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Mitochondrial Replacement Therapy: Let the Science Decide

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MITOCHONDRIAL REPLACEMENT THERAPY: LET THE SCIENCE DECIDE

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ABSTRACT

Mitochondrial replacement therapy (MRT) is an in vitro *fertilization technique designed to prevent women who are carriers of mitochondrial diseases from passing on these heritable genetic diseases to their children. It is an innovative assisted reproductive technology that is only legal in a small number of countries. The United States has essentially stagnated all opportunities for research and clinical trials on MRT through a rider in H.R.2029 – Consolidated Appropriations Act, 2016. The rider bans clinical trials on all therapies in which a human embryo is intentionally altered to include a heritable genetic modification. This note argues that the rider should be amended to permit therapies such as MRT, which do not create artificial DNA sequences, while continuing to prohibit clinical trials on germline therapies that modify the sequence of a gene. MRT is distinct from the types of therapies that Congress intended to ban through the rider. Amending the rider would not automatically approve MRT trials, but rather allow the FDA to evaluate investigational new drug applications and determine whether individual trials may proceed. Without proper FDA oversight, carriers of mitochondrial diseases are denied access to a therapy that provides them with benefits they cannot enjoy by any other means, and researchers may look abroad to conduct the therapy illegally or dangerously. Further, the United States can look to other countries such as the United Kingdom as a model for how to proceed with research and trials on MRT in an ethical manner.*

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INTRODUCTION

Mitochondrial diseases are inherited from a child's mother[1] through her mitochondrial DNA (mtDNA). Many of these diseases are severe, incurable, and can be fatal. Mitochondrial replacement therapy (MRT) is an assisted reproductive technology through which a woman who is a carrier for a mitochondrial disease can prevent transmission to her child. Assisted reproductive technologies are fertility treatments intended to result in pregnancy that involve manipulating the egg, sperm, or both *in vitro*.[2] These include intrauterine insemination and *in vitro* fertilization (IVF).[3] MRT involves alterations to the egg or embryo prior to implantation, and this means that it falls under the broad class of gene therapies that are considered germline therapies.

Currently, clinical trials of MRT cannot proceed in the United States because of a ban on germline therapies enacted by Congress in 2016 through a rider in H.R.2029 – Consolidated Appropriations Act, 2016. This note argues that the rider should be modified to specifically ban germline therapies that create artificial DNA sequences, but permit MRT, which does not edit the sequence of individual genes. Part I describes the technique behind MRT and how it prevents transmission of mitochondrial diseases from mother to child. Part II describes the regulatory landscape in the United States that covers genetic, cellular, and embryonic therapies. Part III proposes an amendment to the rider which would allow research and clinical trials on MRT to progress while addressing and dismantling arguments

1. For the purposes of this note, "mother" refers to a prospective parent who has an egg with mutated mitochondrial DNA and wishes to replace their mutated mtDNA with normal mtDNA from a donor. The author recognizes that this gendered language does not encompass all gender identities of prospective parents who may use this therapy. These terms are used throughout because the field lacks gender-neutral alternatives with the same level of specificity. The author acknowledges that issue has not been adequately addressed by the field.

2. *See generally Assisted Reproductive Technology (ART)*, NAT'L INSTS. OF HEALTH (Jan. 31, 2017), https://www.nichd.nih.gov/health/topics/infertility/conditioninfo/treatments/art.

3. *Id.*

against the use of MRT. This note concludes by reiterating that in order to learn if MRT is a viable therapy, further research must be conducted, and these decisions should be left to the scientific regulatory agency: the FDA.

I. Mitochondrial Replacement Therapy

Every year 1,000 to 4,000 babies born in the United States are affected by mitochondrial diseases.[4] Mitochondrial diseases are a result of mutations[5] in mitochondrial DNA (mtDNA).[6] mtDNA is inherited entirely from a child's mother, as an embryo only receives mtDNA from the mother's egg, not the father's sperm.[7] If the proportion of mutant mtDNA is over a certain threshold, usually sixty percent in humans, then the individual develops a severe disease such as liver failure, sensory deficit disorder, neuropathy, myopathy, or cardiomyopathy.[8] Inherited mitochondrial diseases are not curable, and can be fatal.[9] One disease that results from mutated mtDNA is Leigh syndrome,[10] "a severe neurological disorder that usually becomes apparent in the first year of life. This condition is characterized by progressive loss of mental and movement abilities (psychomotor regression) and typically results in death within two to three years, usually due to respiratory failure."[11] Another mitochondrial disease is myoclonic epilepsy with ragged-red fibers (MERRF) syndrome.[12] This is a rare syndrome which typically affects the muscles and nervous system, and causes twitches, weakness

