BIOETHICS ADVISORY COMMITTEE SINGAPORE

Respondent's Form to the Bioethics Advisory Committee's Consultation Paper on "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology"

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Public Comments to the Singapore Bioethics Committee on the Topic of Mitochondrial Genome Transfer Technology

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June 15, 2018

The Singapore Bioethics Advisory Committee should NOT permit MRGT and should NOT modify its original recommendation against germline genetic modifications set forth in 2005.

INTRODUCTION

I am an Assistant Professor in the College of Public Health at the University of South Florida HEALTH in the United States. My teaching and research focuses in health law, bioethics, and the regulation of emerging technology. I am the author of two comprehensive articles relevant to Mitochondrial Replacement Genome Technology (MRGT, or also referred in this Comment to as Mitochondrial Replacement Therapy or MRT) and human germline modifications.[1]

SUMMARY

1. **Public framing of Mitochondrial Replacement Genome Therapy contains scientific inaccuracies and is misleading.**

Scientists, ethicists, and the media strategically omit crucial risk information, incorrectly describe MRGT as curative, and rely on logical fallacies to obtain public support. Using misleading descriptions undermines the authenticity of the policymaking process.

During discussion in the United Kingdom and the United States, media repeatedly referred to mitochondria as mere batteries of the cell, belying the complex and extensive interaction between mitochondrial and nuclear DNA in evolutionary biology. Ethicists have compared MRGT to a "micro-organ transplantation," alleging there is "no sound basis to oppose MRT" because it constitutes a "cure" so infants can be born without mitochondrial disease.[2]

- MRT is highly risky, experimental, and it is ethically inappropriate to refer to it as curative or a method to prevent mitochondrial disease.
- Touting MRT as a cure for mitochondrial disease is misleading because it will not address most cases. Most instances of mitochondrial disease arise from de novo

mutations and mutations in nDNA.[3] Approximately 80% of mitochondrial disease arises from nDNA mutations, which MRT does not address.[4]

- Appealing to parental suffering relies on a false dilemma fallacy: Proponents for MRGT argue it will prevent incurable genetic disease, save families needless misery, and objections prevent medical progress. Medical research to understand mitochondrial disease or provide more effective therapies does not require sanctioning experimentation on the genomes of future generations.

2. **International law has correctly adopted a principled stance against germline modifications. Singapore's Bioethics Advisory Committee should not modify its stance disallowing germline modifications set forth in 2005.**

MRGT may accurately be classified as nuclear genome transfer and a modification of the human germline, which has prohibited by International Bioethics Committee of the United Nations, The Council of Europe's Convention on Human Rights and Biomedicine, and the European Union's 2001 directive on clinical trials. [5]

Globally, approximately forty countries[6] including Canada,[7] Germany,[8] France,[9] Switzerland,[10] Sweden,[11] and Italy[12] have adopted legislation prohibiting germline intervention on embryos for implantation.[13] Laws enacted in the aforementioned nations not only prohibit germline or heritable modification, but such actions constitute criminal violation subject to fines and or imprisonment.

- Unequivocally prohibiting and criminalizing an action communicates the egregiousness, potential for harm, and social unacceptability of such an action in these nations.
- Nations should reject alarmist rhetoric they are "falling behind": these laws demonstrate many countries acknowledge the lure of technology, but renounce risky experiments that cross the historical bright line of manipulating future generations.[14]
- Prohibitions do not stem from "irrational fear" but instead affirm longstanding precedent based on reasoned deliberation, potential for grave harm, and the principle that no person has the authority to modify the human germline of future generations.

3. **The United Kingdom's process to permit MRGT relied on unsupported scientific assumptions and disregarded credible opposition.**

The Human Fertilisation and Embryology Authority (HFEA) began its consultation process over widespread objections.

- Forty one signatories including notable bioethicists, scholars, and scientists published a letter to the editor of *The Times* in the U.K. expressing alarm over HFEA's proposal for MRT.[15] This letter noted the broad global consensus against germline interventions, stated MRT would "cross the Rubicon" and open the door to other germline modifications, and may pose unforeseen consequences.[16]

4. **The HFEA's Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception assertion that the "evidence does not seem to**

suggest the techniques are unsafe" was not supported by evidence in the policymaking record.[17]

The U.K. Department of Health issued reports and statements describing the process of MRT that strategically characterized the procedure to gain public favor.[18]

- The U.K. Department of Health conceded that MRT constituted a germline modification, but argued that it did not pose a genetic modification because there is not an agreed upon definition of what a genetic modification entails and asserted mtDNA merely functions as batteries of the cell.[19]
- The U.K. Department of Health announced MRT would not contravene the Universal Declaration on the Human Genome and Human Rights' prohibition against germline interventions because it serves a therapeutic corrective purpose so it does not harm human dignity. This characterization failed to account for its highly risky and experimental, not therapeutic, nature.

The HFEA Review acknowledged the potential for complications pertaining to safety and efficacy, but unilaterally dismissed what the scientific community has described as numerous substantial barriers.[20]

- For example, the HFEA Review addressed differential segregation and maternal bottleneck that could result in increasing levels of heteroplasmy during the offspring's course of development in different tissues, and increasing levels of heteroplasmy through subsequent generations.[21]
    - In response to this possibility, the HFEA Review responded -- without explanation -- "there is little evidence of this occurring."[22]
- The HFEA cited animal studies using macaque models where about half of the macaque embryos appeared to develop normally as evidence of "good progress" that MRT appeared to work.[23]
    - In response to the half of embryos following MRT that did not develop correctly, HFEA disregarded these findings, asserting there may be "some differences in embryo development, but nothing has been found to raise concerns of safety."[24]
- The HFEA also noted the concern that there may be incompatibility arising from mixing mtDNA from two sources, but concluded mixing two sources of mtDNA would not pose any complications to interaction with nDNA or cell function.[25]
    - As support for its conclusion, HFEA observed that children from mixed race parents (one source of maternal mtDNA) do not exhibit higher percentages of mitochondrial disease.[26]
    - These circumstances are dissimilar and it is unclear why HFEA considered them comparable.

5. The U.K.'s process dismissed extensive serious scientific concerns raised in public comments.

During the U.K.'s process, the U.K. House of Commons Science and Technology Committee held a hearing on the scientific evidence for MRT and published written correspondence from numerous scientists, physicians, bioethicists, and other stakeholders.[27]

- Although a minority of comments lent support to HFEA's proposed direction and even asserted it would be unethical not to use MRT,[28] the majority of public comments fervently opposed MRT precisely based on unsettling and unresolved issues pertaining to evidence for its safety and efficacy.[29]
- A number of comments highlighted the unpredictability of differential segregation and maternal bottleneck, asserting that attempting to measure carryover of maternal mtDNA in the blastocyst via PGD was an ineffective and improper proxy for predicting long term levels of heteroplasmy and health outcomes.[30]
- Comments also opposed HFEA's characterization of animal models as successful, noting that the 52% of animal embryos that did not develop correctly demonstrated chromosomal abnormalities, and questioned whether these findings may result in unexamined differences in the embryos that scientists proclaimed were developing normally.[31]
- In addition to these responses, multiple comments disputed HFEA's conclusion pertaining to the compatibility of two sources of mtDNA and epigenetic effects resulting from transfer of the nuclear genome from one oocyte or embryo to another.[32]
- A number of interested parties, including the Council for Responsible Genetics, Human Genetics Alert, and several scientific experts submitted similar assessments noting evidence for extensive communication between mtDNA and nDNA expression.[33]
    - Disrupting mtDNA functioning and cross-talk to nDNA directly influences DNA methylation and chromosomal gene expression.[34]
    - Mitochondria are not merely batteries supplying energy to the cell that can be deftly exchanged, but part of a complex interwoven system necessary for the entire organism's subsequent development.[35]
- These observations also highlighted the unprecedented risks related to embryo manipulation, noting the more extreme the level of physical manipulation, the higher the potential for physical damage to the embryo or epigenetic changes resulting from the process of physical manipulation and the risk for functional and developmental health deficits.[36]

6. The U.K.'s policymaking process should not serve as model to other nations because it lacked public consensus and summarily dismissed substantial concerns with safety and efficacy.

- Key shortcomings with the U.K's policymaking process:
    - During the initial proposal, bioethicists, scholars, and scientists voiced dissent because MRT would breach the broad global consensus against germline modifications and urged the government to reconsider.
    - To initially gain favor, the HFEA and the U.K. Department of Health strategically named the techniques MRT rather than accurately describing it as nuclear genome transfer.
    - During the consultation process, numerous scientists provided testimony and correspondence at length relating to safety and efficacy.
    - Scientists objected to HFEA's conclusions based on available evidence, finding not merely a lack of consensus pertaining to safety and efficacy, but that the available scientific evidence demonstrated how unsafe MRT is.

- Despite objections based on international governance, evidence demonstrating insufficient safety and efficacy, and lack of public consensus, British Parliament passed the amendment that would permit HFEA to license fertility clinics to offer MRT.
- This progression reflected a massive disconnect in the legal, scientific, and policymaking process where the policy recommendation and legal change was not supported by the weight of the current scientific evidence.

7. **In the United States, the Cellular, Tissue, and Gene Therapies Advisory Committee of the Federal Food and Drug Administration (FDA) convened a meeting wherein scientists and experts articulated extensive issues with safety, efficacy, and risks.**

The United States has also undertaken steps to begin the process of potentially permitting MRT. In 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee of the Federal Food and Drug Administration (FDA) convened a meeting to discuss scientific risks.

There is currently no legal prohibition against germline modification in the United States (at the time of this Comment, there are federal funding restrictions under the Consolidated Appropriations Act.) Any future clinical investigational use of MRT falls under the purview of the FDA.

8. **Scientific concerns raised in meeting minutes from FDA's 2014 Cellular, Tissue, and Gene Therapies Advisory Committee and current scientific literature do not support investigational clinical applications of MRGT.**

In 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee of the FDA convened meetings to discuss MRT for both the prevention of mitochondrial disease and the treatment of infertility.[37] Participants discussed an extensive list of scientific concerns:

- Unlike other potential clinical trials where the FDA determines calculations of safety and efficacy for the intended patient, the research subject would be *created* using the proposed methodology.
- There are problems with determining efficacy: testing the blastomere for viability is not indicative of the health of the child and subsequent offspring.[38] One scientist also noted that testing a sample is not indicative of the rest of the inner cell mass, meaning different levels of heteroplasmy may exist, and even subsequently develop at varied rates in different tissues though stages of development and the child's life.[39]
- Animal models have not sufficiently addressed maternal bottleneck, where levels of mutant mtDNA can increase from one generation to the next.[40] This could have an unintended negative impact on future generations.
- Segregation and replication of mtDNA occurs according to its own evolutionary system, which makes predicting subsequent levels of heteroplasmy difficult.[41] Even if segregation initially demonstrates favorable drift toward the donor's mtDNA, these levels may jump unpredictably, or segregate at different levels in tissues throughout the body.[42]

- Levels of mtDNA in the child's blood may reflect a low percent of heteroplasmy, but genetic drift can cause segregation toward the mother's mutated mtDNA in specific tissues or organs, wherein the child may experience diseases arising in those systems.[43]
- Segregation occurs throughout the lifespan of the individual which means low levels of the mother's mtDNA in the child's blood or partial tissue testing would also not reflect the possibility of increasing levels of heteroplasmy later in life resulting in latent presentation of mitochondrial disease.[44]
- Some scientific evidence suggests that segregation appears affected by genetic distance between haplotypes and when haplotypes of maternal mtDNA and donor mtDNA are mixed, reversion toward maternal mtDNA occurs.[45]
    - In animal models, mixed mtDNA has resulted in immune rejection, susceptibility to diseases of metabolism, and deficits in performance and learning capabilities.[46]
- MRGT would disrupt crucial cross-talk between mtDNA and nDNA. Mitochondrial DNA not only functions as a source of energy, but affects a wide range of cellular functioning and how nDNA is expressed.[47]
    - Disrupting the cross-talk between mtDNA and nDNA in animal models results in adverse outcomes and disturbs crucial mitochondrial processes.[48]
    - Current research suggests interference in the communication between mtDNA and nDNA can negatively affect individual development, behavior, susceptibility to disease, and fertility.[49]
    - One scientific article summarized, "perturbation of the mito-nuclear interactions…generally attracts grave consequences."[50]
- Initial positive results (or even a live birth) in Animal and In Vitro Models does not mean human offspring would be "healthy": those studies relied on a small sample and may miss problems that would arise with a larger sample; they did not perform extensive testing for heteroplasmy throughout tissues; the studies did not test germ cells for heteroplasmy or assess the health of subsequent generations; and using sample tests for heteroplasmy as a proxy for health may miss other dysfunction.[51]
- Participants voiced concern that scientific evidence failed to demonstrate safety and efficacy, but that MRT may never be a viable option based on level of risk involved.[52]

- Participants at the 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee reiterated *there are less risky alternatives to having children, and the current evidence falls "far short" of showing MRT would be potentially safe and effective.*[53]

9. **The approach to policymaking in the United States rejected global legal consensus and disregarded serious scientific risks. Nations considering MRGT or germline modifications should examine the adequacy of the policymaking *process*, not only other nation's outcomes or recommendations.**

In 2016 the National Academies of Science, Engineering and Medicine (NAS) authored a consensus report reviewing the ethical, social, and policy considerations relating to MRT for limited circumstances.[54]

- The National Academies of Science, Engineering and Medicine consensus report in the U.S. concluding the potential ethical acceptability for using MRT authored recommendations that were not supported by current scientific evidence.

    - The NAS Report concluded it is ethically permissible for the FDA to conduct clinical investigations subject to a set of conditions including: (1) Initial safety is established and risks to all parties directly involved in the proposed clinical investigations are minimized; (2) Likelihood of efficacy is established by preclinical research; (3) Clinical investigations are limited to women who otherwise are at risk of transmitting a serious mtDNA disease; (4) Intrauterine transfer for gestation is initially limited to male embryos (but may be extended to females if safe and effective); (5) FDA may consider haplotype matching as a means of mitigating risk of incompatibilities between mtDNA and nDNA.[55]
    - This framework dismissed the concerns of multiple experts present at FDA's 2014 meeting who warned of novel risks when experimenting on embryos of future generations:
        - MRT would impact every cell in the body, and there are no methodologies currently to ensure the procedure would not inflict novel abnormalities. [56]
        - Based on available research, scientists cannot currently predict lifetime safety nor latent effects.[57]
        - Such mistakes are both inevitable and irreversible, which means MRT could potentially not only create a congenitally impaired child, but introduce those deficits into the germline of all subsequent offspring.[58]
        - Current research suggests disrupting mtDNA through MRT may have the potential to result in developmental disorders,[59] latent fatalities,[60] expedited aging,[61] increased risk of cancer,[62] as well as unknown abnormalities.[63]
    - The NAS adopted the U.K.'s approach to framing MRT in a favorable manner: it reassured that MRT does not "edit genes" and "there is no direct modification of nuclear DNA" and referred to the procedure as switching mitochondria.
    - The NAS rejected the United Nations Universal Declaration on the Human Genome and Human Rights prohibition against germline modifications. It asserted that referring to the genome as "the heritage of humanity" amounts to "vague and aspirational" language.

10. Strong policymaking requires accuracy, transparency, and honest deliberation of available evidence. Public discussions should include the limitations of experimental technology, alternatives, and risks.

11. MRT would not effectively and sustainably address causes of mitochondrial dysfunction and is not designed to address most cases of mitochondrial disease.

Mitochondrial dysfunction may result from either mtDNA mutations or nDNA mutations. Eighty percent of mitochondrial dysfunction arises from nDNA mutations for which MRT would not address.

Focusing on MRGT presumes technology can and will solve these devastating diseases, but neglects to examine disease root causality and alternatives.

- Recent evidence suggests that a variety of environmental factors induce de novo mutations. Mitochondrial dysfunction is not only a cause of rare fatal disease, but also has been implicated as a factor in the development of common diseases, such as neurodegenerative disease, cancer, diabetes, cardiovascular disease.[64]
- Public health researchers hypothesize that the rising rates of chronic and debilitating disease are a product of environmentally mediated epigenetic damage to our mitochondria.
- In the course of one's life mitochondria are "on the frontline of cellular response to the environment."[65] A variety of environmental agents, including pesticides,[66] heavy metals,[67] antibiotics,[68] pharmaceutical drugs,[69] environmental toxicants such as dioxin[70] and Bisphenol A[71] can all exert changes to mitochondrial integrity and development.
- Over time, exposure to mitochondrial disruptors damages the mitochondria and impacts the resulting health of the individual manifesting as common diseases.[72]
- Effective solutions should address the environmental causes of mitochondrial dysfunction and disease as the means of disease prevention.

12. The push to permit MRGT appears driven by the technological imperative, the desire for scientific ingenuity, and potential commercial profit.[73]

- The campaign to push for MRGT operates within the narrow genomics framework of the technological imperative.
    - When we perceive genes as the problem, biotechnology presents us with the solution.[74]
    - Rhetoric– "cure," "prevent," and "treat"– when repeated continuously "bias us toward acceptance"[75] and represent an Orwellian attempt to re-engineer perception that these "optimistic projections" constitute factual science. [76]
- If nations permit fertility clinics to use MRGT as a "solution" for other diseases such as infertility as performed by physicians in Ukraine and the United States, this holds tremendous commercial potential.
    - The World Health Organization evaluated global rates of infertility, finding up to one quarter of couples of childbearing age suffer from infertility.[77]
    - According to Allied Market Research in the U.S., the global fertility services market was valued at $16,761 million in 2016, and is projected to reach $30,964 million by 2023.[78]
- Commercial markets should not drive the adoption of new experimental technology with this risk profile.
    - The market prioritizes expansion and profit increase as a primary goal, not the best interest of the parties involved.
    - This creates a conflict of interest with parents, children, and egg donors required for MRGT, shifting external costs related to latent risks and long term harm onto parents, egg donors, and children.[79]

13. **Recent discussion in Europe calling to reassess the ban on germline modifications should be closely scrutinized because they rely on rhetoric that germline modifications (via MRGT or genome editing) constitute curative therapy, do not sufficiently account for serious scientific risks, and dismiss principled objections.**

Managing perception of the science with a particular outcome in mind may impact public acceptance of germline modifications. Though these discussions pertain to genome editing, they are also relevant to MRGT as technology framed as curative that modifies the human germline.

