,000 people have a mitochondrial disease. But only 15% of these cases are likely to be caused by mutations in mtDNA. Only women of the 15% subset with a very high level of mito-mutations will be eligible for MR.
- To prevent maternal transmission of this subset of mito-disease, the recently enacted UK law permit the use of two mitochondrial donation techniques—pronuclear transfer (PNT) and maternal spindle transfer (MST).
- Pronuclear transfer involves the simultaneous creation of two IVF embryos. The first embryo is generated when the mother's egg (containing faulty mitochondria) is fertilized *in vitro*, i.e., in a petri dish, by the father's sperm. The second embryo is generated after a donor's egg (containing healthy mitochondria) is fertilized *in vitro* by the father's sperm. After the nuclear DNA (nDNA) of the second embryo is removed through a process called enucleation, *the nDNA of the first embryo is also extracted and transferred to the second enucleated embryo*. As a result, the first embryo is intentionally destroyed so that the second embryo, now comprised of DNA from its three parents (nDNA from Mama and Papa and healthy mtDNA from the donor) will, theoretically, be free of its mother's mutated mito-genes and their associated mito-diseases. After the three-parent embryo develops in a petri dish to its blastocyst stage, it is transferred to the mother's uterus for implantation and gestation.
- Maternal spindle transfer uses a donor egg containing healthy mtDNA and an egg from the mother containing faulty or mutated mtDNA. The nDNA of the donor egg is removed in a process called enucleation, leaving behind the normal mtDNA in the cytoplasm of the egg. Then, the *nuclear material from the mother's egg is removed and transferred to the enucleated egg of the donor*. The hybrid

mother/donor egg is then fertilized *in vitro* by the father's sperm and the resultant single cell embryo, because it is genetically composed of nDNA from its mother and father and healthy mtDNA from a donor, has three parents and is also, theoretically, mito-disease free. After the three-parent embryo develops in a petri dish to its blastocyst stage, it is transferred to the mother's uterus for implantation and gestation.

- The principal difference between the two techniques is this: In maternal spindle transfer the nDNA is moved *before* the mother's egg has been fertilized (when the egg's nDNA is attached to a structure called the spindle, hence its name). Whereas in pronuclear transfer the nDNA is moved *after* the mother's egg has been fertilized (when the nDNA is contained in two structures called pronuclei, hence its name).
- The IOMC includes a third technique—polar body technique (PBT)—which is still being tested and reviewed and requires more extensive preclinical research in human oocytes and zygotes.

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The IOMC consensus report lines up the benefits and harms of MRT.

- The possible benefit: If effective, MRT could satisfy the desire of a woman with mitochondrial DNA disease to have a genetically related child without incurring the risk of passing on that mtDNA disease.

- The possible harms: The techniques have a unique combination of characteristics that raises a novel collection of ethical, social, and policy issues. These include that MRT would
  - (1) create embryos that if transferred would result in offspring with genetic material from two women of different maternal lineage, a novel intervention never before approved by U.S. federal regulatory authorities;
  - (2) constitute modifications in the mitochondrial genome that could be heritable (i.e., could be passed down through future generations) if MRT were carried out to conceive female offspring, due to the matrilineal inheritance of mtDNA

- (3) entail genetic modification of which any resulting effects would not, at this time, be reversible; and
- (4) constitute a genetic modification that would affect every cell type of the resulting individual, thus affecting the total organism rather than being confined to a specific organ system.

And then the IOMC addresses and mitigates, if possible, these four harms:

- (1) The IOMC insists that the first harm could be blunted if people understood the critical distinction between substituting healthy mtDNA for diseased mtDNA as is done in MRT (a process not all that fraught with genomic dangers) as opposed to replacing nuclear DNA or genetically editing nDNA which is not done in MRT (but would be more prone to producing genetic errors).
- (2) The IOMC temporarily jettisons the second harm of heritable genetic modification (germline modification) that results in modifications of germ cells that are only inheritable in females by prohibiting the transfer of MRT-produced female blastocysts. The approved MRT production of male offspring would not constitute heritable genetic modification (germline modification) because any changes of mtDNA in the male offspring would not be inherited by their descendants.
- (3) The IOMC cannot prescribe or proscribe anything that could alter the irreversibility of novel genetic changes to the MRT-produced embryo. But IOM guidelines do require every conceivable testing procedure on the embryo itself to guarantee its genetic and chromosomal normalcy before its transfer to the mother's uterus. They also require stringent federal and state research oversight and demand preclinical trials with animal and human embryos to help to improve safety and efficacy for MRT's first-in-human clinical trials. The IOMC also endorses perinatal testing (e.g. chorionic villus sampling) to provide the affected woman with the health status of her MRT-produced fetus with the implication that should any perinatal abnormality be discovered, she could opt to abort the pregnancy (which, I suppose, in the IOMC's mind would also count toward "minimizing harms" to the baby produced through MRT).