4. Emily Mullin, *Patient Advocates and Scientists Launch Push to Lift Ban on "Three-Parent IVF"*, STAT (Apr. 16, 2019), https://www.statnews.com/2019/04/16/mitochondrial-replacement-three-parent-ivf-ban.

5. Most mtDNA mutations are not harmful and have no effect. Everyone carries many of these benign mutations in their mtDNA. For the purposes of this note, "mutant" mtDNA refers only to those mutations that are harmful, while "normal" mtDNA refers to mtDNA that has benign mutations. *See generally* Jing Wang et al., *An Integrated Approach for Classifying Mitochondrial DNA Variants: One Clinical Diagnostic Laboratory's Experience*, 14 GENETICS MED. 620 (2012).

6. *See generally* Tian Wang et al., *Polar Body Genome Transfer for Preventing the Transmission of Inherited Mitochondrial Diseases*, 157 CELL 1591 (2014).

7. *See* César Palacios-González, *A Third MRT-Baby on Its Way*, UNIV. OXFORD: PRACTICAL ETHICS (Jan. 22, 2019), http://blog.practicalethics.ox.ac.uk/2019/01/a-third-mrt-baby-is-on-its-way.

8. Wang et al., *supra* note 6, at 1591.

9. *Id.*

10. *Leigh Disease or Syndrome*, UNITED MITOCHONDRIAL DISEASE FOUND., https://www.umdf.org/mitochondrial-disease-types/leigh-disease-or-syndrome (last visited Apr. 28, 2021).

11. *Leigh Syndrome*, MEDLINEPLUS (June 1, 2016), https://medlineplus.gov/genetics/condition/leigh-syndrome/#:~:text=Leigh%20syndrome%20is%20a%20severe,usually%20due%20to%20respiratory%20failure.

12. *Myoclonic Epilepsy with Ragged-Red Fibers*, MEDLINEPLUS (May 1, 2014), https://medlineplus.gov/genetics/condition/myoclonic-epilepsy-with-ragged-red-fibers.

and progressive stiffness.[13] The physical presentation of MERRF varies widely from one individual to the next.[14] There are over thirty different types of mitochondrial diseases of varying severity, presentation and prevalence.[15]

A. *Mitochondrial Replacement Therapy: Method and Purpose*

Replacing the mother's mutant mitochondrial DNA with normal mitochondria from a donor egg significantly reduces the risk of a woman passing on mutant mtDNA to her child. Animal studies of MRT have demonstrated efficacy in preventing inheritance of mtDNA diseases.[16]

1. Inheritance of mtDNA Diseases

All humans have two types of DNA: nuclear and mitochondrial.[17] Nuclear DNA encodes the vast majority of our traits, while mtDNA codes a small number of mitochondrial proteins.[18] mtDNA accounts for less than one tenth of one percent of an individual's total DNA,[19] encoding only thirty-seven genes.[20] These genes produce proteins which are vital to apoptosis (programmed cell death) and which produce energy within the cell.[21] Each cell contains one complete set of nuclear DNA but there are multiple copies of mtDNA present within the cell.[22]

Fertilization is the process by which the male and female sex cells, called gametes, combine to form an embryo, also called a zygote.[23] The egg is the larger gamete that provides most of the contents of the combined zygote. Mitochondria are present in the cell cytoplasm. The egg, or oocyte, is