- The INSERM Ethics Committee in France, the German National Academy of Sciences, and the European Academies Scientific Advisory Council adopt the same strategic descriptions such as "correcting" a mutation, "targeted," and "unprecedented accuracy and precision" when referring to genome editing and discuss genome editing's ability to "eventually treat or avoid monogenic disorders."[80]
- In a Letter to the Editor, the European Steering Committee proclaimed no international consensus exists pertaining to germline modifications, labeled a moratorium as "not appropriate," and instead proposed a model for risk matrices to implement "responsible use" of a "promising new technology" [referring specifically to genome editing.][81]
- The Letter to the Editor also explicitly called for nations to reassess the ban against germline modifications previously set forth in the Oviedo Convention.[82]
- Calls for reforming policy and law rely upon the rhetoric and promotional claims of genome editing as a curative therapy, which eclipses the current scientific evidence demonstrating significant risks.
- These meetings occurring within the European Union dismiss historical reasons for the prohibition on germline modifications, which exist as a matter of principle that "no individual or scientist has the moral authority" to experiment with modifying the genome of future humans.[83]

CONCLUSION

Based on global legal consensus against germline modification of human embryos and scientific evidence demonstrating serious risks of MRGT, The Singapore Bioethics Advisory Committee should not permit MRGT nor amend its 2005 stance.

[1] Katherine Drabiak, *Untangling the Promises of Human Genome Editing*, JOURNAL OF LAW, MEDICINE & ETHICS, *forthcoming Fall 2018*; Katherine Drabiak, *Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes*, 20 JOURNAL OF HEALTH CARE LAW, 1-63 (2018).

[2] Julian Savulescu, Mitochondrial Disease Kills 150 Children a Year. A Micro-Transplant Can Cure It, THE GUARDIAN (Feb. 2, 2015), available at: https://www.theguardian.com/science/2015/feb/02/mitochondrial-transfer-micro-transplant-parliamentary-debate.

[3] 59th MEETING OF THE CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE, FDA (Feb. 25, 2014), available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM390945.pdf (hereinafter "FDA Meeting") at 58-64; *see also* Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations, NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, AND MEDICINE (2016) (hereinafter "NAS Report") at 27 (discussing mtDNA disease generally relating to later onset milder conditions and nDNA disease constituting earlier onset and more severe expressivity).

[4] *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception: 2014 Update*, HUM. FERTILISATION & EMBRYOLOGY AUTH. at 12 (June 2014) (hereinafter *HFEA Scientific Review*).

[5] Article 9, Directive 2001/20/EC, COUNCIL OF EUROPE (2001), http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf.

[6] Tetsuya Ishii, Potential Impact of Human Mitochondrial Replacement on Global Policy Regarding Germline Gene Modification, 29 REPRODUCTIVE BIOMEDICINE ONLINE 150, 152-153 (2014); Motoko Araki & Tetsuya Ishii, International Regulatory Landscape and Integration of Corrective Genome Editing Into In Vitro Fertilization, 12(108) REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY 9 (2014); Rosario Isasi et al., Editing Policy to Fit the Genome? 351 SCIENCE 337 (2016). See Araki & Ishii at Table S1: Policies on Human Germline Gene Modification for Reproduction Excluding Reproductive Cloning.

[7] Assisted Human Reproduction Act s. 5 (2004); Assisted Human Reproduction Act s. 60 (2004).

[8] Embryo Protection Act, Federal Law Gazette, Part I, No.69 (1990).

[9] Research on Embryos, Bioethics Law, Code of Public Health. Article L2151-5 (2011); Absolute Prohibition on Creating Transgenic Embryos and Chimeras, Bioethics Law, Code of Public Health. Article L2151-2 (2011); *see also* Sylvain Beaumont & Sandra Tripathi, France's Loi du 7 Julliet 2011 Clarifies The Human Embryonic Research System, Life Sciences Bulletin, Fasken Martineau (Aug. 2, 2011), http://www.fasken.com/files/Publication/ad92fa84-d869-497e-80d7-071bfef919e5/Presentation/PublicationAttachment/f3b681c6-78fc-4379-aa6d-19456049955c/Life%20Sciences%20Bulletin%20-%20Beaumont-Tripathi%20-%20August%202%202011.pdf.

[10] Article 35, Federal Act on Medically Assisted Reproduction, Federal Assembly of the Swiss Confederation (1998).

[11] *See* Sections 3-4, The Genetic Integrity Act, Swedish Code of Statutes no.2006:351 (2006).

[12] Article 13, Rules of Medically Assisted Procreation, No. 40 (2004).

[13] Some laws prohibit germline modification to any embryo, some prohibit modification for implantable embryos. *See* Isasi et al., *supra* note 6.

[14] *The Science and Ethics of Genetically Engineered Human DNA*, Hearing Before the Subcommittee on Research and Technology, 114TH CONGRESS (2015).

[15] Letter to the Editor, *Alarm Over Genetic Control of Embryos*, THE TIMES (March 20, 2013), http://www.thetimes.co.U.K./tto/opinion/letters/article3717615.ece.

[16] *Id.*

[17] Mitochondrial Donation: Correspondence Received Relating to the Evidence Hearing on 22 October 2014, SCIENCE AND TECHNOLOGY COMMITTEE, HOUSE OF COMMONS (2014) at 23, 29, 33-49, 73, available at: https://www.parliament.U.K./documents/commons-committees/science-technology/Mitochondrial%20donation/MITCorrespondence.pdf (hereinafter "U.K. Correspondence).

[18] Steve Connor, Scientists Accuse Government of Dishonesty Over GM Babies in Its Regulation of New IVF Technique, THE INDEPENDENT (July 28, 2014), available at: http://www.independent.co.U.K./news/science/exclusive-scientists-accuse-government-of-dishonesty-over-gm-

babies-in-its-regulation-of-new-ivf-9631807.html; *Mitochondrial Donation: A Consultation on Draft Regulations to Permit the Use of New Treatment Techniques To Prevent the Transmission of A Serious Mitochondrial Disease From Mother to Child*, U.K. DEP'T OF HEALTH (Feb. 2014) at 13-14, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf.

[19] *Id.*

[20] *See generally* U.K. Correspondence, *supra* note 17; FDA Meeting, *supra* note 3.

[21] HFEA Scientific Review, *supra* note 4, at 26.

[22] *Id.*

[23] *Id.* at 20.

[24] *Id.* at 20.

[25] *Id.* at 23, 28-31.

[26] *Id.*

[27] U.K. Correspondence, *supra* note 17.

[28] *Id.* at 7-8. Progress Educational Trust asserted there was prevailing support for HFEA's regulation to permit MRT rationalizing al medical treatment entails experimental results, and it would be unethical not to employ MRT.

[29] *Id.* at 23, 29, 33-49, 48, 73.

[30] *Id.* at 33-35, 50, 64-66.

[31] *Id.* at 23; *see also* Aditi Shah, *"Not Unsafe" Does Not Equal Safe: An Evaluation of the HFEA's Report on MST and PNT*, COUNCIL FOR RESPONSIBLE GENETICS (June 3, 2014), http://www.councilforresponsiblegenetics.org/pageDocuments/Q2M4IDTBFZ.pdf (hereinafter "Council for Responsible Genetics").

[32] U.K. Correspondence, *supra* note 17, at 29, 33-35, 39-49, 53, 64-65, 73.

[33] *Id.* at 33-35, 39-49; Council for Responsible Genetics, *supra* note 31; Human Genetic Engineering on the Doorstep, *Human Genetics Alert* (Nov. 2012) , available at: http://www.hgalert.org/Mitochondria%20briefing.pdf; *Report on the Safety of "Mitochondrial Replacement" Techniques: Epigenetic Issues*, HUMAN GENETICS ALERT (March 2013), http://www.hgalert.org/Report%20on%20the%20safety%20of%20mitochondrial%20transfer.pdf.

[34] *Id.*

[35] *Id.*

[36] *Id.*

[37] FDA Meeting, *supra* note 3; FDA Briefing Document: Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or the Treatment of Infertility, CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE, FDA (Feb. 25-26, 2014)(hereinafter "FDA Brief").

[38] *Id.*

[39] FDA Meeting, *supra* note 3, at 84-87, 85.

[40] FDA Meeting, *supra* note 3, at 34-35, 141-142; FDA Brief, *supra* note 37, at 7, 21.

[41] *Id.*

[42] *Id.*; Ewen Callaway, *Three-Person Embryos May Not Expel Harmful Genes*, 533 NATURE 445 (2016).

[43] Joerg Patrick Burgstaller et al., mtDNA Segregation in Heteroplasmic Tissues Is Common In Vivo and Modulated By Haplotype Difference and Developmental Stage, 7 CELL REPORTS 2031 at 2031, 2036 (2014)

[44] *Id.* at 2031.

[45] *Id.*; Eunju Kang et al., *Mitochondrial Replacement In Human Oocytes Carrying Pathogenic Mitochondrial Mutations*, 540 NATURE 270 (2016).

[46] FDA Meeting, *supra* note 3, at 196-187; Kimberly Dunham-Snary & Scott Ballinger, *Mitochondrial-nuclear DNA Mismatch Matters*, 349 SCIENCE 1449, 1150 (2015); Klaus Reinhardt et al. Mitochondrial Replacement, Evolution, and the Clinic 341 SCIENCE 1345 (2013); Paula Amato et al., Three Parent In Vitro Fertilization: Gene Replacement for the Prevention of Inherited Mitochondrial Disease, 101 FERTILITY AND STERILITY 31, 34 (2014).

[47] FDA Brief, *supra* note 37, at 13

[48] NAS Report, *supra* note 3, at 56.

[49] Human Genetic Alert, *supra* note 33; Reinhardt et al., *supra* note 46, at 1346; *see also* Martin Horan et al., From Evolutionary Bystander to Master Manipulator: The Emerging Roles for the Mitochondrial Genome As A Modulator of Nuclear Gene Expression, 21 EUROPEAN JOURNAL OF HUMAN GENETICS 1335 at 1335-1336 (2013); Rebecca Muir et al., Mitochondrial Content Is Central To Nuclear Genome Expression: Profound Implications for Human Health, 38 BIOESSAYS 150 at 152-153 (2015); Kimberly Dunham-Snary & Scott Ballinger, Mitochondrial-nuclear DNA Mismatch Matters, 349 SCIENCE 1449 (2015).

[50] Horan et al., *supra* note 49, at 1335.

[51] FDA Meeting, *supra* note 3, at 185, 251; Dunham-Snary & Ballinger, *supra* note 49.
[52] FDA Meeting, *supra* note 3, at 248, 261-271.
[53] *Id.*
[54] NAS Report, *supra* note 3, at xiii.
[55] *Id.* at 10-11.
[56] FDA Meeting, *supra* note 11, at 278.
[57] *Id.* at 220.
[58] FDA Brief, *supra* note 37, at 22.
[59] Sarah Knapton, Three Parent Babies Could Be At Greater Risk of Cancer, Warn Scientists, THE TELEGRAPH (Feb. 3, 2015), available at: http://www.telegraph.co.U.K./news/science/science-news/11385370/Three-parent-babies-could-be-at-greater-risk-of-cancer-warn-scientists.html.
[60] Burgstaller et al., *supra* note 43.
[61] Horan et al., *supra* note 49.
[62] *Id.*
[63] *See also* FDA Meeting, *supra* note 3, at 216 (discussing list of potential risks) and at 278 (discussing the potential for introducing additional abnormalities through MRT).
[64] Joel Meyer et al., Mitochondria as a Target of Environmental Toxicants, 134(1) TOXICOLOGICAL SCIENCES 1 ,3 (2013).
[65] Luca Lambertini & Hyang-Min Byun, Mitochondrial Epigenetics and Environmental Exposure, 3(3) CURRENT ENVIRONMENTAL HEALTH REPORTER 214 (2016).
[66] Meyer et al., *supra* note 64, at 8; Maria Paraskevaidi et al., Underlying Role in Mitochondrial Mutagenesis in the Pathogenesis of Disease and Current Approaches for Translational Research, 32(3) Mutagenesis 335-342 (2017).
[67] *Id.*; Kelly Brunst et al., Integrating Mitochondriomics In Children's Environmental Health, 35(9) JOURNAL OF APPLIED TOXICOLOGY 976 at 982-983 (2015).
[68] Sameer Kalghati et al., *Bactericidal Antibiotics Induce Mitochondria Dysfunction and Oxidative Damage in Mammalian Cells*, 5(192) SCIENCE TRANSLATIONAL MED. 192ra85 (2013); Norman Moullan et al., *Tetracyclines Disturb Mitochondrial Function Across Eukaryotic Models: A Call for Action in Biomedical Research*, 10 CELL REPS. 1681 (2015).
[69] Meyer et al., *supra* note 64 at 3-4; Paraskevaidi et al., *supra* note 66.
[70] Meyer et al., *supra* note 64, at 3-4.
[71] Brunst et al., *supra* note 67, at 983.
[72] *Id.* at 3-4; Paraskevaidi et al., *supra* note 66.
[73] *See* Drabiak, *supra* note 1.
[74] N. Comfort, "Can We Cure Disease Without Slipping Into Eugenics?," *The Nation* (July 16, 2015), available at https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/.
[75] "The New Technologies of Human Genetic Modification: A Threshold Challenge for Humanity," *Center for Genetics and Society* (2002), available at https://www.geneticsandsociety.org/article/threshold-challenge-new-human-genetic-technologies> (quoting Evelyne Schuster in the Report on the Conference Beyond Cloning: Protecting Humanity from Species Altering Procedures).
[76] Editorial, "Scientific Buzzwords Obscure Meaning," *Nature* 538, no. 7624 (2016): 140 (stating "buzzwords are Orwellian and obfuscate even as they pretend to enlighten.")
[77] *Global Prevalence of Infertility, Infecundity, and Childlessness*, WHO, http://www.who.int/reproductivehealth/topics/infertility/burden/en/.
[78] Allied Market Research, Global Fertility Services Market Expected to Reach $30,964 Million, by 2023 - Allied Market Research (February 23, 2018), available at https://www.prnewswire.com/news-releases/global-fertility-services-market-expected-to-reach-30964-million-by-2023---allied-market-research-674951703.html.
[79] Sonia Suter, Giving In To Baby Markets: Regulation Without Prohibition, 16 MICHIGAN JOURNAL OF GENDER & LAW 217 at 256-257 (2009).
[80] *See* Genome Editing: Scientific Opportunities, Public Interests and Policy Options in the European Union, European Academies Scientific Advisory Council, March 2017, available at http://www.easac.eu/fileadmin/PDF_s/reports_statements/Genome_Editing/EASAC_Report_31_on_Genome_Editing.pdf; Barbel Friedrich, Human Genome Editing: Scientific and Ethical Considerations, German National Academy of Sciences, European Experts Meeting (March 16, 2016) available at https://www.inserm.fr/content/download/150254/1139400/version/2/file/2016-03-16+INSERM+meeting+B.+Friedrich.pdf at 20; Herve Chneiweiss, Fostering Responsible Research With CRISPR-Cas9, INSERM Ethics Committee, European Experts Meeting (March 16, 2016), available at

<https://www.inserm.fr/content/download/150255/1139405/version/2/file/2016-03-16+INSERM+meeting+H.+Chneiweiss.pdf>.

[81] *Id.*

[82] *Id.* at 713.

[83] Stuart Newman, CRISPR Will Never Be Good Enough to Improve People, *Gene Watch* 30, no.1 (2017): 5-6; George Annas et al., Protecting the Endangered Human: Toward An International Treaty Prohibiting Cloning and Inheritable Alterations, *American Journal of Law and Medicine* 28, no. 2-3 (2002):153-178 at 157-160; Sheila Jasanoff et al., CRISPR Democracy: Gene Editing and the Need for Inclusive Deliberation, *Issues in Science and Technology*, Fall 2015, available at: http://issues.org/32-1/crispr-democracy-gene-editing-and-the-need-for-inclusive-deliberation/.

ADDENDUM to:

Public Comments to the Singapore Bioethics Committee on the Topic of Mitochondrial Genome Transfer Technology

Please find attached on the following pages:

Katherine Drabiak, *Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes*, 20 JOURNAL OF HEALTH CARE LAW, 1-63 (2018).

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Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes

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Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes

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The author would like to thank Spencer Bockover for his research assistance on international law pertaining to human germline modification.

Emerging Governance of Mitochondrial Replacement Therapy: Assessing Coherence Between Scientific Evidence and Policy Outcomes

I. Introduction

In the fall of 2016, media headlines reported news of the first baby born as a result of what has been called "three parent IVF" or mitochondrial replacement therapy ("MRT").[1] The initial report indicated Dr. John Zhang, of the New York New Hope Fertility Center worked with a couple from Jordan and traveled to Mexico to perform a procedure called maternal spindle transfer.[2] *New Scientist* first described the "great news" of the first known birth of the child born to the Jordanian couple at risk for mitochondrial disease.[3] Reports asserted the infant "appeared to be healthy," but did not provide substantive evaluation of the infant.[4]

Science Magazine characterized this transnational arrangement as a means for desperate parents who wish to bear a genetically related child free from fatal genetic disease.[5] Media described MRT as a technique that allows parents with rare genetic mutations "to have healthy babies" because it constitutes a "treatment, or even a cure" and praised the courageous Dr. Zhang as a pioneer whose work "should fast-forward progress" against regulatory barriers in the United

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[1] Jessica Hamzelou, *World's First Baby Born With New "3 Parent" Technique*, NEW SCIENTIST (Sept. 27, 2016), https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/; Jennifer Couzin-Frankel, *Unanswered Questions Surround Baby Born to Three Parent*, SCIENCE (Sept. 27, 2016), http://www.sciencemag.org/news/2016/09/unanswered-questions-surround-baby-born-three-parents.

[2] *Id.*

[3] *Id.*

[4] Couzin-Frankel, *supra* note 1; *see also* Sara Reardon, *Reports of "Three-Parent Babies" Multiply*, NATURE NEWS (Oct. 19, 2016), http://www.nature.com/news/reports-of-three-parent-babies-multiply-1.20849.

[5] *Id.*

States.[6] One stem cell biologist asserted regulatory barriers have "[put] novel treatments on the long bench, and therefore it had to be done that way."[7] The British Broadcasting Corporation (BBC) praised Dr. Zhang as acting ethically on his mission to "save lives" and assist families in need of treatment.[8]

Weeks later, more reports surfaced that Dr. Valery Zukin, a physician in Kiev, Ukraine used MRT to "treat" general infertility for two patients in his clinic.[9] Similar to descriptions of Dr. Zhang's actions, *Nature* reported during the pregnancies that Dr. Zukin's technique "seems to have fixed the problem" on the premise that the pregnancy continued to progress.[10] Months later following the birth of the first infant, the media repeated the claim of good news, asserting that after fifteen years of infertility, the patient in Dr. Zukin's clinic finally gave birth to a "healthy baby" that is genetically her own.[11]

MRT described in this article currently refers to two procedures. In the first procedure, maternal spindle transfer ("MST:), the nucleus in the mother's oocyte is removed and transferred

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[6] *Id.;* Alexandra Ossola, *FDA Expected to Approve Technique to Create "The Three-Parent Babies,"* POPULAR SCIENCE (Feb. 3, 2016), http://www.popsci.com/fda-approves-technique-to-create-three-parent-babies.