- (4) The IOMC cannot do anything to undo the fact that MRT will change the genetic makeup of every cell of the MRT-produced embryo. Its restrictive permission for clinical trials using MRT will ultimately demonstrate whether the results of genetic modification of the MRT-produced child will prove entirely or proportionately positive OR whether it will be entirely or proportionately negative. After MRT children grow up, the health and normalcy of their physical and psychic profiles would define how much risk future women affected with mito-disease are willing to take.

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NCER's response to major fault lines of the IOMC's final report on the clinical use of MRT:

FIRST: The IOMC sets down the whole panoply of arguments regarding the moral status of the early embryo—from "it's a person" to "it's a cluster of human cells that will, at some post-blastocyst stage, attain personhood." And, while the Committee does not align itself with any specific theory of personhood, the conclusions of the IOMC practically align themselves with the following:

> Although the early human embryo is human and is to be given respect commensurate with its nascent form, because it is incapable of representative, brain-dependent, person-defining activities such as consciousness, reasoning, self-motivated activity, capacity to communicate, and so on, the early human embryo's membership in the species *homo sapiens* is not enough to also earn it a place in the moral community of persons who enjoy basic rights to life, liberty and the pursuit of happiness. Hence, since the IOMC approves research or clinical use of MR techniques involving the intentional destruction of early human embryos (as long as (a) they are pre-gastrulation or pre-primitive streak embryos and (b) medical benefits could redound to the embryo as a result of the research), the Committee views such human destruction as legal/moral, that is, as something distinct from murder/homicide.

NCER argues that the powers that define personhood, both natural and functional, are present in the organic structure of every human being and are essential to it nature. Person-defining powers are present in their developed or functional state in adult human beings, but they are also present in their undeveloped state—simply as radical capacities to develop mature and effective human behavior—in embryonic, fetal, and neonatal human beings. Both phases of human powers, the natural and the functional, are real, and both define the same human being in which they reside, whether at its embryonic or adult phase, as a human person. Thus, every embryonic human being, though lacking the functional capacity of the adult state, has the natural, real capacity or potential to be a free, self-aware moral agent, and is, therefore, naturally and really, a human person. It follows, then, that embryonic human beings not only deserve a seat at the table of more neurologically mature human persons but also merit the natural enjoyment of the concomitant human rights to life, liberty and the pursuit of happiness. It follows then, that the intentional destruction of early human embryos in MRT constitutes homicide/murder. While the IOMC's restriction of transferring only male embryos *temporarily solves* the serious concern over introducing unpredictable heritable genetic changes, *it does not eliminate another serious moral problem with MRT: the intentional destruction of human embryos.*

- One of the MRT techniques (PNT) involves the IVF production of two embryonic human beings, the first of which is "discarded," that is, intentionally killed, the second of which will be transferred to the mother's uterus (provided it passes subsequent genetic screening tests).

- The most plausible meaning behind IOMC's insistence that the focus of clinical use of MRT must be to "minimize risk of harm to the child born as the result of MRT" seems to be this: apply every sort of genetic screening possible to *in vitro* male embryos until you end up with one who has proven to be free of genetic diseases, including and especially mtDNA disease, and who qualifies for transfer. Little note is given to how many other male embryonic human beings—because they failed to meet MRT quality assurance standards—are destroyed in the wake

of the embryonic human being who is transferred. How such blatant destruction of human beings at their embryonic state constitutes "diminishing risks to the health of the MRT-produced human embryo" simply tortures logic beyond belief.

Due to IOMC's restriction of female transfers, all MRT-produced embryos will be screened for their male sex using the sex selection technique. What's the fate of the female MRT-produced embryos? Tipping their hat to political correctness with "not that we prefer one sex over the other," the IOMC seemingly attempts to deflect any allegations of sexist discrimination or of perpetrating a "war on women." But the fate of female embryonic human beings produced through MRT is, in fact, bleak. All MRT-produced female embryos will, apparently, be cryopreserved (frozen in liquid nitrogen) and could be transferred *only* after completion of the long surveillance period that's needed to test and evaluate their MRT male cohorts, a process that might continue well into adulthood, as researchers continuously assess the health, especially genetic health, and wellbeing of the MRT-produced male children. At one point, the final report alludes to the (admittedly regrettable) reality should mothers of MRT-produced female embryos have a change of heart regarding transfer and gestation of the frozen female embryos, they will be denied access to them until the ban on transferring females is lifted. The sad truth is, depending on the length of surveillance of MRT-produced males, and the possibility of deleterious genetic errors with the male babies, the woman affected with serious mito-disease may *never* be given an opportunity to gestate her daughter. The odds are in favor of the mother being left to deal with the psychological pain of knowing her daughter(s?) is condemned to surrealistic suspension indefinitely or to death through thawing or further destructive embryonic research.