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13. *Id.*
14. *Id.*
15. *Types of Mitochondrial Disease*, UNITED MITOCHONDRIAL DISEASE FOUND., https://www.umdf.org/what-is-mitochondrial-disease/types-of-mitochondrial-disease (last visited Apr. 3, 2021).
16. *See* Masahito Tachibana et al., *Mitochondrial Replacement Therapy and Assisted Reproductive Technology: A Paradigm Shift Toward Treatment of Genetic Diseases in Gametes or Early Embryos*, 17 REPROD. MED. & BIOL. 421, 423, 425–26 (2018).
17. *Clinical Investigations of Mitochondrial Replacement Techniques Are 'Ethically Permissible' if Significant Conditions Are Met, Says New Report*, NAT'L ACADS. SCIS., ENG'G & MED. (Feb. 3, 2016), https://www.nationalacademies.org/news/2016/02/clinical-investigations-of-mitochondrial-replacement-techniques-are-ethically-permissible-if-significant-conditions-are-met-says-new-report [hereinafter NAT'L ACADS. *Report*].
18. Robert W. Taylor & Doug M. Turnbull, *Mitochondrial DNA Mutations in Human Disease*, 6 NATURE REVS. GENETICS 389, 391 (2005).
19. Rosa J. Castro, *Mitochondrial Replacement Therapy: The UK and US Regulatory Landscapes*, 3 J.L. & BIOSCIS. 726, 727 (2016).
20. Tachibana et al., *supra* note 16, at 422.
21. *Id.*
22. Taylor & Turnbull, *supra* note 18, at 389.
23. Katerina Georgadaki et al., *The Molecular Basis of Fertilization (Review)*, 38 INT'L J. MOL. MED. 979, 979 (2016).

the gamete that provides all of the cell cytoplasm and organelles to the combined zygote once fertilization is complete. There is a significantly higher number of mtDNA molecules in an oocyte than in a sperm cell, or spermatocyte: a mature oocyte has 200,000 to 300,000 mtDNA copies, whereas a spermatocyte has approximately 100 mtDNA copies.[24] Any mitochondria present in a zygote that come from the spermatocyte are specifically eliminated during early embryo development.[25] This means that the mother provides all of the mitochondria and mtDNA, and so mitochondrial diseases can only be passed down from the mother.[26] Because mtDNA and mitochondrial diseases can only be passed on to a child by the mother, mtDNA therapies must deal with eggs or embryos at the preimplantation stage in order to prevent the inheritance of mutant mtDNA.

The severity of a mitochondrial disease is highly dependent on the number of mutated mtDNA copies, so the physical manifestation of the disease varies greatly from one individual to the next.[27] A higher ratio of mutant to normal mtDNA molecules within a person's cells can cause disease presentation to be more severe.[28] Typically, in order for a mtDNA disease to manifest in a human, sixty percent or more of the mtDNA must be mutated.[29]

2. MRT Can Prevent mtDNA Diseases

Germline therapy is a type of gene therapy. Gene therapy is a technique that can be used to treat a genetically inherited disease or illness.[30] There are two types of cells in which gene therapy can be performed: somatic and germline. Somatic cells are normal body cells, whereas germline cells are sex cells that create offspring. Somatic gene therapy involves changing, fixing, or replacing genes in one individual, whereas germline therapy results in genetic changes to the individual on which the therapy is performed as well as all of their offspring.[31] Genetic changes made in germline cells are passed down to the offspring of that individual because germline cells are involved in the creation of the embryos, if that individual chooses to reproduce.

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24. Tachibana et al., *supra* note 16, at 422.
25. *See, e.g.*, Peter Sutovsky et al., *Ubiquitin Tag for Sperm Mitochondria*, 402 NATURE 317, 371–72 (1999).
26. *E.g.*, Castro, *supra* note 19, at 727.
27. Taylor & Turnbull, *supra* note 18, at 391–92.
28. *See* Tachibana et al., *supra* note 16, at 422.
29. *Id.* at 426.
30. *What Is Gene Therapy?* MEDLINEPLUS (Sept. 21, 2020), https://medlineplus.gov/genetics/understanding/therapy/genetherapy/#:~:text=Gene%20therapy%20is%20an%20experimental,of%20using%20drugs%20or%20surgery.
31. Tachibana et al., *supra* note 16, at 422.