[7] Reardon, *supra* note 4.

[8] Michelle Roberts, *First "Three Person Baby" Born Using New Method*, BBC NEWS (Sept. 27, 2016), http://www.bbc.com/news/health-37485263.

[9] Andy Coghlan, *"3-Parent" Baby Method Already Used for Infertility*, NEW SCIENTIST (Oct. 10, 2016), https://www.newscientist.com/article/2108549-exclusive-3-parent-baby-method-already-used-for-infertility/.

[10] Reardon, *supra* note 4; *see also* Andy Coghlan, *First Baby Born Using 3-Parent Technique to Treat Infertility*, NEW SCIENTIST (Jan. 18, 2017), https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/.

[11] 59th MEETING OF THE CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE, FDA (Feb. 25, 2014), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM390945.pdf at 19-21 [hereinafter "FDA Meeting"].

into a donor oocyte whereby the donor oocyte is subsequently fertilized.[12] The second method is referred to as pronuclear transfer ("PNT"), where both the mother's oocyte is fertilized and the donor oocyte is fertilized with sperm in vitro, which creates two zygotes. The nucleus from the fertilized donor zygote is removed and is then replaced with the nucleus from the mother's stage matched zygote.[13] These experimental techniques that promise to "swap in healthy mitochondria" have come under additional scrutiny because MRT entails nuclear genome transfer, which constitutes a modification of the germline that breaches the historical bright line of impermissible interventions on human embryos used for implantation.[14]

Despite a number of international agreements and criminal prohibitions against germline modification in other countries abroad, there is no such legal prohibition in the United States.[15] Last year in the United Kingdom, the Human Fertilisation and Embryology Authority announced it would begin reviewing license applications from fertility clinics that wished to offer MRT to patients as a means to avoid mitochondrial disease. In the United States, the FDA has discussed scientific considerations and the National Academy of Sciences, Engineering, and Medicine

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[12] *Id.*

[13] Rosa Castro, *Mitochondrial Replacement Therapy: the U.K. and US Regulatory Landscapes*, 3 J. OF L. & THE BIOSCIENCES 726, 728 (2016); FDA Briefing Document: *Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or the Treatment of Infertility*, CELLULAR, TISSUE, & GENE THERAPIES ADVISORY COMM., FDA (Feb. 25-26, 2014) [hereinafter "FDA Brief"]; *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, NAT'L ACADS. OF SCI. ENG'G & MED. at 20-21 (2016) [hereinafter "NAS Report"].

[14] *FDA Should Preserve International Consensus Against Human Germline Modifications, Center for Genetics and Society* (Feb. 19, 2014), http://www.geneticsandsociety.org/article.php?id=7528.

[15] Tetsuya Ishii, *Potential Impact of Human Mitochondrial Replacement on Global Policy Regarding Germline Gene Modification*, 29 REPROD. BIOMEDICINE ONLINE 150, 152-53 (2014); Motoko Araki & Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing Into In Vitro Fertilization*, 12 REPROD. BIOLOGY & ENDOCRINOLOGY 9 (2014); Rosario Isasi et al., *Editing Policy to Fit the Genome?* 351 SCIENCE 337 (2016).

concluded it is ethically permissible to conduct clinical investigations subject to a set of conditions. Notably, FDA discussions have not only considered MRT as a potential investigational method for treating mtDNA disease, but also as an option for treating infertility.

Drawing upon the process in the U.K., this article examines the regulatory framework developed in the U.K., contrasts this system with nations that prohibit or criminalize germline interventions, and describes the regulatory and policymaking discussions that have occurred in the United States. In response to the recent amendments to the law in the U.K. and current reproductive tourism for MRT, this article will describe efforts at public engagement during the policymaking process and the ethical divide pertaining to germline modifications. This article will synthesize the currently known scientific considerations pertaining to safety, efficacy, and risk related to mitochondrial biology, oocyte modification, and oocyte donation. Finally, the article will evaluate the medical rationale provided by proponents that such technology is both necessary and beneficial and consider the impact of commercial interests on the development of MRT.

II. Primer on Mitochondrial Biology

Mitochondria are organelles found in almost every cell in the human body and serve a number of functions including energy production, controlling metabolic processes, and programming cell growth and apoptosis.[16] Far from being mere "batteries" of the cell, scientists now recognize extensive interaction between mitochondrial DNA ("mtDNA") and nuclear DNA

[16] FDA Brief, *supra* note 13, at 5; Anne Claiborne et al., *Finding an Ethical Path Forward for Mitochondrial Replacement*, 351 SCIENCE 668 (2016); Kimberly Dunham-Snary & Scott Ballinger, *Mitochondrial-Nuclear DNA Mismatch Matters*, 349 SCIENCE 1449 (2015); Eli Adashi & I. Glenn Cohen, *Going Germline: Mitochondrial Replacement as a Guide to Genome Editing*, 164 CELL 832 (2016).

("nDNA") that directly impacts gene expression and cell function.[17] Mitochondria are maternally inherited, and pathogenic mutations in mtDNA can present as a number of serious and potentially fatal diseases.[18] Mitochondrial dysfunction may result in a variety of disorders affecting tissues with a high metabolic demand, such as the brain, heart, muscle, and central nervous system.[19]

Although many individuals in the population may carry mtDNA mutations, these mutations will not result in dysfunction unless the percent of mutant mitochondria reaches a particular threshold.[20] Currently, in the process of both MST and PNT a small percent of cytoplasm is transferred along with the nucleus during the nuclear genome transfer from the mother's oocyte or zygote into the donor's.[21] Although the rate of carryover of mtDNA has been reportedly low, scientists believe the percent of the mother's mutated mtDNA could increase.[22] Scientists refer to the percent mix of mutant mitochondria as degree of heteroplasmy.[23] When cells divide during embryogenesis, gametogenesis, and during the course of normal development, the levels of mutant mitochondria may increase in the dividing cells, which can lead to differential replication and segregation toward a higher degree of heteroplasmy, even in

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[17] FDA Brief, *supra* note 13, at 5; FDA Meeting, *supra* note 11, at 18, 24-31; Klaus Reinhardt et al., *Mitochondrial Replacement, Evolution, and the Clinic*, 341 SCIENCE 1345, 1346. (2013)(discussing the impact of mtDNA on nDNA expression and cross-talk between mtDNA and nDNA).

[18] FDA Brief, *supra* note 13, at 8.

[19] Paula Amato et al., *Three Parent In Vitro Fertilization: Gene Replacement for the Prevention of Inherited Mitochondrial Disease*, 101 FERTILITY & STERILITY 31 (2014).

[20] FDA Meeting, *supra* note 11, at 34-41 (discussing heteroplasmy and disease threshold) and at 66 (hypothesis that we all have naturally occurring heteroplasmy).

[21] FDA Meeting, *supra* note 11, at 21, 123, 168; FDA Brief, *supra* note 13, at 14-15, 20; NAS Report, *supra* note 13, at 47.

[22] FDA Meeting, *supra* note 11, at 34-41

[23] *Id.*

varying levels through different tissues in the body.[24] Scientists describe a phenomenon referred to as maternal bottleneck, defined as when levels of heteroplasmy increase from one generation to the next.[25] For example, a mother with a low level of heteroplasmy who may not display signs of mitochondrial dysfunction and appears healthy could give birth to a child with a high level of heteroplasmy that would reach the threshold and present as mitochondrial disease.[26]

Mitochondrial disease can arise from either mtDNA mutations or nDNA mutations, though inherited mtDNA mutations are rare. According to evidence presented at the Cellular, Tissue, and Gene Therapies Advisory Committee meeting in 2014, maternal transmission of mtDNA disease is rare and only occurs in 1/10,000 individuals.[27] This distinction provides crucial perspective, because failing to distinguish between maternally inherited mtDNA disease and nDNA mitochondrial disease can skew public perceptions of statistical occurrence in a misleading manner. During the public engagement process in the U.K., Human Fertilisation and Embryology Authority characterized the frequency of mitochondrial mutations as affecting 1/200 individuals, and one headline proclaimed nearly 2500 women could benefit from MRT in the U.K.[28] Yet these figures omitted discerning between mtDNA disease and mitochondrial disease resulting from nDNA mutations.[29] Most cases of mitochondrial disease arise from de novo

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[24] *Id.*
[25] *Id.* at 34-35.
[26] *Id.* at 132-35.
[27] *Id.* at 64.
[28] *Human Genetic Engineering on the Doorstep*, HUMAN GENETICS ALERT (Nov. 2012) at 4, http://www.hgalert.org/Mitochondria%20briefing.pdf; *Nearly 2,500 Women Could Benefit from Mitochondrial Donation in the U.K.*, SCIENCE DAILY (Jan. 29, 2015), https://www.sciencedaily.com/releases/2015/01/150129094353.htm.
[29] *See* Francoise Baylis, *The Ethics of Creating Children With Three Genetic Parents*, 26 REPROD. BIOMEDICINE ONLINE 531 (2013).

mutations (new mutations in mtDNA not present in the maternal line) and mutations in nDNA.[30] Approximately 80% of mitochondrial disease arises from nDNA mutations, for which MRT does not address.[31] When subtracting the incidence of nDNA disease, the final potential pool of cases where MRT may apply falls to ten persons a year for the population cited in the discussion pertaining to the U.K.[32]

There is currently no FDA approved treatment for mitochondrial disease.[33] Literature has discussed potential alternative methods designed to avoid mitochondrial disease: adoption, pre-implantation genetic diagnosis ("PGD"), and use of an oocyte donor.[34] Some scholars have rejected adoption and use of an oocyte donor because it overlooks parental desire to bear a genetically related child.[35] PGD may reduce, but not eliminate the chance for a child without mitochondrial disease based on uncertainty of whether the subsequent cellular division would result in genetic drift, defined as increasing rates of mutant DNA and heteroplasmy that reaches the threshold for disease.[36]

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[30] FDA Meeting, *supra* note 11, at 58-64; *see also* NAS Report, *supra* note 13, at 27 (discussing mtDNA disease generally relating to later onset milder conditions and nDNA disease constituting earlier onset and more severe expressivity).

[31] *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception: 2014 Update*, HUM. FERTILISATION & EMBRYOLOGY AUTH. at 12 (June 2014) [hereinafter "HFEA Scientific Review"].

[32] Ishii, *supra* note 15, at 151; *Mitochondrial Donation: Correspondence Received Relating to the Evidence Hearing on 22 October 2014*, SCI. & TECH. COMM., HOUSE OF COMMONS at 15 (2014), https://www.parliament.U.K./documents/commons-committees/science-technology/Mitochondrial%20donation/MITCorrespondence.pdf [hereinafter "U.K. Correspondence"].

[33] FDA Brief, *supra* note 13, at 9.

[34] Baylis, *supra* note 29; FDA Brief, *supra* note, at 10.

[35] Sarah Fogleman et al., *CRISPR/Cas9 and Mitochondrial Replacement Therapy: Promising Techniques and Ethical Considerations*, 5 AM. J. OF STEM CELLS 39 (2016).

[36] Amato et al., *supra* note 19, at 32.

III. International Law and Policy Pertaining to Germline Modification

Contrary to the common parlance discussing the procedure, MRT does not replace mitochondria or "swap in healthy mitochondria," but instead constitutes transferring the nucleus containing 20,000 genes from one oocyte or zygote to another.[37] This procedure is more accurately classified as nuclear genome transfer and a modification of the human germline, which has prohibited by numerous declarations, directives, and laws promulgated by international entities and other nations.[38]

A. United Nations Position on Germline Modification

The United Nations Universal Declaration on the Human Genome and Human Rights has declared that the "human genome underlies the fundamental unity of all member of the human family…it is the heritage of humanity."[39] In Article 5, the Declaration states "research, diagnosis, or treatment affecting an individual's genome shall be undertaken only after rigorous and prior assessment of potential risks and benefits," this intervention requires informed consent that the procedure would be guided by the individual's best interest, and if the individual does not have the capacity to consent then the intervention may only be carried out for the direct benefit or, alternatively, "pose such minimal risk and burden" to the individual that the research is "compatible with the protection of the individual's human rights."[40] These articles do not distinguish between somatic and germline interventions, but suggest a high level of scrutiny

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[37] *3-Person IVF A Resource Page*, CTR. FOR GENETICS AND SOCIETY, http://www.geneticsandsociety.org/article.php?id=6527.
[38] *Id.*; Isasi et al., *supra* note 15; Ishii, *supra* note 15; Araki & Ishii, *supra* note 15.
[39] Universal Declaration on the Human Genome and Human Rights, UNITED NATIONS SCI. EDUC., SCI. & CULTURAL ORG., UNITED NAT'L GEN. ASSEMB. (1997), http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights/.
[40] *Id.*

regarding risks must be applied in this area of research and individual consent must be prioritized. These points interpreted together would likely prohibit germline engineering based both on the risk profile and inability for future generations to consent to modification of their genomes.

In subsequent discussions specifically pertaining to the human genome and the appropriate uses of emerging technology, the International Bioethics Committee of the United Nations Educational, Scientific, and Cultural Organization ("UNESCO") promulgated additional guiding principles.[41] Importantly, the International Bioethics Committee noted that the human genome does not constitute raw material that scientists may manipulate at leisure, cautions against genetic reductionism and parsing component parts when attempting to treat the complex nature of human disease while noting the uncertain and highly variable state of the genome and the unpredictable impact of modifications.[42] Recognizing the transnational nature of research, the International Bioethics Committee also directly stated that we should renounce the possibility of scientists acting alone and discourage avenues of regulatory circumvention, in this instance, through reproductive tourism.[43] Finally, the International Bioethics Committee called upon the media to avoid sensationalist journalism, asserted the media's duty to promote scientific literacy, and cautioned that the direction and limitations of science should not be determined by market forces.[44]

Together, these crucial points recognize the complexities of human health and appear to

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[41] Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights, UNITED NATIONS SCI. EDUC., SCI. & CULTURAL ORG., UNITED NAT'L GEN. ASSEMB. (2015), http://unesdoc.unesco.org/images/0023/002332/233258E.pdf.
[42] *Id.* at 4.
[43] *Id.* at 3-4.
[44] *Id.* at 4.

caution against precisely the campaign occurring in support of MRT – a risky experimental procedure that separates and patches together building blocks of an embryo heralded by the media a miracle therapy – wherein the media praises physicians engaging in fertility tourism to allegedly dodge unnecessary regulations while generating publicity and expanding a highly profitable commercial market into for patients with infertility.

B. Council of Europe Position on Germline Modification

The Council of Europe has also promulgated several documents pertaining to prohibitions on germline interventions. The Council of Europe's Convention on Human Rights and Biomedicine states "an intervention seeking to modify the human genome may only be taken for preventive, diagnostic, or therapeutic purposes, and only if its aim is not to introduce any modification in the genome of any descendants."[45] This Convention clearly demarcates therapeutic somatic interventions as potentially permissible, but unequivocally distinguishes that any germline or inheritable modifications are prohibited. Aligned with this prohibition, in 2001 the European Union promulgated a directive on clinical trials that further specified, "No gene therapy trials may be carried out which result in modifications to the subject's germline genetic identity."[46] Both statements prohibit both clinical trials designed to investigate MRT because it would result in germline modifications.

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[45] Article 13, Convention on Human Rights and Biomedicine, COUNCIL OF EUROPE (1997), https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=090000168007cf98.

[46] Article 9, Directive 2001/20/EC, COUNCIL OF EUROPE (2001), http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf.

C. Comparing U.S. Governance Pertaining to Germline Modification to Other Nations

Globally, approximately forty countries[47] including Canada,[48] Germany,[49] France,[50] Switzerland,[51] Sweden,[52] and Italy[53] have adopted legislation prohibiting germline intervention on embryos.[54] Laws enacted in the aforementioned nations not only prohibit germline or heritable modification, but such actions constitute criminal violation subject to fines and or imprisonment. Unequivocally prohibiting and criminalizing an action communicates the egregiousness, potential for harm, and social unacceptability of such an action in these nations. Unlike the widespread alarmist rhetoric that the United States is "falling behind" and failing to invest in promising genomic technologies, these laws demonstrate the opposite: many countries acknowledge the lure of technology, but renounce risky experiments that cross the historical

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[47] *See* Araki & Ishii, *supra* note 15, at Table S1: Policies on Human Germline Gene Modification for Reproduction Excluding Reproductive Cloning.
[48] Assisted Human Reproduction Act § 5 (2004); Assisted Human Reproduction Act § 60 (2004).
[49] Embryo Protection Act, Federal Law Gazette, Part I, No.69 (1990).
[50] Research on Embryos, Bioethics Law, Code of Public Health Article L2151-5 (2011); Absolute Prohibition on Creating Transgenic Embryos and Chimeras, Bioethics Law, Code of Public Health. Article L2151-2 (2011); *see also* Sylvain Beaumont & Sandra Tripathi, *France's Loi du 7 Julliet 2011 Clarifies The Human Embryonic Research System*, LIFE SCIENCES BULLETIN, Fasken Martineau (Aug. 2, 2011), http://www.fasken.com/files/Publication/ad92fa84-d869-497e-80d7-071bfef919e5/Presentation/PublicationAttachment/f3b681c6-78fc-4379-aa6d-19456049955c/Life%20Sciences%20Bulletin%20-%20Beaumont-Tripathi%20-%20August%202%202011.pdf.
[51] Article 35, Federal Act on Medically Assisted Reproduction, Federal Assembly of the Swiss Confederation (1998).
[52] *See* Sections 3-4, The Genetic Integrity Act, Swedish Code of Statutes no.2006:351 (2006).
[53] Article 13, Rules of Medically Assisted Procreation, No. 40 (2004).
[54] Some laws prohibit germline modification to any embryo, some prohibit modification for implantable embryos. *See also* Isasi et al., *supra* note 15; Anna Zaret, *Editing Embryos: Considering Restrictions on Genetically Engineering Humans*, 67 HASTINGS L. J. 1805, 1810-11 (2016).

bright line of manipulating future generations.[55]

Canada's Assisted Human Reproduction Act in particular contains notable provisions that prioritize central concepts to guide appropriate application of technology relating to reproductive and genomic interventions.[56] Section 2 of Canada's Assisted Human Reproduction Act states that the "health and well-being of future children must be given priority," and that the Parliament seeks to uphold the "protection of human health, safety, dignity and rights" relating to the use of assisted reproductive technologies, and prohibits compensation for oocyte donors due to the potential for health risks and exploitation.[57] Further, Subsection (g) of Section 2 explicitly states "the integrity of the human genome must be preserved and protected."[58] These provisions together recognize the commercial nature of technology and declare neither commercial nor other interests, such as the technological imperative, ought to drive the adoption of technology and modification of the germline is prohibited.[59]

In 2015, the National Academy of Sciences, Engineering and Medicine, the Royal Society, and the Chinese Academy of Sciences sponsored the International Summit on Human Gene Editing to discuss broader issues relating to gene editing and modification of the

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[55] *The Science and Ethics of Genetically Engineered Human DNA*, Hearing Before the Subcommittee on Research and Technology, 114TH CONGRESS (2015). Rather than discussing human dignity or risks of technology, attendees at this hearing pled for federal funding, noted the global market competitiveness, and asserted regulation must not "squelch the science" or the United States would "fall behind." Attendees also mischaracterized the experimental nature of germline modification, asserting that parents merely have a "desire to protect their children" [by modifying their genomes] and there may be a time when we consider it unethical not to modify our children's genomes.