- All MRT-produced embryos will be screened for genetic diseases before implantation and only those without genetic anomalies will be transferred; those with genetic abnormalities will be intentionally destroyed, i.e., killed.

- Before in-human clinical trials of MRT will be allowed, the clinics—probably only two or three in the U.S.—must prove they have done sufficient pre-clinical research on animals *and* on human embryos. As the IOMC admits:

> Because MRT is still in development, preclinical research could involve the creation and destruction of many embryos in efforts to improve the techniques to the point at which clinical investigations could safely proceed. Any preclinical data required by regulators for consideration in advance of first-in-human investigations could increase the numbers of embryos created, *many of which would likely not be transferred for implantation.*

In other words, NCER notes, these experimental embryos will be discarded: intentionally deprived of their existence because, essentially, they can be of no further use.

SECOND: The IOMC argues for absolute parental rights: the right of parents to follow their desires trump any or all of the child's rights. The "procreative liberty" guaranteed in our liberal democratic society guarantees couples can procreate in ways that pose unknown risks to their children. "With regard to procreative liberty," the IOMC insists "the U.S. societal experience with the use of Assisted Reproductive Technology [ART] to treat infertility has revealed great tolerance for parental decisions to impart unknown risks to future children in the pursuit of relatively novel reproductive technologies. *In those cases, the desire to conceive and bear children (whether genetically related or not) rather than to adopt or remain childless has effectively been given priority over concerns about risks to children born as a result of the novel technologies."*

In other words, IOMC concludes, for better or for worse, current societal values dictate parents have a proprietary control over the characteristics of their prospective offspring. And that's just the way it is.

> **NCER argues** children are persons to be loved and conceived as individuals in their own right. Parents, then, are entrusted with the responsibility of making health decisions for their children—*in vivo* or *in vitro*--that will not harm them and certainly that will not deliberately deprive them or anyone else of their life.

THIRD: IOMC speculates that once the public understands the critical distinction between substituting healthy mtDNA for diseased mtDNA (not all that fraught with genomic dangers) AND replacing nuclear DNA or genetically editing nDNA (much more prone to producing genetic errors) their concerns about causing genetic errors through MRT would be blunted. Plus, all sorts of preclinical testing is going to be required before permission for first-in-human trials is granted. Stringent policy oversight of both stages of research—preclinical and clinical—to optimize the safety and efficacy of MRT should also amelitorate public and parental concerns about MRT introducing novel genetic anomalies.

> **NCER sides** with reputable scientists who argue the Achilles heel of MRT is the attempt to use a technique involving mtDNA *before* geneticists have thoroughly studied the mitochondrial genome and before they have sufficiently understood the complex interactions between the mito-genome and the nuclear genome. Given their current ignorance, these scientists contend, and NCER agrees, the pursuit of MRT is irresponsible especially when, given the large margin for genetic error, mistakes can never be erased. Certainly these male persons will not pass on any genomic flaws to later generations. But any genetic pathologies with which theses male children/adults might present and from which they might suffer to one degree or another cannot, give our current capabilities, be reversed.

FOURTH: The IOMC final report on the ethical permissibility of first-in-human MRT trials focuses on the need, and rightly so, to have a good or worthy intention for the use of MRT in clinical investigations: the opportunity for a woman with a mtDNA disease to have a child who is not burdened with mito-diseases and who still shares her nuclear DNA. Thus they reason: Since MRTs are currently the only available means to bear genetically related offspring, coupled with a reduced risk of passing on mtDNA disease to offspring, then parents or researchers or the

general population needn't concern themselves unduly about the morality of the using the various techniques of MR. MRT is morally legitimate by virtue of effecting favorable consequences: MRT will bring the greatest good for the greatest number.

> **NCER argues** the IOMC's report disregards the need to discern whether mitochondrial replacement techniques, in themselves, constitute a good means to that good end. NCER argues that the goodness of an act—here the use of MRT—is not determined by its proportionate good effects but rather by whether the intentionality of using MRT is wholly good, both as a means and as an end. NCER concludes, for all the reasons it puts forth here, that because MRT is an immoral means—an unreasonable way to realize a good goal—the entire act: both the means (using MRT) and the end (to conceive genetically related children who are mito-disease free)—is ethically unacceptable.