Mitochondrial Replacement Therapy is an IVF technique that is designed to prevent a mother[32] from passing down mutated mtDNA to a child.[33] There are two processes by which MRT can be performed: maternal spindle fiber transfer (MST) and pronuclear transfer. Both processes use a donor egg who has normal mtDNA.[34]

In the first process, maternal spindle transfer, the nucleus is removed from the donor egg.[35] The mother's nuclear DNA, in the form of a spindle-chromosome complex, is removed from the egg cell in a karyoplast (membrane-enclosed nuclear DNA).[36] The nucleus in the donor egg is replaced with the mother's nuclear DNA.[37] The combined egg is fertilized, and then the embryo is implanted into the mother or a surrogate.[38]

The second process, pronuclear transfer, is essentially the same as MST, but the donor's egg nucleus is replaced with the mother's nucleus after fertilization.[39] In pronuclear transfer, both eggs are fertilized, and then the nucleus of the zygote formed with the donor egg is removed and replaced with the nucleus from the zygote formed with the mother's egg.[40] MRT is sometimes called "three-parent IVF" because a child born from this technique has inherited genetic material from three people, although the genetic contribution from the donor is small and only present in the mitochondria.[41]

The nuclear DNA contains the bulk of human genetic material, which means the person providing the nuclear DNA is the biologically related to the child.[42] The person who provides the egg is a donor, and that nuclear DNA is replaced before implantation, and so the egg donor is not the parent.[43] Since mitochondria are only present in female sex cells, using a donor egg with normal mitochondrial DNA (instead of an egg from a carrier of a mitochondrial disease) prevents the transmission of a mitochondrial disease

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32. To differentiate between the parents providing the egg and the sperm in this section, "mother" refers to the parent providing the egg with mutant mitochondrial DNA. *See* note 1 and accompanying text.

33. *See, e.g.*, Sara Reardon, *US Congress Moves to Block Human-Embryo Editing*, NATURE (June 25, 2015), https://www.nature.com/news/us-congress-moves-to-block-human-embryo-editing-1.17858.

34. Castro, *supra* note 19, at 728.

35. *Id.*

36. Tachibana et al., *supra* note 16, at 425–26.

37. The mother's nuclear DNA is inserted into the donor egg in the form of a karyoplast. *See* Palacios-González, *supra* note 7.

38. Tachibana et al., *supra* note 16, at 426.

39. *See, e.g.*, *id.* at 425.

40. *See id.*

41. Taylor & Turnbull, *supra* note 18, at 389.

42. *See* Mary Herbert & Doug M. Turnbull, *Progress in Mitochondrial Replacement Therapies*, 19 NATURE REVS. MOL. CELL BIOL. 71, 71 (2018).

43. While this is not a settled issue, this note follows the legal framework of the United Kingdom in which the donor has, through informed consent, relinquished parental rights.

to the offspring.[44] The mother's nuclear DNA is inserted into the donor egg and so the mother's nuclear DNA is passed on to the child. There is a risk that some residual mutant mtDNA from the carrier is still passed down to the child, but since the threshold for disease pathology is typically sixty percent, a slight residual amount of mutant mtDNA is not a concern.[45]

Additionally, some research teams are modifying the MRT method to account for this concern. One team has conducted experiments using polar bodies rather than the mother's oocyte as the source of the mother's nuclear DNA, as discussed above.[46] Polar bodies are nonviable byproducts of meiosis in female sex cell division. Polar bodies contain the same nuclear DNA as a mature oocyte, however, they contain significantly fewer organelles, including mitochondria,[47] and the risk of carryover of the mother's mutant mtDNA is much lower.[48] The procedure of visualizing and manipulating a polar body is easier because it is membrane-enclosed.[49] This study had undetectable levels of mutant donor mtDNA in all offspring, and so the use of polar bodies looks to be a feasible and promising method of carrying out MRT in the future.[50]

3. MRT Trials in Animals Have Been Successful

MRT was initially tested in primate oocytes[51] and then in mice, and successfully prevented the mother from passing on a significant amount of mutant mtDNA to the offspring, which prevented the development of mtDNA diseases.[52] This therapy has since been validated by multiple teams in nonhuman trials.[53] *In vitro* MST tests involving healthy donor oocytes resulted in almost complete transfer of cytoplasm, which is sufficient to prevent mtDNA disease presentation.[54] In the initial MST trials, approximately half of the zygotes had abnormal fertilization,[55] however, after adjusting ex-