[56] Assisted Human Reproduction Act § 2 (2004).

[57] *Id.*

[58] *Id.*

[59] *Id.*

germline.[60] Though the meeting discussed recent research relating to other genetic modification technologies such as CRISPR, many of the considerations are also applicable to MRT. The National Academies Press published a meeting summary that called for a moratorium on clinical germline modification, noting safety and efficacy issues are unresolved, and such action could impose irreversible risks and long term harms.[61] Commentators at the International Summit also recognized the potential for economic interests to capitalize on the global nature of science and technology, where technology adopted in one location prompts international forum shopping. [62]

Situating the actions of Dr. Zhang and Dr. Zukin against the backdrop of the global climate where many nations not only prohibit, but impose criminal penalties for these risky experiments it becomes exceedingly clear how radical these events were. Numerous scientists, bioethicists, and policymakers swiftly voiced vehement opposition, asserting that "going rogue" was "irresponsible and unethical" because it combined reproductive tourism promoting commercial interests with "highly experimental science."[63] These characterizations stand in stark contrast to media articles praising Dr. Zhang, decrying slow "progress" in the United States, and

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[60] International Summit on Human Gene Editing: A Global Discussion, NAT'L ACAD. OF SCI., ENG'G & MED. (2015), https://www.nap.edu/catalog/21913/international-summit-on-human-gene-editing-a-global-discussion.

[61] *Id.*

[62] *Id.*

[63] *Comment on the Use of Mitochondrial Manipulation Techniques by US Scientists in Mexico*, CTR. FOR GENETICS & SOC'Y (Sept. 27, 2016), http://www.geneticsandsociety.org/article.php?id=9697; *Comment on "3-Person IVF" Procedures Reportedly Conducted in Ukraine*, CTR. FOR GENETICS & SOCIETY (Oct. 10, 2016), http://www.geneticsandsociety.org/article.php?id=9730; *3-Person IVF A Resource Page*, *supra* note 37; *see also* Paul Knoepfler, *First 3-Person IVF Baby Born Via "Rogue" Experiment in Mexico Clinic? The Niche* (Sept. 27, 2016), https://ipscell.com/2016/09/first-3-person-ivf-baby-born-via-rogue-experiment-at-mexico-clinic/; Pete Shanks, *Wrong Steps: The First One From Three*, DECCAN CHRON. (Oct. 2, 2016), http://www.deccanchronicle.com/lifestyle/viral-and-trending/021016/wrong-steps-the-first-one-from-three.html.

intimating these procedures constitute an effective "treatment, or even cure."[64] Perpetuating such bias and gross mischaracterization in scientific media deliberately skews the framing of the discussion as an intentional means to gain favor and direct the outcome. This campaign not only lacks transparency, but promotes a policymaking process premised upon inaccurate scientific information and false characterizations of global legal consensus that renders it egregiously unethical. Furthermore, Dr. Zhang's actions to evade regulatory structures in the United States by performing MRT in Mexico were precisely the type predicted by the International Summit, and will likely continue to occur based on a public statement from the New Hope Fertility Center branch in Mexico promising plans for more "three-parent babies."[65]

IV. United Kingdom's Process to Permit MRT

In 2013, the Human Fertilisation and Embryology Authority (HFEA) began its consultation process to consider the process of permitting MRT. The HFEA is the entity in the U.K. that oversees reproductive technologies such as IVF and commercial surrogacy and promulgates criteria for licensing fertility clinics.[66] During the policymaking process in the United Kingdom, scientists, bioethicists, and other stakeholders raised concerns about how both the British media, the U.K. Department of Health, and the HFEA presented MRT to the public.[67]

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[64] Ossola, *supra* note 6; Michael Le Page, *Mexico Clinic Plans 20 "Three-Parent" Babies in 2017*, NEW SCIENTIST (Dec. 9, 2016), https://www.newscientist.com/article/2115731-exclusive-mexico-clinic-plans-20-three-parent-babies-in-2017/.

[65] *Id.*

[66] Castro, *supra* note 13; 3-Person IVF: A Resource Page, *supra* note 37; About the HFEA, Human Fertilisation and Embryology Authority, http://www.hfea.gov.U.K./25.html.

[67] *See generally* Steve Connor, *Scientists Accuse Government of Dishonesty Over GM Babies in Its Regulation of New IVF Technique*, THE INDEPENDENT (July 28, 2014), http://www.independent.co.U.K./news/science/exclusive-scientists-accuse-government-of-dishonesty-over-gm-babies-in-its-regulation-of-new-ivf-9631807.html; Stuart Newman, *Deceptive Labeling of a Radical Embryo Construction Technique*, HUFFINGTON POST (Dec. 1, 2014),: http://www.huffingtonpost.com/stuart-a-newman/deceptive-labeling-of-a-r_b_6213320.html.

At the start of this initial period of consultation, forty one signatories including notable bioethicists, scholars, and scientists published a letter to the editor of *The Times* expressing alarm over HFEA's proposal for MRT.[68] This letter noted the broad global consensus against germline interventions, stated MRT would "cross the Rubicon" and open the door to other germline modifications, and may pose unforeseen consequences.[69] The authors also noted the transnational implications and urged HFEA against acting alone, declaring the U.K. must consider its "international responsibilities."[70] Despite exceedingly clear widespread opposition and breach of longstanding international precedent against germline modifications, HFEA continued its deliberative process.

A. HFEA Review and U.K. Department of Health

In 2014, the HFEA published a Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease Through Assisted Conception ("HFEA Review").[71] The HFEA Review referenced a provision from an amendment passed in 2008 that defined a "[permitted] egg or embryo" as one that has been altered through a technique designed to avoid the transmission of mitochondrial disease.[72] Unlike the indicated use under consideration in the United States, the regulation in the U.K. only pertains to MRT for the purpose of avoiding mitochondrial disease and the HFEA Review specifies it does not currently encompass treatment for infertility. The HFEA Review reflected a favorable option toward MRT, basing its presumptions on measuring low preliminary levels of carryover maternal mutant mtDNA, asserting the methods of MRT are

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[68] Letter to the Editor, *Alarm Over Genetic Control of Embryos*, THE TIMES (March 20, 2013), http://www.thetimes.co.U.K./tto/opinion/letters/article3717615.ece.
[69] *Id.*
[70] *Id.*
[71] HFEA Scientific Review, *supra* note 31.
[72] *Id.* at 10.

"efficient" and "reassuring."[73] The HFEA Review also characterized that existing animal models demonstrated "good progress"[74] and concluded "the evidence does not seem to suggest the techniques are unsafe."[75]

During this process, the U.K. Department of Health issued several reports and statements describing the process of MRT that strategically characterized the procedure in a manner to avoid scrutiny for the crossing the bright line prohibition against germline modifications.[76] First, the U.K. Department of Health conceded that MRT constituted a germline modification, but argued that it did not pose a genetic modification because there is not an agreed upon definition of what a genetic modification entails.[77] The U.K. Department of Health suggested modifying mtDNA and performing nuclear genome transfer does not alter the oocyte or embryo's genetic information, asserting mtDNA merely functions as batteries of the cell.[78] Second, the U.K. Department of Health extended this presumption by maintaining MRT would not contravene the Universal Declaration on the Human Genome and Human Rights' prohibition against germline interventions because it serves a therapeutic corrective purpose so it does not harm human

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[73] *Id.* at 14.
[74] *Id.* at 18-19.
[75] *Id.* at 4.
[76] Connor, *supra* note 67; *Mitochondrial Donation: A Consultation on Draft Regulations to Permit the Use of New Treatment Techniques To Prevent the Transmission of A Serious Mitochondrial Disease From Mother to Child*, U.K. DEP'T OF HEALTH at 13-14 (Feb. 2014), https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf.; *Mitochondrial Donation: Government Response to the Consultation on Draft Regulations to Permit the Use of New Treatment Techniques To Prevent the Transmission of A Serious Mitochondrial Disease From Mother to Child*, U.K. DEP'T OF HEALTH at 15 (July 2014), https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf.
[77] *Id.*
[78] *Id.*

dignity.[79] This bizarre twisting of terminology not only distorted the characterization of MRT to the public, but fueled scientifically incorrect descriptions in British media aimed at garnering public support.

The HFEA Review acknowledged the potential for complications pertaining to safety and efficacy, but unilaterally disregarded what the scientific community has described as numerous substantial barriers.[80] For example, the HFEA Review addressed differential segregation and maternal bottleneck that could result in increasing levels of heteroplasmy during the offspring's course of development in different tissues, and increasing levels of heteroplasmy through subsequent generations.[81] In response to this possibility, the HFEA Review responded "there is little evidence of this occurring."[82] Importantly, HFEA's evaluation is based on the premise that PGD testing of the blastocyst (cells in early stages of embryonic development) constitutes an accurate representation of both lifetime heteroplasmy in all subsequently developed tissues and health of the eventual offspring.[83]

The HFEA cited animal studies using macaque models where about half of the macaque embryos appeared to develop normally as evidence of "good progress" that MRT appeared to work.[84] In response to the half of embryos following MRT that did not develop correctly, HFEA disregarded these findings, asserting there may be "some differences in embryo development, but nothing has been found to raise concerns of safety."[85] The HFEA also noted the concern that there may be incompatibility arising from mixing mtDNA from two sources, but concluded

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[79] *Id.*
[80] *See generally* U.K. Correspondence, *supra* note 32; FDA Meeting, *supra* note 11.
[81] HFEA Scientific Review, *supra* note 31, at 26.
[82] *Id.*
[83] *Id.* at 13.
[84] *Id.* at 20.
[85] *Id.* at 20.

mixing two sources of mtDNA would not pose any complications to interaction with nDNA or cell function.[86] As support for its conclusion, HFEA observed that children from mixed race parents (one source of maternal mtDNA) do not exhibit higher percentages of mitochondrial disease.[87]

B. Public Comments in the U.K. Policymaking Process

During this process, the U.K. House of Commons Science and Technology Committee held a hearing on the scientific evidence for MRT and published written correspondence from numerous scientists, physicians, bioethicists, and other stakeholders.[88] Although a minority of comments lent support to HFEA's proposed direction and even asserted it would be unethical not to use MRT,[89] the majority of public comments fervently opposed MRT precisely based on unsettling and unresolved issues pertaining to evidence for its safety and efficacy.[90] A number of comments highlighted the unpredictability of differential segregation and maternal bottleneck, asserting that attempting to measure carryover of maternal mtDNA in the blastocyst via PGD was an ineffective and improper proxy for predicting long term levels of heteroplasmy and health outcomes.[91] Comments also opposed HFEA's characterization of animal models as successful, noting that the 52% of animal embryos that did not develop correctly demonstrated chromosomal abnormalities, and questioned whether these findings may result in unexamined differences in

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[86] *Id.* at 23, 28-31.
[87] *Id.*
[88] U.K. Correspondence, *supra* note 31.
[89] *Id.* at 7-8. Progress Educational Trust asserted there was prevailing support for HFEA's regulation to permit MRT rationalizing al medical treatment entails experimental results, and it would be unethical not to employ MRT.
[90] *Id.* at 23, 29, 33-49, 48, 73.
[91] *Id.* at 33-35, 50, 64-66.

the embryos that scientists proclaimed were developing normally.[92]

In addition to these responses, multiple comments disputed HFEA's conclusion pertaining to the compatibility of two sources of mtDNA and epigenetic effects resulting from transfer of the nuclear genome from one oocyte or embryo to another.[93] A number of interested parties, including the Council for Responsible Genetics, Human Genetics Alert, and several scientific experts submitted similar assessments noting evidence for extensive communication between mtDNA and nDNA expression.[94] Disrupting mtDNA functioning and cross-talk to nDNA directly influences DNA methylation and chromosomal gene expression.[95] That is, mitochondria are not merely batteries supplying energy to the cell that can be deftly exchanged, but part of a complex interwoven system necessary for the entire organism's subsequent development.[96] These observations also highlighted the unprecedented risks related to embryo manipulation, noting the more extreme the level of physical manipulation, the higher the potential for physical damage to the embryo or epigenetic changes resulting from the process of physical manipulation and the risk for functional and developmental health deficits.[97]

Notably, these comments independently evaluated the status of scientific evidence underlying HFEA's conclusion that the techniques appear "not unsafe" and concluded the

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[92] *Id.* at 23; *see also* Aditi Shah, *"Not Unsafe" Does Not Equal Safe: An Evaluation of the HFEA's Report on MST and PNT*, COUNCIL FOR RESPONSIBLE GENETICS (June 3, 2014), http://www.councilforresponsiblegenetics.org/pageDocuments/Q2M4IDTBFZ.pdf [hereinafter "Council for Responsible Genetics"].

[93] U.K. Correspondence, *supra* note 31, at 29, 33-35, 39-49, 53, 64-65, 73.

[94] *Id.* at 33-35, 39-49; Council for Responsible Genetics, *supra* note 92; Human Genetics Alert, *supra* note 28; *Report on the Safety of "Mitochondrial Replacement" Techniques: Epigenetic Issues*, HUMAN GENETICS ALERT (March 2013), http://www.hgalert.org/Report%20on%20the%20safety%20of%20mitochondrial%20transfer.pdf

[95] *Id.*

[96] *Id.*

[97] *Id.*

opposite: *these techniques are likely to be unsafe.*[98] Human Genetics Alert questioned why HFEA would blatantly dismiss substantial categories of potential risks, alleging its process was based on "disastrously flawed scientific assumptions," charged that the public consultation process was "biased" because HFEA did not accurately describe MRT, and asserted the amendment lacked public support.[99] Cell biologist Professor Stuart Newman reiterated Human Genetics Alert's objection to improper framing to the public because HFEA the technology as "mitochondrial donation." [100] Newman implored HFEA to appropriately label the technology as nuclear genome transfer, pointing out this technique creates a child through an evolutionary unprecedented experiment because it removes 20,000 chromosomes from one ooctye or embryo and transfer this nDNA into another oocyte or embryo.[101] Critics exhorted that "harmful consequences of these methods could impair entire generations," and issued proclamations that HFEA's conclusions were both "incomplete and unsubstantiated."[102] Reiterating this warning, cell biologist Professor Paul Knoeplfer proclaimed the U.K. was on the verge of an "historic mistake."[103]

C. The Role of British Media

The press quickly rebounded and parroted the U.K. Department of Health and HFEA's strategic framing to garner support for the 2015 amendment to the Human Fertilisation and

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[98] U.K. Correspondence, *supra* note 31, at 29, 48.
[99] *Id.* at 48.
[100] *Id.* at 73.
[101] *Id.* at 74.
[102] Council for Responsible Genetics, *supra* note 92, at 17; Reinhardt et al., *supra* note 17.
[103] Sarah Knapton, *Three Parent Babies Could Be At Greater Risk of Cancer, Warn Scientists*, THE TELEGRAPH (Feb. 3, 2015), http://www.telegraph.co.U.K./news/science/science-news/11385370/Three-parent-babies-could-be-at-greater-risk-of-cancer-warn-scientists.html.

Embryology Act that would expressly regulate MRT.[104] Professor Julian Savulescu compared MRT to a "micro-organ transplantation," alleging there is "no sound basis to oppose MRT" because it constitutes a "cure" so infants can be born without mitochondrial disease.[105] An article in the *Guardian* appealed to the pathos of parental suffering touting MRT as a method to prevent incurable genetic disease and "[save] families needless misery" over ill-advised objections of religious groups.[106] Both Savulescu and an article in the *New York Times* chided opposition to MRT, scoffing that "preventing medical advancement" is so illogical, it could only be based on being improperly informed.[107]

These pieces in the media not only reinforced incorrect scientific characterizations set forth by the U.K. Department of Health and the HFEA, but employed a dangerous precedent of classifying legitimate scientific dissent supported by credible evidence outside the parameters of acceptable discussion. Elevating the U.K. Department of Health and HFEA's presumptions as sacrosanct is not only scientifically disingenuous, but dangerous to the honesty and transparency required in the policymaking process.

D. Outcome of the U.K. Policymaking Process and Lessons for the U.S.

In November of 2016, HFEA recommended "cautious use" of MRT subject to a set of

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[104] Polly Toynbee, *This Isn't About Three-Parent Babies. Its About Saving Families Needless Misery*, THE GUARDIAN (Feb. 3. 2015), https://www.theguardian.com/commentisfree/2015/feb/03/three-parent-babies-families-religious-mps-vote-mitochondrial-replacement; Julian Savulescu, *Mitochondrial Disease Kills 150 Children a Year. A Micro-Transplant Can Cure It*, THE GUARDIAN (Feb. 2, 2015), https://www.theguardian.com/science/2015/feb/02/mitochondrial-transfer-micro-transplant-parliamentary-debate; Kenan Malik, *The Three-Parent Baby's First Step,* NEW YORK TIMES (Feb. 22, 2015), https://www.nytimes.com/2015/02/23/opinion/the-three-parent-babys-first-step.html.

[105] Savulescu, *supra* note 104.

[106] Toynbee, *supra* note 104.

[107] Savulescu, *supra* note 104; Malik, *supra* note 104.

conditions where individual fertility clinics must apply for a license to conduct the procedure.[108] Following HFEA's decision, the Newcastle Fertility Center announced its intent to submit an application for a license and begin the process of offering MRT to its fertility patients meeting the criteria set forth by HFEA.[109]

A number of key points emerged during the lengthy policymaking process in the U.K. that provides perspective when considering the process in the U.S. When HFEA and the U.K. Department of Health initially raised the possibility of MRT, bioethicists, scholars, and scientists noted MRT would breach the broad global consensus against germline modifications and urged the government to reconsider. To initially gain favor, the HFEA and the U.K. Department of Health strategically named the techniques MRT rather than accurately describing it as nuclear genome transfer. Relabeling a procedure by comparing it to an acceptable practice such as organ donation or replacing batteries obfuscated the gravity and risk involved. During the consultation process, numerous scientists provided testimony and correspondence at length relating to safety and efficacy. These scientists objected to HFEA's conclusions based on available evidence, finding not merely a lack of consensus pertaining to safety and efficacy, but that the available scientific evidence demonstrated how unsafe MRT is. Despite objections based on international governance, evidence demonstrating insufficient safety and efficacy, and lack of public consensus, British Parliament passed the amendment that would permit HFEA to license fertility

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[108] U.K.'s Independent Expert Panel Recommends "Cautious Adoption of Mitochondrial Donation in Treatment, HUM. FERTILISATION AND EMBRYOLOGY AUTH. (Nov. 30, 2016), http://www.hfea.gov.U.K./10559.html.

[109] Ian Sample, *U.K. Doctors To Seek Permission to Create Baby With DNA From Three People*, THE GUARDIAN (Nov. 30, 2016), https://www.theguardian.com/science/2016/nov/30/U.K.-doctors-to-seek-permission-to-create-baby-with-dna-from-three-people-mitochondrial-replacement-therapy; Ian Sample, *First U.K. Baby From Three People Could Be Born Next Year*, THE GUARDIAN (Dec. 30, 2016), https://www.theguardian.com/science/2016/dec/15/three-parent-embryos-regulator-gives-green-light-to-U.K.-clinics.

clinics to offer MRT reflecting a massive disconnect in the legal, scientific, and policymaking process.

V. United States Governance and Policymaking Related to MRT

Similar to the United Kingdom, the United States has undertaken steps to begin the process of permitting MRT. There is currently no legal prohibition against germline modification in the United States.[110] In 2014, the FDA convened meetings to discuss the medical rationale and scientific evidence pertaining to MRT for both the prevention of mitochondrial disease and the treatment of infertility.[111] In 2015, the White House announced that germline modifications constituted a line "that should not be crossed at this time"[112] and the NIH issued a statement it would not fund research involving germline modification.[113] However, in 2016, the National Academies of Science, Engineering, and Medicine issued a report (NAS Report) on the ethical and policy implications of MRT and concluded it is ethically permissible to conduct clinical investigations subject to a set of conditions.[114] Based on another subsequent report issued by NAS endorsing therapeutic germline modification through gene editing, it appears likely that the governance climate in the U.S. favors MRT, and any present prohibitions related to federal funding may potentially be lifted in the future.[115]

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[110] *See supra* notes 11-16.
[111] FDA Meeting, *supra* note 11; FDA Brief, *supra* note 13.
[112] *A Note on Genome Editing*, THE WHITE HOUSE (May 26, 2015), https://obamawhitehouse.archives.gov/blog/2015/05/26/note-genome-editing.
[113] Xavier Symons, *Interview: Carrie D. Wolinetz of the NIH on Gene Editing*, BIOEDGE (Feb. 23, 2016), https://www.bioedge.org/bioethics/interview-carrie-d.-wolinetz-of-the-nih-on-gene-editing/11770.
[114] NAS Report, *supra* note 13.
[115] *Human Genome Editing: Science, Ethics, and Governance*, NAT'L ACAD. OF SCI., ENG'G, & MED. (2017), https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance. The Dickey-Wicker Amendment prohibiting federal funding of research on human embryos contains an exception that permits research where the research would provide medical benefit to the embryo. *See* NAS Report, *supra* note 13, at 64.

A. Applicable FDA Regulations to MRT

In the United States, any clinical investigational use of MRT falls under the purview of the FDA. Under the Public Health Service Act ("PHSA"), the FDA regulates human cell and tissue products ("HCT/Ps"), which refers to articles "containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[116] These regulations are designed to prevent contamination and communicable disease rather than to ensure safety and efficacy.[117] They impose several requirements such as registering the HCT/Ps with the FDA and promulgating standards for Good Tissue Practices, including monitoring the procedures, facilities, processing equipment, and supplies and reagents used in the manufacturing process.[118] Under the HCT/P system set forth in 21 CFR §1271, the FDA classifies different types of human cells, tissues, and cellular and tissue-based products into categories for regulation based on the public health risks they pose: (1) products not subject to HCT/P regulations, (2) HCT/Ps regulated under Section 361 of the PHSA, and (3) products posing the most risk that are to be regulated stringently as a biological product or drug.[119]

In the late 1990s and early 2000s several clinics began to conduct cytoplasm transfers. These procedures differed from MRT currently under consideration because the procedure involved injecting cytoplasm from a donor containing mitochondria into the mother's oocyte and did not involve nuclear genome transfer.[120] Though technically distinct, these procedures

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[116] 21 C.F.R. § 1271.3(d) (2016).
[117] 21 C.F.R. § 1271.145 (2016).
[118] 21 C.F.R. § 1271.150 (2016).
[119] *Id.*; 21 C.F.R. § 1271.151 (2016).
[120] Carol A. Brenner et al., *Mitochondrial DNA Heteroplasmy After Human Ooplasmic Transplantation*, 74 FERTILITY & STERILITY 573 (2000); Serena Chen et al., *A Limited Survey-Based Uncontrolled Follow-Up of Study of Children Born After Ooplasmic Transplantation in a Single Centre*, 33 REPROD. BIOMEDICINE ONLINE 737 (2016); *see also* Castro, *supra* note 13, at 731.

resulted in the birth of seventeen children, two of whom had chromosomal abnormalities and one whom had with pervasive developmental disorder.[121] Only cursory follow-up has been conducted on the health of the resulting children, but the incident prompted the FDA to assert its jurisdiction over this area of reproductive technology.[122]

In 2001, the FDA expanded its definition of "human cells, tissues, or cellular or tissue based products" HCT/Ps to include semen or other reproductive tissue.[123] This required fertility clinics handling gametes and reproductive tissue to comply with requirements for laboratory registration, minimal procedures to screen HCT/Ps for communicable disease, and good manufacturing procedures.[124] FDA considers standard procedures such as IVF "minimal manipulation" and subject only to the requirements set forth in Section 1271.[125]

Around this time in 2001, the FDA sent a warning letter to the scientists conducting cytoplasm transfers, asserting clinical research involving the transfer of genetic material must be conducted pursuant to an investigational new drug application.[126] In 2009, the FDA issued guidance affirming this position, asserting procedures currently used for MRT including

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[121] *Id.*

[122] The subsequent health of the children was assessed using self-reported parent questionnaires but did not rely on physical medical testing. *See* Brenner et al., *supra* note 120; Chen et al., *supra* note 120; Castro, *supra* note 13, at 730-731; *Warning Letter, Letter to Sponsors/Researchers- Human Cells Used in Therapy Involving the Transfer of Genetic Material By Means Other Than the Union of Gamete Nuclei*, FDA (July 2, 2001), https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105852.htm [hereinafter "Ooplasm Warning Letter"].

[123] Evita Grant, *FDA Regulation of Clinical Applications of CRISPR-CAS Gene Editing Technology*, 71 FDA L. J. 608, 621 (2016); *What You Should Know: Reproductive Tissue Donation*, FDA, https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm232876.htm; FDA Meeting, *supra* note, at 14-17.

[124] *Id.*

[125] NAS Report, *supra* note, at 22.

[126] *Id.*; Ooplasm Warning Letter, *supra* note 122.

maternal spindle transfer and pronuclear transfer that involve the transfer of genetic material constitute "more than minimal manipulation" and require the investigator to submit an investigational new drug application.[127] Thus, clinical investigation of MRT would require "submitting preclinical data and information on product safety, details about technique, and proposed clinical investigation protocols" pursuant to an investigational new drug application.[128] If the FDA were to approve MRT and license its use for only one indication such as the prevention of mtDNA disease, clinics would be able to expand the scope of indications through off label use for other uses such as infertility and therapeutic energetic correction.[129] As with other drugs and biologics, off label use dramatically expands both the potential market and opportunity for commercial profit.

B. Federal Funding Considerations

In addition to federal regulations set forth by the FDA, clinical investigation using embryos would be subject to federal funding restrictions and subject to state laws pertaining to research on embryos, some of which appear to prohibit MRT.[130] At the federal level, the Dickey-Wicker Amendment prohibits the use of federal funds for research in which an embryo is created or destroyed.[131] However, some state laws as well the Dickey-Wicker Amendment contain exceptions in circumstances where the research on the embryo would provide benefit to the embryo or if the investigation is defined as therapeutic research designed to lead to gestation and birth of that embryo.[132] Finally, the Consolidated Appropriations Act of 2016 currently

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[127] FDA Meeting, *supra* note 11, at 15-17; *see* NAS Report, *supra* note 13, at 22.
[128] *Id.*
[129] NAS Report, *supra* note 13, at 68-69.
[130] *Id.* at 66-67.
[131] Grant, *supra* note 123, at 615.
[132] *See* NAS Report, *supra* note 13, at 59, 67.

prohibits the FDA from using federal funds to consider applications for an exemption for investigational use of a drug or biological product "in research in which a human embryo is intentionally created or modified to include heritable genetic modification."[133] Although the Consolidated Appropriations Act appears to prohibit the FDA from using federal funding to review applications for MRT, the NAS Report recently questioned whether MRT constitutes heritable germline modification, asserting it would require additional legal analysis which makes the application of the spending prohibition uncertain.[134]

C. FDA Meetings to Discuss Safety, Efficacy, and Risks of MRT

In 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee of the FDA held a meeting titled "Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or Treatment of Infertility," ("MRT Meeting") which addressed the intersecting regulatory and scientific considerations pertaining to safety and efficacy of MRT based on available data and the state of scientific knowledge.[135] In conjunction with this meeting, the FDA published a briefing document ("MRT Brief") on the same summarizing the proposed methodology and areas of concern pertaining to safety.[136]

1. Determining Efficacy and Defining Success

During the MRT Meeting, the FDA addressed the patient population and indicators of how to define success. Significantly, the MRT Meeting not only addressed MRT for the prevention of mtDNA disease, but also for treating infertility. Unlike other potential clinical trials where the FDA determines calculations of safety and efficacy for the intended patient, the

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[133] Section 749, Consolidated Appropriations Act, PUBLIC LAW NO. 114-113, 114th Congress (2015-2016); *see also* Castro, *supra* note 13, at 732.
[134] NAS Report, *supra* note 13, at 2.
[135] FDA Meeting, *supra* note 11.
[136] FDA Brief, *supra* note 13.

subject would be created using the proposed methodology. Past reports issued by the President's Council on Bioethics and the NAS have asserted that because the clinical investigation occurs on the embryo, it would not constitute human subjects research as defined in the Common Rule.[137] Under this interpretation, any research conducted prior to implantation need not meet the requirements set forth in the Common Rule such as its specific requirements for informed consent and the provision that the benefits must be greater than the risks as applied to the resulting child.

Participants at the MRT Meeting posed the question of how to define efficacy, with some participants proposing that efficacy can be determined from a viable pregnancy.[138] During the course of the meeting, however, commentators noted lack of scientific consensus pertaining to defining the parameters of efficacy, and some commentators urged testing the blastomere (cells in early stages of embryonic development) for viability is not indicative of the health of the child and subsequent offspring.[139] One scientist also noted that testing a sample is not indicative of the rest of the inner cell mass, meaning different levels of heteroplasmy may exist, and even subsequently develop at varied rates in different tissues though stages of development and the child's life.[140] Based on those metrics, efficacy could not be determined merely from a viable pregnancy but instead requires examining the health of the child and potentially the child's

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[137] NAS Report, *supra* note 13, at 92; "*Research Involving In Vitro Human Embryos,*" *Reproduction and Responsibility: The Regulation of New Biotechnologies*, THE PRESIDENT'S COMM. ON BIOETHICS at 164, 180 (2004), https://repository.library.georgetown.edu/bitstream/handle/10822/559381/_pcbe_final_reproduction_and_responsibility.pdf?sequence=1&isAllowed=y; *see also* Niklaus Evitt et al., *Human Germline CRISPR-CAS Modification: Toward a Regulatory Framework*, 15(12) AM. J. BIOETHICS 25 (2015).

[138] FDA Meeting, *supra* note 11, at 168, 246, 261-71.

[139] *Id.*

[140] *Id.* at 84-87, 85.

offspring. Scientists and scholars have commented on this bind, observing that we simply cannot know with certainty whether MRT would be safe and effective because germline intervention necessarily imposes substantial risk that cannot be eliminated.[141]

2. Current Barriers to Safety and Efficacy in MST and PNT

Throughout the course of the meeting, the participants discussed a number of barriers to safety and efficacy arising from mitochondrial biology described *supra* in Section II.

a. Maternal Bottleneck, Segregation, and Heteroplasmy

According to participants at the MRT Meeting, animal models have not sufficiently addressed maternal bottleneck, where levels of mutant mtDNA can increase from one generation to the next.[142] Currently, it is difficult to predict the child's pattern of inheritance based on the mother's percent of mutated mtDNA. Thus, a mother presenting without mtDNA disease based on her low level of heteroplasmy could give birth to a child with a high level of heteroplasmy that reaches the threshold to be affected by mtDNA disease. Furthermore, maternal bottleneck can increase the percent heteroplasmy in each subsequent generation.[143] A blastomere, or even a child that initially demonstrates low levels of heteroplasmy from mutant mtDNA carryover who appears healthy may pass on amplified risk to future generations who would present with mtDNA disease.[144] Some evidence exists to suggest these risks would particularly affect female generations.[145] These observations pertaining to maternal bottleneck mirror the shortcomings of PGD as a method of currently screening embryos at risk for mtDNA disease, and underscore the

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[141] Baylis, *supra* note, at 533; Lanphier et al., *Don't Edit the Human Germline*, 519 NATURE 410, 411 (2015) (Discussing the uncertainty of germline modifications, stating "The precise effects of genetic modification to an embryo may be impossible to know until after birth.").
[142] FDA Meeting, *supra* note 11, at 34-35, 141-142; FDA Brief, *supra* note 13, at 7, 21.
[143] *Id.*
[144] *Id.* at 132-35.
[145] FDA Brief, *supra* note 13, at 21, 39.

inability to predict efficacy based on testing the blastomere.[146] Additionally, even testing adult tissues may demonstrate no mtDNA mutations, but mtDNA mutations could be present in the germ cells of the individual and be passed on through reproduction to the subsequent generation, and increase from one generation to the next.[147]

Currently, effective methodology does not exist to account for testing the fluid mutations of mtDNA in every tissue over the human lifespan.[148] Following the procedure of MST or PNT, the combination of maternal mtDNA carried over into the donor oocyte continues to divide and increase in each cell of the growing organism. Biologist Dr. Shoukhrat Mitalipov, whose lab had been conducting investigations based on animal models, asserts segregation in tissues drifts toward homoplasmy, which would result in the donor's mtDNA dominance.[149] Despite Mitalipov's testimony at the MRT Meeting declaring favorable genetic drift, this presumption is not universally shared by other experts.[150] According to other research, there is little known about the dynamic by which mtDNA evolves within an organism, because one haplotype (the group of genes in mtDNA–here there is the maternal haplotype of mtDNA and the donor haplotype of mtDNA) could replicate faster than the other, which could result in a dramatic increase in the level of heteroplasmy.[151]

Segregation and replication of mtDNA occurs according to its own evolutionary system, which makes predicting subsequent levels of heteroplasmy difficult.[152] Even if segregation

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[146] *See* FDA Meeting, *supra* note 11, at 137; NAS Report, *supra* note 13, at 58.
[147] FDA Meeting, *supra* note 11, at 180, 239; NAS Report, *supra* note 13, at 58.
[148] FDA Meeting, *supra* note 11, at 180.
[149] *Id.* at 144.
[150] *See* U.K. Correspondence, *supra* note 32, at 33-35; Joerg Patrick Burgstaller et al., *mtDNA Segregation in Heteroplasmic Tissues Is Common In Vivo and Modulated By Haplotype Difference and Developmental Stage*, 7 CELL REPORTS 2031, 2036 (2014).
[151] Burgstaller et al., *supra* note 150, at 2031.
[152] *Id.*

initially demonstrates favorable drift toward the donor's mtDNA, these levels may jump unpredictably, or segregate at different levels in tissues throughout the body.[153] Levels of mtDNA in the child's blood may reflect a low percent of heteroplasmy, but genetic drift can cause segregation toward the mother's mutated mtDNA in specific tissues or organs, wherein the child may experience diseases arising in those systems.[154] Specifically, one study demonstrated initial carryover rates of maternal mtDNA of 1.2% unexpectedly increased to 53% when studying embryos in culture, leading one biologist in favor of MRT to admit that "it would defeat the purpose of doing mitochondrial replacement" and "it is wise not to move forward with this uncertainty."[155] Finally, segregation occurs throughout the lifespan of the individual which means low levels of the mother's mtDNA in the child's blood or partial tissue testing would also not reflect the possibility of increasing levels of heteroplasmy later in life resulting in latent presentation of mitochondrial disease.[156] Thus, statements that claim heteroplasmy would not pose a problem if initial carryover of mtDNA appears unsupported by existing evidence.[157]

In addition to maternal bottleneck and segregation shifting the percent of mutant mtDNA, mutations in mtDNA that cause heteroplasmy naturally occur through aging and increases throughout one's life.[158] In addition to mutated mtDNA, both de novo (new) mutations and mutations to nDNA occur that can result in mitochondrial dysfunction.[159] Some scientists hypothesize there are naturally occurring levels in heteroplasmy in everyone contributing to

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[153] *Id.*; Ewen Callaway, *Three-Person Embryos May Not Expel Harmful Genes*, 533 NATURE 445 (2016).
[154] *Id.*
[155] Callaway, *supra* note 153.
[156] Burgstaller et al., *supra* note 150, at 2031.
[157] FDA Meeting, *supra* note, at 214-215, 222.
[158] *Id.* at 34-35.
[159] *Id.* at 194; FDA Brief, *supra* note 13, at 6.

common disease such as heart disease, diabetes, and neurodegeneration.[160] These mutations suggest two points: first, there are other factors influencing the evolution of mtDNA; and second, attempting to find a donor without mtDNA mutations would be difficult.[161]

b. Haplotype Incompatibility

Participants at the MRT Meeting also raised concerns relating to the potential for incompatibility arising from mixing two haplotypes of maternal mtDNA and donor mtDNA.[162] Although proponents of MRT state that haplotype mixing does not appear to result in abnormalities, these presumptions rest upon extrapolating projections that rely on two parent scenarios.[163] Some scientific evidence suggests that segregation appears affected by genetic distance between haplotypes and when haplotypes of maternal mtDNA and donor mtDNA are mixed, reversion toward maternal mtDNA occurs.[164] In animal models, mixed mtDNA has resulted in immune rejection, susceptibility to diseases of metabolism, and deficits in performance and learning capabilities.[165]

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[160] Joel Meyer et al., *Mitochondria as a Target of Environmental Toxicants*, 134 TOXICOLOGICAL SCI. 1, 3 (2013).
[161] FDA Meeting, *supra* note, at 66; *see also Letter from David Keefe, MD, to Anna Rajakumar, Human Fertilisation and Embryology Authority* (Mar. 24, 2014), http://www.biopoliticaltimes.org/downloads/DKeefeMRconsiderations.pdf.
[162] FDA Meeting, *supra* note 11, at 21, 42, 66; FDA Brief, *supra* note at 13, 14-15; NAS report, *supra* note 13, at 54-56.
[163] During the FDA MRT Meeting, proponent Dr. Dieter Egli dismissed concerns relating to haplotype mismatch, stating there is "good evidence" not to be concerned because the process of segregation (selection of one haplotype over another) is similar maternal inheritance of mtDNA to a son. Other proponents at the meeting repeated the presumption set forth during the U.K. discussions that analogized combining two maternal haplotypes in MRT to combining one maternal and one paternal haplotype during unassisted reproduction with interracial parents. *See* FDA Meeting, *supra* note 11, at 150-51, 213, 232-38.
[164] Burgstaller et al., *supra* note 150, at 2031; Eunju Kang et al., *Mitochondrial Replacement in Human Oocytes Carrying Pathogenic Mitochondrial Mutations*, 540 NATURE 270 (2016).
[165] FDA Meeting, *supra* note 11, at 196-187; Kimberly Dunham-Snary & Scott Ballinger, *Mitochondrial-nuclear DNA Mismatch Matters*, 349 SCIENCE 1449, 1550 (2015); Reinhardt et al., *supra* note 17, at 1345; Amato et al., *supra* note 19, at 34.

c. Cross-talk between mtDNA and nDNA

Contrary to the media representations that mtDNA's role is negligible except for unidirectional provision of energy, participants at the MRT meeting as well as substantial additional evidence demonstrate what scientists refer to as cross-talk, symbiosis, and co-evolution between mtDNA and nDNA.[166] Mitochondrial DNA not only provide energy, but control metabolic processes, programs cell growth and apoptosis, and impacts nDNA expression.[167] Scientists have described the interaction between mtDNA and nDNA as a complex evolutionary model, where the genome should be considered comparable to an ecosystem where every interconnected element affects the functioning of the whole.[168] Mitochondrial DNA not only functions as a source of energy, but affects a wide range of cellular functioning and how nDNA is expressed.[169] Disrupting the cross-talk between mtDNA and nDNA in animal models results in adverse outcomes and disturbs crucial mitochondrial processes.[170] Current research suggests interference in the communication between mtDNA and nDNA can negatively affect individual development, behavior, susceptibility to disease, and

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[166] *See generally* FDA Meeting, *supra* note, at 194; FDA Brief, *supra* note at 13, 18; Dunham-Snary & Ballinger, *supra* note 165; Reinhardt et al., *supra* note 17, at 1346; Martin Horan et al., *From Evolutionary Bystander to Master Manipulator: The Emerging Roles for the Mitochondrial Genome As A Modulator of Nuclear Gene Expression*, 21 EUR. J. OF HUM. GENETICS 1335 (2013); Rebecca Muir et al., *Mitochondrial Content Is Central To Nuclear Genome Expression: Profound Implications for Human Health*, 38 BIOESSAYS 150 (2015).
[167] FDA Brief, *supra* note, at 5; Claiborne et al., *supra* note 16; Dunham-Snary & Ballinger, *supra* note 165; Eli Adashi & I. Glenn Cohen, *Going Germline: Mitochondrial Replacement as a Guide to Genome Editing*, 164 CELL 832 (2016).
[168] Human Genetic Alert, *supra* note 94, at 4; Reinhardt et al., *supra* note 17, at 1346; Nathaniel Comfort, *Can We Cure Disease Without Slipping Into Eugenics?* THE NATION (July 16, 2015), https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/.
[169] FDA Brief, *supra* note 13, at 13
[170] NAS Report, *supra* note 13, at 56.

fertility.[171] As one scientific article summarized, "perturbation of the mito-nuclear interactions . . . generally attracts grave consequences."[172]

d. Animal and In Vitro Models

Based on the current knowledge of animal models, participants at the MRT Meeting raised the same concerns as in the U.K. discussions about characterizing the current evidence and limitations of current studies.[173] Proponents have highlighted animal models using a small population of macaques, finding low initial percentages of heteroplasmy and declaring "positive results" that the offspring are "healthy."[174] However, participants at the MRT meeting noted several shortcomings: those studies relied on a small sample and may miss problems that would arise with a larger sample; they did not perform extensive testing for heteroplasmy throughout tissues; the studies did not test germ cells for heteroplasmy or assess the health of subsequent generations; and cautioned that using sample tests for heteroplasmy as a proxy for health may miss other dysfunction.[175]

In vitro studies evaluating the development of embryos appeared to raise similar concerns from participants at the MRT Meeting.[176] According to Dr. Paula Amato and colleagues, some studies demonstrated 50% reduced embryo development following PNT, higher rates of

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[171] Human Genetic Alert, *supra* note 94, at 4; Reinhardt et al., *supra* note 17, at 1346; *see also* Horan et al., *supra* note 166, at 1335-1336; Muir et al., *supra* note 166, at 152-153; Dunham-Snary & Ballinger, *supra* note 165.
[172] Horan et al., *supra* note 166, at 1335.
[173] Amato et al., *supra* note 19, at 32; Fogleman et al., *supra* note 35; FDA Meeting, *supra* note 11, at 134, 251.
[174] *Id. See also* Adashi & Cohen, *supra* note 167, at 833.
[175] FDA Meeting, *supra* note 11, at 185, 251; Dunham-Snary & Ballinger, *supra* note 165, at 250.
[176] FDA Meeting, *supra* note 11, at 203; Shah, *supra* note 92, at 8; Human Genetic Alert, *supra* note 94, at 5.

abnormal fertilization, and aberrant chromosomal segregation.[177] Despite these findings, Dr. Amato and colleagues presume that the development of the remaining embryos signals viability and health.[178] Participants at MRT Meeting disagreed, and instead suggested the remaining embryos that survive may also be affected with developmental shortcomings.[179] These findings have led Dr. David King of Human Genetics Alert to conclude the embryos that do survive may develop subtle latent deficits, and has asserted that presuming the opposite– that embryo survival equates to safety and efficacy– seems risky.[180]

3. Risks Arising from Assisted Reproductive Technology, Oocyte Manipulation, and Epigenetic Impact

In addition facing unpredictability and uncertainty arising from mitochondrial biology, the participants at the MRT Meeting and additional research have examined background risks arising from using assisted reproductive technology ("ART"), risks from the process and procedures involved with MRT, and epigenetic impact on the health of the child.

Numerous studies have assessed the impact of "considerable epigenetic changes" on the health outcomes of children born through the process of ART.[181] According to some figures, children born through ART have a 30-40% increased rate of major congenital malformations,[182]

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[177] Amato et al, *supra* note 19, at 33.
[178] *Id.*
[179] FDA Meeting, *supra* note 11, at 203; *see also* Human Genetics Alert, *supra* note 94, at 6.
[180] Human Genetics Alert, *supra* note 94, at 5.
[181] FDA Meeting, *supra* note 11, 91-92.
[182] Yue-hong Lu et al., *Long Term Follow-up of Children Conceived Through Assisted Reproductive Technology*, 14 BIOMEDICINE & BIOTECHNOLOGY 359, 361 (2013); Claudia Wallis, *Studies Link Infertility Treatments to Autism*, TIME (May 20, 2010), http://content.time.com/time/health/article/0,8599,1990567,00.htm; Jorien Seggers et al., *Congential Abnormalities in the Offspring of Subfertile Couples: A Registry Based-Study in the Northern Netherlands*, 103(4) FERTILITY & STERILITY 1001 (2015).

increased risk of autism,[183] more childhood illness,[184] a higher occurrence of cardiovascular conditions,[185] and an increased risk of cancer.[186]

Researchers have hypothesized a number of reasons for such outcomes, including drugs used by the mother during ovarian stimulation;[187] that impaired fertility may signal existing genetic mutations, in either mtDNA or nDNA, in the mother's oocytes;[188] and the impact of damage caused to the embryo arising from physical manipulation and the processes used during ART.[189] Current research suggests a correlation between the amount of physical manipulation to the embryo and level of damage resulting in potentially serious health deficits.[190] Physical damage may result from temperature shifts;[191] reagents used and time the embryo spends in culture;[192] destruction to cellular architecture;[193] and with MRT, potential for viral contamination based on a particular virus used during the procedures.[194] These factors could result in damage

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[183] Wallis, *supra* note 182.
[184] Lu et al., *supra* note 182.
[185] Maia Szalaviz, *The Link Between Infertility Treatments and Birth Defects*, TIME (May 7, 2012), http://healthland.time.com/2012/05/07/the-link-between-infertility-treatments-and-birth-defects/.
[186] E. Susan Amirian & Melissa Bondy, *Assisted Reproductive Technology and Risk of Cancer in Children*, 137 PEDIATRICS e20154509 (2016); Marte Reigstad el al., *Risk of Cancer in Children Conceived by Assisted Reproductive Technology*, 137 PEDIATRICS e20152061 (2016).
[187] FDA Meeting, *supra* note 11, at 77, 88; NAS Report, *supra* note 13, at 58.
[188] *Id.* at 87, 172; Anonymous, *Experts Warn of IVF Timebomb*, U.K. DAILY MAIL, http://www.dailymail.co.U.K./health/article-195627/Expert-warns-IVF-timebomb.html.
[189] FDA Meeting *supra* note 11, at 203, 232-233; NAS Report, *supra* note 13, at 58; FDA Brief, *supra* note 13, at 14-15, 20.
[190] Human Genetics Alert, *supra* note 28, at 4-5; U.K. Correspondence, *supra* note 32, at 39-49.
[191] FDA Brief, *supra* note 13, at 15.
[192] FDA Brief, *supra* note 13, at 20; NAS Report, *supra* note 13, at 58; FDA Meeting, *supra* note 11, at 104-105; Human Genetics Alert, *supra* note 94, at 3.
[193] FDA Brief, *supra* note 13, at 19; Human Genetics Alert, *supra* note 94, at 3; Human Genetics Alert, *supra* note, 28 at 5.
[194] Participants at the MRT Meeting discussed the use of the Sendai virus during MRT, citing it would be a potential viral contaminant because it may not be fully washed away following the procedure, and it may lie dormant and pose latent risks to children. *See* FDA Meeting, *supra* note 11, at 121-130; FDA Brief, *supra* note 11, at 19. The NAS Report also stated the Sendai

to cellular structure, aneuploidy, or disruption of chromosomal segregation and division.[195]

Some of the elements introduced during MRT such as temperature changes, use of reagents, and changing the composition of mitochondria through MST or PNT may have an epigenetic impact on the embryo and modify the expression of nDNA.[196] During discussions in both the U.K. and the U.S., participants described a critical window of vulnerability during which changes to the embryo will influence long term health outcomes through modifying gene expression.[197] These epigenetic changes could result in "imprinting or programming of future disease in children."[198]

During the closing statements by participants at the MRT Meeting, an overwhelming number of speakers voiced concern not only that scientific evidence failed to demonstrate safety and efficacy, but that MRT may never be a viable option based on level of risk involved.[199] Participants reiterated there are less risky alternatives to having children, and the current evidence falls "far short" of showing MRT would be potentially safe and effective.[200] Germline modification by its nature means MRT would pose unprecedented risks to the children born as a result.[201] MRT would impact every cell in the body, and there are no methodologies currently to

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virus has the potential for immunogenicity and poses unknown risks to children born using the virus during the procedure. NAS Report, *supra* note 13, at 38; *see also* Letter from David Keefe, *supra* note 161.

[195] FDA Brief, *supra* note 13, at 19.

[196] *See* NAS Report, *supra* note 13, at 58; FDA Meeting, *supra* note 11, at 95-98, 276; Muir et al. *supra* note 166, at 151; Human Genetics Alert, *supra* note 94, at 1, 3.

[197] FDA Meeting, *supra* note 11, at 96; U.K. Correspondence, *supra* note 32, at 39-49.

[198] The participants at the FDA Meeting discussed fetal origins of disease, where factors in the mother's environment such as nutrition and stress have a dramatic impact on the subsequent development of the child's risk for disease. *See* FDA Meeting, *supra* note 11, at 95-98.

[199] FDA Meeting, *supra* note 11, at 248, 261-271.

[200] *Id.*

[201] Mark Frankel, *Inheritable Genetic Modification and a Brave New World: Did Huxley Have It Wrong?* 33HASTINGS CTR REP. 31, 32 (2003).

ensure the procedure would not inflict novel abnormalities.[202] Based on available research, scientists cannot currently predict lifetime safety nor latent effects.[203] Such mistakes are both inevitable and irreversible, which means MRT could potentially not only create a congenitally impaired child, but introduce those deficits into the germline of all subsequent offspring.[204] Indeed, current research suggests disrupting mtDNA through MRT may have the potential to result in developmental disorders,[205] latent fatalities,[206] expedited aging,[207] increased risk of cancer,[208] as well as unknown abnormalities.[209] The weight of the evidence unquestionably points not merely to insufficient evidence of safety and efficacy, but should raise utmost alarm for the severity of potentially imposing novel risks. These extensive considerations do not support the National Academies of Science, Engineering, and Medicine Report's conclusion that conducting clinical trials for MRT is ethically permissible.

D. NAS Report on the Ethical Permissibility of MRT

Following the FDA's MRT Meeting and MRT Brief that cited numerous risks and lack of evidence pertaining to safety and efficacy, the FDA requested that the National Academies of Science, Engineering and Medicine develop a consensus report reviewing the ethical, social, and policy considerations relating to MRT.[210] The NAS Report concluded it is ethically permissible for the FDA to conduct clinical investigations subject to a set of conditions including: (1) Initial

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[202] FDA Meeting, *supra* note 11, at 278.
[203] *Id.* at 220.
[204] Zaret, *supra* note 54, at 1816; FDA Brief, *supra* note 13, at 22.
[205] Knapton, *supra* note 103.
[206] Burgstaller et al., *supra* note 150.
[207] Horan et al., *supra* note 166.
[208] *Id.*
[209] *See also* FDA Meeting, *supra* note 11, at 216 (discussing list of potential risks) and at 278 (discussing the potential for introducing additional abnormalities through MRT).
[210] NAS Report, *supra* note13, at xiii.

safety is established and risks to all parties directly involved in the proposed clinical investigations are minimized; (2) Likelihood of efficacy is established by preclinical research; (3) Clinical investigations are limited to women who otherwise are at risk of transmitting a serious mtDNA disease; (4) Intrauterine transfer for gestation is initially limited to male embryos (but may be extended to females if safe and effective); (5) FDA may consider haplotype matching as a means of mitigating risk of incompatibilities between mtDNA and nDNA.[211]

The NAS Report stated its goals are to minimize risks to the future child and ensure safety and efficacy of clinical interventions.[212] Despite setting forth this goal, the substance of the NAS Report discussion focused on prioritizing novel technological interventions as a means to advance science and medicine, asserting the FDA should exercise caution but not impose absolute limits on technology.[213] Echoing the position set forth in British media, the NAS Report maintained that opposition to MRT arises out of unfounded fear, poor understanding of the science, and an irrational belief that "natural" is necessarily better.[214] According to the NAS Report, parents take steps daily to improve their children through education and using medicine when children are ill, and categorized MRT as another option for parents to choose on behalf of their children's health and well-being.

However, comparing providing an existing child with a proper education against undertaking an unprecedented experiment to create a child with known risks that contravenes multiple global legal prohibitions are incommensurate actions. By refusing any absolute limits, the NAS Report necessarily weighs the scale in favor of finding benefit in the sake of pursing

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[211] *Id.* at 10-11.
[212] *Id.* at 2.
[213] *Id.* at 7.
[214] *Id.* at 89.

research for its own sake even when serious reservations of safety and efficacy exist. At times, the notion of progress requires a prudent pause and adherence to limits where technology would pose grave risk of harm to the intended recipient.

The NAS Report also justified the use of MRT based on longstanding jurisprudence respecting parental autonomy and procreative liberty.[215] In the history of ART, the desire to bear genetically related children has been prized, and parents have traditionally been provided wide lenience to pursue their "reproductive projects."[216] However, a number of bioethicists have observed this right need not be absolute nor demand all technology available without regard to whether the original conception of procreative liberty even encompasses such a right, or how exercising that right would impinge upon the rights of the child.[217]

In a similar manner as the U.K., the NAS Report employed linguistic creativity, asserting that although MRT is germline modification, it is not heritable because initial transfer for gestation would be limited to males who would not pass on mtDNA to their children.[218] Throughout the NAS Report the NAS took great care to minimize the role of mtDNA, reassuring that MRT does not "edit genes" and "there is no direct modification of mtDNA"[219] because MRT merely replaces pathogenic mtDNA with unaffected mtDNA.[220] Designed to minimize the impact of MRT as heritable germline modification, this statement is scientifically inaccurate and

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[215] *Id.* at 82-83.
[216] *Id.* at 82-83, 87; Baylis, *supra* note 29, at 533; Leon Kass, *Life, Liberty, and the Defense of Dignity* (2002).
[217] Baylis, *supra* note 29, at 533; Kass, *supra* note 216, at 163-164. Kass asserts: "When the exercise of a previously innocuous freedom now involves or impinges on troublesome practices the original freedom was never intended to encompass the general presumption of liberty needs to be reconsidered."
[218] NAS Report, *supra* note 13, at 29.
[219] *Id.* at 6-8.
[220] *Id.* at 107-108.

perpetuates misunderstanding. The description minimizing the actual procedure of a nuclear genome transfer by describing it as switching mitochondria echoes the misleading descriptions provide by the HFEA and the U.K. Department of Health. Furthermore, all germline modifications are heritable because changes to the oocyte or embryo globally impact all the resulting cells, impacting the growth and development of the child and the expression of nDNA, which is passed on by both males and females.[221] This attempt at extricating MRT from the category of heritable modifications is likely both a move to slowly introduce the concept of germline modification as well as a carefully executed strategy to assert that current limitations prohibiting federal funding for heritable germline modifications would not apply to MRT.[222]

Finally, the NAS Report addressed international treaties and global prohibitions against germline modification.[223] According to the NAS Report, the language set forth in the United Nations Universal Declaration on the Human Genome and Human Rights declaring that the genome constitutes "the heritage of humanity" amounts to "vague and aspirational" language, and the NAS is "not persuaded that MRT should be prohibited based on arguments that the genome represents the inviolable heritage of humanity."[224] The NAS Report's blatant disregard for conclusive positions set forth by the United Nations along with persuasive nonbinding precedent set forth by the Council of Europe entails the very action cautioned by the UNESCO's International Bioethics Committee when it warned of parsing component parts of the genome,

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[221] Frankel, *supra* note 201, at 32.
[222] Sec. 749, Consolidated Appropriations Act, *supra* note 133. The Omnibus Spending Bill "Prohibits the FDA from acknowledging applications for an exemption for investigational use of a drug or biological product in research in which a human embryo is intentionally created or modified to include a heritable genetic modification. Provides that any submission is deemed not to have been received, and the exemption may not go into effect." *See also* NAS Report, *supra* note 13, at 65.
[223] NAS Report, *supra* note 13, at 63, 89.
[224] *Id.* at 93.

renouncing limitations, and permitting market forces to stretch the boundaries of permissible endeavors. Furthermore, the position of UNSECO's International Bioethics Committee, the Council of Europe, and criminal prohibitions on germline modification set forth by numerous nations demonstrates the United Nations' language constitutes an unwavering and unmistakable directive rather than "vague and aspirational language."

VI. Additional Scientific and Ethical Considerations

After reviewing the scientific elements pertaining to safety, efficacy, and risks at the FDA MRT Meeting and the ethical, social, and policy issues contained in the NAS Report, these discussions omitted significant additional considerations. First, permitting clinical investigation of MRT and announcing the ethical acceptability of MRT relies upon expanding the pool of oocyte donors. Second, discussions at the FDA and in the NAS Report accept proponent's medical rationale for MRT for uses such as to treat mitochondrial disease and infertility without substantive analysis. Each of these points warrants further discussion to consider how clinical investigation would impact crucial parties involved in the process–potentially a new pool of egg donors, and whether available evidence supports the findings that MRT constitutes an effective method to treat mitochondrial disease and infertility.

A. Increasing Oocyte Donation and Risks to Donors

Although limited literature in the area addresses the impact of permitting MRT on oocyte donors and increasing risk in the pool potential oocyte donors, these considerations were not mentioned during the FDA MRT Meeting nor in the NAS Report.[225] MRT not only poses significant risks to the child, but because it relies upon oocyte donation, it would require increasing the number of oocyte donors and compound the current ethical debates pertaining to

[225] *See* Baylis, *supra* note 29, at 532; Fogleman et al., *supra* note 35, at 46.

the acceptability of risk and conflicts of interest present in this sector of the fertility industry.[226] Although some scholars reason autonomy and informed consent obviate ethical hesitation, this conclusion deserves further investigation.[227]

Every year, millions of women donate oocytes and are generally paid $5,000-$20,000 per cycle.[228] The process of egg donation requires multiple steps, beginning with a medical screening questionnaire and blood tests to check for infectious disease. If the fertility clinic selects this egg donor, then the clinic will begin the process of coordinating the donor's hormonal cycle with the intended mother's by starting a ten to twenty one day cycle of a hormone such as Lupron to suppress ovulation followed by a seven to twelve day regimen of injections of high doses of follicular stimulating hormones.[229] When the donor's oocytes have matured, the fertility clinic administers a final injection of human chorionic gonadotropin. After the injection of human chorionic gonadotropin, the donor undergoes surgery with anesthesia, where the physician inserts a needle through her vagina to remove the eggs that were produced.[230] Unlike a normal monthly cycle that produces one egg, this procedure generally produces around ten to twenty eggs or more depending on the amount of fertility drugs the clinic uses.[231]

The process of egg donation exposes donors to a number of short term physical risks in

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[226] *See generally* Justine Durrell, *Women's Eggs: Exceptional Endings*, 22 HASTINGS WOMEN'S L. J., 187 (2011); Joseph Gregorio, *Hatching A Plan Toward Comprehensive Regulation in Egg Donation*, 65 DEPAUL L. REV. 1283 (2016); Lisa Ikemoto, *Reproductive Tourism: Equality Concerns in the Global Market for Fertility Services*, 27 LAW & INEQUALITY 277 (2009).
[227] *See* Fogleman et al., *supra* note 35, at 46.
[228] Gregorio, *supra* note 226, at 1285-86.
[229] *Id.* at 1288-1290; Durrell, *supra* note 226, at 192-94.
[230] *Id.*
[231] *Id.* Some clinics report retrieving up to forty eggs in one cycle compared to the one egg naturally released per cycle.

connection to the fertility drugs used and the surgical process of retrieving the eggs. Adverse effects from the hormone injections may include pain, nausea, hot flashes, mood swings, hair loss, depression, bone pain, chronic enlargement of the thyroid, liver dysfunction, and heavy bleeding.[232] Ironically, evidence also suggests hormone injections of Lupron, a drug to suppress ovulation commonly during the process of syncing the donor's cycle to the mother's, can lead to the donor's own infertility because it may disrupt long term ovarian function in the donor.[233] Drugs used during this process can also result in ovarian torsion, where the ovaries change position from the drug induced stimulation in a manner that blocks blood flow and twists the ovary.[234] This condition requires medical intervention to remediate and may result in loss of ovarian function or surgical removal of the ovary.[235] The surgical process of egg retrieval carries risks associated with general surgery such as danger of infection, complications from anesthesia, and hemorrhage, as well risks related to the process of egg retrieval such as injury to adjacent areas like the ureter, bladder, or bowel.[236]

Donors may also experience ovarian hyperstimulation syndrome ("OHSS"), which is

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[232] Fogleman et al., *supra* note 35, at 46; Durrell, *supra* note 226, at 195-198; Gregorio, *supra* note 226, at 1291; Danielle Vera, *R-egg-Ulation: A Call for Greater Regulation of the Big Business of Human Egg Harvesting*, 23 MICH. J. GENDER & L. 391, 397 (2016).

[233] *Id. See also* Amicus Curiae, Karin Klein v. TAP Pharmaceutical Products, Inc. and Abbott Laboratories, 11-CV-17250 at 13 (2013), http://www.lupronvictimshub.com/lawsuits/Klein_Amicus_Published.pdf. Dr. David Redwine accessed Tap Pharmaceutical's raw data from clinical trials for Lupron and found data to suggest sixty-five percent of women who used Lupron did not return to their baseline ovarian function and the data suggested Lupron induced long term ovarian damage; Donna de la Cruz, *Should Young Women Sell Their Eggs?* NEW YORK TIMES (Oct. 20, 2016), https://www.nytimes.com/2016/10/20/well/family/young-women-egg-donors.html.

[234] Vera, *supra* note 232, at 397; Sandhya Krishnan et al., *Ovarian Torsion in Infertility Management- Missing the Diagnosis Means Losing the Ovary: A High Price to Pay*, 4 J. HUM. REPRO. SCI. 39 (2011).

[235] *Id.*

[236] Durrell, *supra* note 226, at 195.

fluid build-up in the abdomen and chest caused by gonadotropin stimulation of the ovaries.[237] Fluid leads to pressure on the diaphragm that causes difficulty breathing and decreases blood volume. In severe cases, OHSS can lead to kidney damage, blood clotting disorders, stroke, and death.[238] Estimates suggest the majority of women undergoing egg retrieval experience at least mild OHSS.[239] Although the fertility industry has stated complications from donation and OHSS are rare, such an assertion is not supported by available data.[240] Although fertility clinics keep statistics on pregnancy outcomes, they generally do not keep records on medical complications associated with the process of donating.[241] Recent independent research that studied the frequency of complications found varying rates of adverse events: approximately thirty percent of donors suffered OHSS, and between eleven and thirty percent of donors suffered complications so severe they required hospitalization.[242]

Despite the American Society for Reproductive Medicine's claim that there are no long term adverse risks of egg donation, this statement inaccurately represents both the known and unknown long terms risks associated with being an egg donor.[243] There are currently no registries tracking either short term or long term donor outcomes, so comprehensive data for all donors simply does not exist.[244] Despite lack of donor wide registries, numerous studies have

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[237] *Ovarian Hyperstimulation Syndrome*, AM. SOC'Y FOR REPROD. MED., https://www.asrm.org/FACTSHEET_Ovarian_Hyperstimulation_Syndrome/.
[238] *Id.* at 196-197.
[239] Vera, *supra* note 232, at 418-19.
[240] *Id.*
[241] Durrell, *supra* note 226, at 195.
[242] Vera, *supra* note 232, at 418-19.
[243] Sandra Boodman, *Do Women Who Donate Their Eggs Run A Health Risk?* WASHINGTON POST (June 20, 2016), https://www.washingtonpost.com/national/health-science/do-women-who-donate-their-eggs-run-a-health-risk/2016/06/20/8755b22e-1c7a-11e6-b6e0-c53b7ef63b45_story.html?utm_term=.699a554b5edb.
[244] *Id*; *see also* Durrell, *supra* note 226, at 219-20.

explored the link between different drugs used during the donation process and in numerous cases found an increased risk for a variety of cancers, including colon, breast, endometrial, uterine, ovarian cancer as well as malignant melanoma and non-Hodgkins lymphoma.[245] Donation may also result in long term compromise of the donor's own fertility, chronic pelvic pain and ovarian cysts.[246]

Critics of the current donation process have noted deficiencies arising from insufficient informed consent and conflicts of interest inherent in the egg donation process. Despite evidence demonstrating these short term and long term risks, donors may not even be aware of these risks when deciding to undergo donation.[247] One study found twenty percent of donors were not aware there were health risks involved, let alone serious complications such as OHSS, loss of her own fertility, and increased risk of cancer.[248] This discrepancy suggests serious deficiencies in the informed consent process.[249] Fertility clinics' metrics of success hinge upon successful pregnancies, which also creates an incentive for clinics to increase the dosage of fertility drugs to produce more eggs in one cycle.[250] Although higher doses of drugs will yield more eggs and benefit the clinic, it also places the egg donor at greater risk of adverse health consequences.[251]

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[245] Vera, *supra* note 232, at 395-96 (*citing* a thirty to forty percent increased risk for colon cancer); Durrell, *supra* note 226, at 200-02 (*citing* a 2.3-fold increase risk for ovarian cancer from Clomiphene, a three to four-fold increased risk for uterine cancer, an increase in breast cancer and malignant melanoma from Clomiphene use, and an increase in non-Hodgkins lymphoma); Gregorio, *supra* note 226, at 1291.
[246] Durrell, *supra* note 226, at 212.
[247] Boodman, *supra* note 243.
[248] *Id.*
[249] *Id.*
[250] Gregorio, *supra* note, at 1289-90.
[251] Sonia Suter, *Giving In To Baby Markets: Regulation Without Prohibition*, 16 MICH. J. GENDER & L. 217, 233, 254 (2009); Ikemoto, *supra* note 226, at 304-05 (observing "this normative dynamic creates an inverse relation between the donor's intrinsic worth and her extrinsic value in the fertility industry"); Hannah Devlin, *Increase In IVF Complications Raises Concerns Over Use of Fertility Drugs*, THE GUARDIAN (Nov. 13, 2016),

Legal scholars assert this creates a system that treats oocyte donors as separate and fungible producers of raw materials for a lucrative industry.[252] If the fertility industry would accurately disclose and assess risks, this would jeopardize donor willingness and undermine the supply of raw material upon which fertility clinics rely.[253] Discussions that euphemistically refer to "cytoplasm donors,"[254] and swapping out mitochondria obscures the fact that MRT relies on a supply of eggs that entails potentially serious risks to egg donors, of which they may not even be aware. Failing to address where the raw materials for MRT originated and focusing solely on risks to the child skews the risk-benefit ratio of this experimental procedure. Thus, even those who believe MRT in potential benefit to the child must also evaluate whether this benefit is justified at the expense of placing a pool of women's health at risk for the "reproductive projects" of third parties.[255]

B. Evaluating the Medical Rationale of Using MRT to Treat Mitochondrial Disease and Infertility

1. Sources of Mitochondrial Dysfunction

In addition to the risk profile for MRT, it is crucial to analyze whether MRT would effectively and sustainably address causes of mitochondrial dysfunction. As stated in Section II, dysfunction may result from either mtDNA mutations or nDNA mutations. Eighty percent of mitochondrial dysfunction arises from nDNA mutations for which MRT would not address. Mitochondrial DNA mutations may either be maternally inherited or arise de novo, as new

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https://www.theguardian.com/society/2016/nov/13/increase-in-serious-ivf-complications-raises-concerns-over-use-of-fertility-drugs-ovarian-hyperstimulation-syndrome.

[252] Ikemoto, *supra* note 226, at 285; Suter, *supra* note 251, at 224.

[253] *Id.*

[254] Fogleman et al, *supra* note 35.

[255] *See* Baylis, *supra* note 29, at 233.

mutations. Recent evidence suggests that a variety of environmental factors induce de novo mutations. Mitochondrial dysfunction is not only a cause of rare fatal disease, but also has been implicated as a factor in the development of common diseases, such as neurodegenerative disease, cancer, diabetes, cardiovascular disease.[256] Public health researchers hypothesize that the rising rates of chronic and debilitating disease are a product of environmentally mediated epigenetic damage to our mitochondria.[257] Changes in mitochondrial integrity appear to influence a number of diseases, more than the traditionally defined classes of maternally inheritance of mtDNA disease and nDNA mitochondrial disease.

Mitochondria undergo rapid development called mitochondrial biogenesis during embryonic and fetal development, and continue to replicate throughout one's lifetime. During this critical window of early development, altered maternal mitochondrial function directly impacts fetal development.[258] If mitochondria are damaged during these early stages, scientists believe the mtDNA deficiencies will continue to replicate during the growth of the organism.[259] Mitochondria undergo continual growth and repair throughout the life cycle of the organism, but if the cell's repair mechanisms cannot keep pace with external assaults that induce these changes, cumulative damage will eventually manifest phenotypically in a disease state.[260]

In the course of one's life mitochondria are "on the frontline of cellular response to the

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[256] Meyer, *supra* note 160, at 3.
[257] Luca Lambertini & Hyang-Min Byun, *Mitochondrial Epigenetics and Environmental Exposure*, 3 CURRENT ENVTL. HEALTH REP. 214 (2016).
[258] Kelly Brunst et al., *Integrating Mitochondriomics In Children's Environmental Health*, 35 J. APPLIED TOXICOLOGY 976 (2015).
[259] Meyer, *supra* note 160.
[260] *Id.* at 6; Maria Paraskevaidi et al., *Underlying Role in Mitochondrial Mutagenesis in the Pathogenesis of Disease and Current Approaches for Translational Research*, 32 MUTAGENESIS 335, 336 (2016).

environment."[261] Recent research demonstrates how environmental factors induce epigenetic changes in mitochondrial activity that can also lead to alternation in nDNA.[262] A variety of environmental agents, including pesticides,[263] heavy metals,[264] antibiotics,[265] pharmaceutical drugs,[266] environmental toxicants such as dioxin[267] and Bisphenol A[268] can all exert changes to mitochondrial integrity and development. Over time, exposure to mitochondrial disruptors damages the mitochondria and impacts the resulting health of the individual. As discussed in Section II, proper functioning of each cell and the organism as a whole relies on cross-talk between mtDNA and nDNA. Environmentally mediated mtDNA damage undermines bidirectional cross-talk and interferes with nDNA repair pathways, which can influence nDNA methylation and produce epigenetic changes in the expression of nDNA.[269] When accumulations of mtDNA damage and nDNA damage reaches a particular threshold, this manifests as common diseases.[270]

This research suggests that even presuming the initial procedure of MRT could ever be safe and effective, it would not address underlying causes of de novo mtDNA mutations nor de novo nDNA mutations that phenotypically present as disease. These findings have several implications for the long term safety and efficacy of MRT over the course of the child's life.

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[261] Lambertini & Byun, *supra* note 257.
[262] *Id.*
[263] Meyer, *supra* note 160, at 8; Paraskevaidi, *supra* note 260, at 1.
[264] *Id.*; Brunst, *supra* note 258, at 982-983.
[265] Sameer Kalghati et al., *Bactericidal Antibiotics Induce Mitochondria Dysfunction and Oxidative Damage in Mammalian Cells*, 5 SCI. TRANSLATIONAL MED. 1 (2013); Norman Moullan et al., *Tetracyclines Disturb Mitochondrial Function Across Eukaryotic Models: A Call for Action in Biomedical Research*, 10 CELL REPS. 1681 (2015).
[266] Meyer, *supra* note 160 at 3-4; Paraskevaidi, *supra* note 260, at 3-4.
[267] Meyer, *supra* note 160, at 3-4.
[268] Brunst, *supra* note 258, at 983.
[269] Meyer, supra note 160, at 9.
[270] *Id.* at 3-4; Paraskevaidi, *supra* note 260, at 2-4.

First, even if MRT could be safe and effective in principle (a hypothesis that is currently unsupported), exposure to mitochondrial disruptors during biogenesis and over the course of the child's life has the potential to undo theoretical mitochondrial correction as damage accumulates. Based on scientific concerns related to cross-talk between mtDNA and nDNA, this also raises questions of whether disrupting the naturally occurring cross-talk would have negative implications for the mitochondria's evolutionary ability to adapt to the influence of mitochondrial disruptors.[271] Finally, this area of research demonstrates that rare fatal disease arising from mitochondrial dysfunction merely constitutes the tip of the iceberg. Promoting MRT as a viable option distracts from the heavy burden of environmentally mediated mtDNA and nDNA damage quietly influencing the rates of common and chronic disease. Recognizing and reducing these exposure levels should constitute the focus of the inquiry, along with concurrent low risk interventions such as exercise and dietary measures, which have been shown to enhance mitochondrial function. [272]

2. Causes of Infertility

The FDA MRT Meeting also considered the possibility of clinical trials to explore using MRT to treat infertility, and some have suggested treating infertility constitutes the end goal.[273] Though the NAS Report limited its recommendation that the FDA limit applications to treatment of mtDNA disease, the FDA is not bound by NAS's recommendation. Furthermore, even if the

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[271] Stuart Newman, *CRISPR Will Never Be Good Enough to Improve People*, 30 GENE WATCH (2017) (discussing scientists' limited understanding of genetic mutations and the role of evolution to sustain an organism).

[272] Paraskevaidi, *supra* note 260, at 6. Paraskevaidi and colleagues suggest simple low risk measures such as exercise and nutrition carry the potential for positive impact because they encourage mitochondrial formation.

[273] Iishi, *supra* note 15, at 151; Don Wolf et al., *Mitochondrial Replacement Therapy in Reproductive Medicine*, 21 TRENDS IN MOLECULAR MEDICINE 68 (2015).

FDA were to approve an investigational new drug application related to MRT, the fertility clinic could subsequently use the approved MRT procedure off label for infertility and other purposes. Investigating the medical rationale of using MRT to treat infertility raises a similar set of findings with research demonstrating that rising rates of impaired fertility are likely due to a variety of complex environmental and lifestyle causes including aging, not inherent genetic flaws.[274]

A portion of infertility stems from aging, and as one gynecologist observed, trying to change biology is "incredibly difficult and expensive to alter."[275] Popular media articles and scholars have questioned the social messaging behind the cultural phenomenon of delaying motherhood, asking why addressing age related reproductive complications and limitations have become taboo.[276] During the FDA MRT Meeting, participants discussed a number of age related biological changes such as diminished ovarian function, risk of aneuploidy, genetic segregation errors, and oocyte structural defects.[277] If aging increases the risk of aneuploidy or mutations to

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[274] Theo Colburn et al., *Our Stolen Future* (1996); Ake Bergman et al. (eds.), *State of the Science on Endocrine Disrupting Chemicals*, WHO & UNITED NATIONS ENV'T PROGRAM (2012) [hereinafter "State of the Science"]; Carlos Guerro-Bosagna & Michael Skinner, *Environmentally Induced Epigenetic Transgenerational Inheritance of Male Infertility*, 26 CURRENT OPINION IN GENETICS AND DEV. 79 (2014); Evanthia Diamanti-Kandarakis et al., *Endocrine Disrupting Chemicals: An Endocrine Society Scientific Statement*, 30 ENDOCRINE REV. 293 (2009); *Fertility and Infertility and the Environment*, NAT'L CTR. FOR ENVTL. HEALTH, CTS. FOR DISEASE CONTROL & PREVENTION, https://ephtracking.cdc.gov/showRbFertilityInfertilityEnv.

[275] Viv Groskop, *The Fertility Industry is One That Sells Hope- Sometimes That Hope Is False*, THE GUARDIAN (June 1, 2015), https://www.theguardian.com/lifeandstyle/2015/jun/01/fertility-industry-sells-hope-false-delay-having-baby.

[276] *Id.*; *see* David Adamson, *The Hot Topic of Egg Freezing and What You Should Know*, THE HUFFINGTON POST (Sept. 2, 2016), http://www.huffingtonpost.com/dr-david-adamson/the-hot-topic-of-egg-freezing-and-what-you-should-know_b_11765436.html; Katie Hammond, *Egg Freezing: An Empowering Option for Women?*, RES. U. OF CAMBRIDGE (Nov. 17, 2014), http://www.cam.ac.U.K./research/discussion/egg-freezing-an-empowering-option-for-women.

[277] FDA Meeting, *supra* note 11, 75-77; 172-175.

nDNA contained in maternal oocytes, MRT would not address these concerns because the procedure transfers nDNA from the mother to the donor.[278]

In addition to age, research suggests lifestyle choices can directly impact both female and male fertility outcomes. Factors such as smoking, alcohol use, diet, and sedentary lifestyle have been shown to negatively correlate to fertility outcomes.[279] Some promising research suggests positive effects of dietary changes and moderate exercise as an avenue to improve fertility.[280]

Despite these potential causes, infertility is dramatically rising in the population of young adults in their twenties which has led researchers to investigate additional causes. Research implicates a variety of environmental toxicants including pesticides, PCBs, phthalates, parabens, and Bisphenol A that are present in our daily environment and act as endocrine disrupting chemicals (EDCs) contributing to rising rates of impaired fertility.[281] In 2012, the World Health Organization and the United Nations Environment Program published a report, "State of the Science on Endocrine Disrupting Chemicals" on the impact of EDCs on human reproduction.[282] Currently, there are eight hundred chemicals that are known or suspected to be capable of interfering with human reproduction.[283] Exposure to EDCs can interfere with hormone synthesis, conversion, and signaling, which can impair growth throughout the life cycle and

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[278] Kara Manke, *With Gene Disorders, The Mother's Age Matters, Not the Egg's*, NAT'L PUBLIC RADIO (July 7, 2014), http://www.npr.org/sections/health-shots/2014/07/07/328132687/with-gene-disorders-the-mothers-age-matters-not-the-eggs; Ross Rowsey et al., *Examining Variation in Recombination Levels in the Human Female: A Test of the Production-Line Hypothesis*, 95 AM. J. OF HUMAN GENETICS 108 (2014).
[279] Guerro-Bosagna & Skinner, *supra* note 274, at 80-83; *see also* Rakesh Sharma et al., *Lifestyle Factors and Reproductive Health: Taking Control of Your Fertility*, 11 REPROD. BIOLOGY & ENDOCRINOLOGY (2013).
[280] *Id.*
[281] *Id.*
[282] State of the Science, *supra* note 274.
[283] *Id.*, at vii.

reproductive capability.[284]

Scientists describe a period called the critical window of development during gestation and early infancy, during which exposure to toxicants can alter normal development and manifest in acute or long term health effects.[285] During fetal development, the brain and fetal tissue undergo rapid development along a specific pathway.[286] Any exposure to toxicants during this crucial stage could halt or alter the normal course of proper hormone signaling and fetal tissue differentiation leading to long lasting and permanent health deficits.[287] These deficits may manifest through a number of avenues in females including ovarian dysgenesis, premature ovarian failure, anovulation, and irreversible morphological abnormalities in the human reproductive tract.[288] Importantly, an extensive body of research demonstrates both females and males are affected by rising rates of infertility.[289] In males, the impact of EDCs may result in low testosterone, a decrease in semen quality, reduction in sperm, and deficiencies in sperm motility, disruption of testicular development, and abnormalities of the male reproductive tract.[290]

Exposures to EDCs during the critical window and throughout the course of one's life have the potential to exert epigenetic changes not only to the individual's somatic cells, but also to the germ cells.[291] This means EDCs are not only changing the individual's reproductive

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[284] *Id.*, at viii.
[285] *Id.*, at ix.
[286] *Id.*
[287] *Id.*
[288] Andre Marques-Pinto & Davide Carvalho, *Human Infertility: Are Endocrine Disruptors To Blame?* 2 ENDOCRINE CONNECTIONS R15 at 21 (2013).
[289] *Id.*
[290] Marques-Pinto & Carvalho, *supra* note 288, at 19; State of the Science, *supra* note 274, at 57-58, 65, 74; Guerro-Bosagna & Skinner, *supra* note 274, at 80-83.
[291] Guerro-Bosagna & Skinner, *supra* note 274, at 81-82.

capacities, but also transmitting altered epigenetic marks to subsequent generations and potentially compromising the offspring's fertility as well.[292]

As a whole, this research suggests that the medical rationale of using MRT to treat infertility contains numerous flaws. Even presuming MRT could ever be safe and effective, it fails to address impaired fertility that could be prevented through social policy movements that encourage reproduction during biologically viable years and lifestyle modifications that support fertility potential. MRT also would not address the various deficiencies in female reproductive capacity such as reproductive tract abnormalities or insufficient ovarian reserve. MRT would also not address any of the growing concerns related to male infertility. Scientific research in this area suggests a need to systematically address the underlying factors contributing to population level fertility impairment.

C. Assessing the Potential for Market Expansion

After deconstructing the medical rationale, proponents' claims that MRT could treat mitochondrial disease and infertility become less compelling. This raises questions of why proponents would aggressively push a highly risky experimental technology. Developing MRT to offer as the newest option in the treatment of infertility holds substantial value for industry revenue and commercial expansion, both domestically and as a means to increase the U.S. fertility industry's global market share.[293]

Statistics vary, but according to the Centers for Disease Control, approximately twelve percent of couples in the U.S. suffer from impaired fecundity, defined as the inability to get

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[292] *Id.*, at 83-84.
[293] Claiborne et al., *supra* note 16, at 12.

pregnant or carry a baby to term.[294] The World Health Organization evaluated global rates of infertility, finding up to one quarter of couples of childbearing age suffer from infertility.[295] In the U.S., 62 million women of childbearing age are infertile and 7.4 million women seek fertility services during their life.[296] These figures translate into a lucrative industry and "sprawling commercial enterprise,"[297] estimated to be between $3 to 4 billion dollars in the United States, with demand growing approximately ten percent annually.[298]

Rising rates of impaired fertility combined with the promise of a genetically related child have produced a booming market. Having a genetically related child satisfies a deeply held primal desire, but as legal scholar Lisa Ikemoto observed, industry's focus on emotional stories "is compelling because it is real" but it "elides the commercial nature of the practice."[299] Focusing on the pathos of parental yearning distracts from the consumerism, including how potential parents also constitute vulnerable participants in their quest for parenthood.[300] Historian Nathaniel Comfort maintains prioritizing the technological imperative and mastery of science over nature categorizes emerging technology as a "humane" option for medical suffering

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[294] *Infertility*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/reproductivehealth/Infertility/.
[295] *Global Prevalence of Infertility, Infecundity, and Childlessness*, WHO, http://www.who.int/reproductivehealth/topics/infertility/burden/en/.
[296] Gregorio, *supra* note 226, at 1285.
[297] Ikemoto, *supra* note 226, at 278.
[298] *Fertility Market Overview*, HARRIS WILLIAMS & CO. (May 2015), http://www.harriswilliams.com/sites/default/files/content/fertility_industry_overview_-_2015.05.19_v10.pdf. Harris Williams estimates $1.7-2.5 billion is spent on ART services annually in the U.S., and approximately $1.5 million is spent on fertility medications in the US. It also estimates the global fertility market is between $30-40 billion annually. *See also* Michael Cook, *IVF World Market to Reach US $12Billion*, BIOEDGE (March 11, 2017), https://www.bioedge.org/bioethics/ivf-world-market-to-reach-us12-billion/12225.
[299] Ikemoto, *supra* note 226, at 306-07.
[300] Suter, *supra* note 251, at 237; Newman, *supra* note 271.

offered with a "veneer of benevolence."[301] Yet Comfort notes viewing new technology in this manner fails to situate it within the broader context of a free market system that brutally capitalizes on the newest technology, at times at the expense of those who seek it. [302]

We must be cautious of the commercial market driving the adoption of new technology such as MRT, because the market prioritizes expansion and profit increase as a primary goal, which creates a conflict of interest with parents, children, and egg donors in MRT.[303] Minimal regulation combined with a high demand for services means the ART industry has little incentive to collect and analyze important data related to risk, outcomes, and efficacy beyond basic statistics related to viable pregnancies.[304] This shifts external costs related to latent risks and long term harm onto parents, donors, and children.[305] Unlike other classes of physicians who are passive providers, the fertility industry constitutes influential stakeholders where the physicians themselves consistently push for implementing risky experimental techniques as a means of expanding and increasing their market position.[306] If the fertility industry offers MRT in the U.S. pursuant to an FDA submission, this provides the imprimatur of safety and efficacy, even though the procedure may indeed pose long term and latent risks to the child and the child's offspring. Alternatively, the fertility industry may opt to forgo pursuing an investigational new drug submission but continue to offer MRT as a service the clinic coordinates to perform in another country.

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[301] Comfort, *supra* note 168.
[302] *Id.*
[303] Frankel, *supra* note 201.
[304] Suter, *supra* note 251, at 256-57.
[305] *Id.*
[306] Ikemoto, *supra* note 226, at 280-281; Suter, *supra* note 251, at 255; Kimberly Mutcherson, *Welcome to the Wild West: Protecting Access to Cross Border Fertility Care in the United States*, 22 CORNELL J. L. & PUB. POL'Y 349, 390-91 (2012).

Permitting, or even insisting, that individuals have access to risky experimental reproductive techniques has the potential to increase reproductive tourism into the U.S. as destination point for MRT.[307] Legal scholars have described how the convergence of globalization and the fertility market has resulted in potential parents crossing borders, seeking a country that permits them to fulfill their parental desire.[308] Restrictions in some countries have led to strategic jurisdictional forum shopping, precisely illustrated by the example of Dr. Zhang. Potential parents willing to travel great lengths may seek out niche markets that offer what appear to be the newest and best products and services in an attempt to achieve a pregnancy, or even elect to use MRT as an energetic corrective preventive practice against aging, obesity, and common disease in the future child.[309]

VII. Recommendations

Promoting MRT as a method to assist suffering potential parents fails to acknowledge the substantial weight assigned to scientific innovation and commercial profit incentives driving the scientific and fertility industry. This framing not only lacks transparency, but appears ethically troublesome based on the concerted effort during the policymaking process to dismiss the risks involved in MRT and modifying the human germline.[310] As one bioethicist questioned, "Who is applying the brakes? Private entities are profit driven, which is the last question we should consider when altering the human race."[311] The U.S. appears poised to not only to accept

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[307] Mutcherson, *supra* note 306, at 371.
[308] *See generally* Mutcherson, *supra* note 306; Ikemoto, *supra* note 226; April Cherry, *The Rise of the Reproductive Brothel in the Global Economy: Some Thoughts on Reproductive Tourism, Autonomy, and Justice*, 17 U. PA. J. L. & SOC. CHANGE 257 (2014).
[309] During the FDA MRT Meeting, participants suggested using MRT as an option to not only "treat" mitochondrial disease and infertility, but some participants also suggested it could be a treatment for age, obesity, and common disease. *See* FDA Meeting, *supra* note 11, at 208.
[310] *Id.* at 182-183.
[311] Frankel, *supra* note 201.

inflated promises of MRT, but to do so through a policymaking process that provided the appearance of deliberation while issuing conclusions against the weight of the scientific evidence. This sets a dangerous precedent, where implicit prioritization of scientific exploration and commercial interests directs governance outcomes in a manner that implicitly subverts considering risks to human health. In this instance, the weight of the scientific evidence not only suggests creating children through MRT may not be safe or effective, but that the procedure may impose new health deficits such as an increased risk of developmental disorders, latent fatalities, expedited aging, cancer, and congenital abnormalities.

Although some appear resigned to the power of these "baby markets,"[312] I assert we have a duty to use federal regulation as a mechanism to insulate parents, donors, and children from substantial risks inherent in MRT as well as new technological iterations that promise to correct genomic flaws by prohibiting modification of the human germline. Commercial and scientific interests have painted a false double bind: regulation that entails callous prohibitions stifling innovation to that could otherwise help parents have healthy children, or an unhampered free market wherein the fertility industry can produce miracles. Confined to the impossible choices in this narrative blocks us from considering the crucial questions raised here: such as whether the scientific risks mirror the policymaking outcome; why the discussion glosses over risks to oocyte donors; how the science fails to support the medical rationale for MRT; and the inappropriateness of permitting commercial motivations to drive the adoption of MRT.

Rather than prioritizing scientific ingenuity and economic profit, the U.S. and other nations have a duty to enact measures that discourage risky experimentation on future generations through MRT and other forms of germline modifications. I affirm the proposition

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[312] *See generally* Suter, *supra* note 251.

that future generations have a right to an "untampered genome." [313] I further assert that each individual has a human right to be born without intentional germline interventions, and we have an ethical duty to investigate and mitigate sources that threaten the integrity of our health. This duty encompasses a diligence to properly situate and analyze whether proponents' medical rationale matches available evidence or constitutes a strategic appeal to our pathos. This stance against MRT and other germline interventions coincides with the scientific opinion that our inability to accurately predict the outcomes of potential interventions means germline modifications including MRT should not be permitted.[314] Germline interventions pose significant risk and carry the threat of unintended consequences that are both irreversible and permanent.[315] The consensus against germline modifications set forth by UNESCO's International Bioethics Committee, the Council of Europe, and numerous other nations should remain intact to protect the health of future generations.

New regulations enacted in other nations should affirm this prohibition through unambiguous legislative measures. At the federal level, nations should not rely on funding restrictions, but enact criminal prohibitions for human germline modification of human embryos. These statutes should prohibit the creation of embryos with germline modifications for implantation and include additional mechanisms to dissuade implantation. Nations should recognize the transnational nature of this research and the convergence of forum shopping and reproductive tourism. As a mechanism to deter avenues of legal circumvention through reproductive tourism, nations should include prohibitions on recruitment of potential patients for

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[313] *See Human Enhancement*, STAN. ENCYCLOPEDIA OF PHIL., https://plato.stanford.edu/entries/enhancement/.
[314] Newman, *supra* note 271; Lanphier, *supra* note 141.
[315] Comfort, *supra* note 168.

impermissible procedures to create embryos with germline modifications, whether through MRT or another procedure, performed in another nation. These laws could also include a prohibition on the import and export of unauthorized human embryos for implantation. The statute should specify explicit criminal penalties that would reflect the gravity for potential harm of experimenting on future generations.

VIII. Conclusion

UNESCO's International Bioethics Committee cautioned against a number of elements that appear to be driving the shift in U.S. policy to permit MRT. Proponents of MRT employed reductionist explanations and simplified mitochondria's function, belying its complex evolutionary role, its impact on nDNA expression, and dismissed extensive doubts in the scientific community pertaining to safety and efficacy. Media articles in the U.S. praised Dr. Zhang for traveling to Mexico to perform MRT as a "therapy" to "save lives" and circumvent FDA jurisdiction. These actions directly contravened the International Bioethics Committee's directives for the media to avoid sensationalist journalism and renounce regulatory circumvention. During FDA meetings to discuss MRT to treat mitochondrial disease or infertility, many participants concluded the evidence falls "far short" of showing MRT could be safe and effective and asserted MRT could induce new permanent and irreversible health deficits in the child, in addition to existing risks arising from ART. MRT would also require increasing the pool of oocyte donors, which imposes potentially serious health consequences such as OHSS, impaired fertility, and increased risk of cancer on a class of women in exchange for payment to satisfy the reproductive projects of third parties. These risks pose significant burdens on both future children and oocyte donors. Furthermore, analysis of the medical rationale reveals MRT would not address a substantial portion of conditions related to mitochondrial dysfunction and

the complex factors influencing rising rates of infertility. The NAS Report's conclusion that conducting clinical investigations for MRT is ethically permissible is unsupported by the weight of the evidence and appears to prioritize the technological imperative and its potential to grow the U.S. global market share in novel fertility industry options.