44. NAT'L ACADS. *Report, supra* note 17.
45. Tachibana et al., *supra* note 16, at 426.
46. Wang et al., *supra* note 6, at 1593.
47. Caroline M. Dalton & John Carroll, *Biased Inheritance of Mitochondria During Asymmetric Cell Division in the Mouse Oocyte,* 126 J. CELL SCI. 2955, 2955 (2013).
48. Wang et al., *supra* note 6, at 1593.
49. *Id.*
50. *Id.* at 1601.
51. The studies were conducted using *rhesus macaque* oocytes.
52. Tachibana et al., *supra* note 16, at 426.
53. *See generally* Masahito Tachibana et al., *Towards Germline Gene Therapy of Inherited Mitochondrial Diseases*, 493 NATURE 627 (2013); Eunju Kang et al., *Mitochondrial Replacement in Human Oocytes Carrying Pathogenic Mitochondrial DNA Mutations*, 540 NATURE 270 (2016).
54. Tachibana et al., *supra* note 16, at 427.
55. Tachibana et al., *supra* note 53, at 630.

perimental conditions, fertilization was improved.[56] Feasibility and efficacy of MST has been confirmed by other independent laboratories.[57]

Recent MRT experiments by the MST method have eliminated inherited mtDNA variants in the embryos of nonhuman primates and humans.[58] The primate offspring had minimal carryover of mutant mtDNA, as did the human embryonic stem cells, though the human embryos did not proceed to the implantation stage.[59] The spindle apparatus that must be removed from the mother's egg and inserted into the donor's egg is sensitive, so the results of this procedure depend on the operator.[60]

Preliminary studies on the pronuclear transfer method of MRT in mouse embryos were effective at eradicating mutant phenotypes related to mtDNA mutations.[61] However, these studies found that 300 days after birth, the mice had five percent to forty-four percent mutant mtDNA, due to amplification of residual mutant mtDNA.[62] When the mother's nucleus is inserted into the donor egg, some of the mother's mutant mtDNA ends up in the combined embryo.[63] This occurs because the separation of the nucleus from the rest of the cell is a physical process, and a perfect split between the nucleus and the cell cytoplasm is not usually achievable.[64] There will often be a small amount of cytoplasm surrounding the nucleus after it is removed, and this may contain a residual amount of the mother's mutant mtDNA.[65] Residual mutant mtDNA is replicated within the embryo by the same mechanisms as the rest of the normal mtDNA, and so a residual amount of mutant mtDNA can become a more substantial amount of mutant mtDNA over the time it takes to complete many replications.[66] This level of mutant mtDNA does not usually cause mutant phenotypes.[67] Studies on pronuclear transfer in humans has shown minimal carryover of mutant mtDNA to the early em-

56. Kang et al., *supra* note 53, at 271–72.

57. *See* Daniel Paull et al., *Nuclear Genome Transfer in Human Oocytes Eliminates Mitochondrial DNA Variants*, 493 NATURE 632, 632 (2013); *see also* Masahito Tachibana et al., *Chromosome Transfer in Mature Oocytes*, 5 NATURE PROTOCOLS 1138, 1138–39 (2010).

58. Paull et al., *supra* note 57, at 632; *see also* Masahito Tachibana et al., *Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells*, 461 NATURE 367, 371 (2009); *see generally* Tachibana et al., *supra* note 53.

59. Paull et al., *supra* note 57, at 632; Tachibana et al., *supra* note 53, at 628.

60. Tomoya S. Kitajima et al., *Complete Kinetochore Tracking Reveals Error-Prone Homologous Chromosome Biorientation in Mammalian Oocytes*, 146 CELL 568, 579 (2011).

61. Akitsugu Sato et al., *Gene Therapy for Progeny of Mito-Mice Carrying Pathogenic mtDNA by Nuclear Transplantation*, 102. PROC. NAT'L ACAD. SCIS. U.S. 16765, 16765 (2005).

62. *Id.* at 16768.

63. Tachibana et al., *supra* note 16, at 425.

64. Wang et al., *supra* note 6, at 1593.

65. Tachibana et al., *supra* note 16, at 425.

66. Wang et al., *supra* note 6, at 1591.

67. *See id.*

bryo.[68] Because of the restrictions on research and clinical trials on MRT, scientists do not have much data on the carryover of mutant mtDNA in humans who receive MRT. This is an area that requires further study.

B. *Current Treatment Options for Women Who Are Carriers of Mitochondrial Diseases*

A woman who has some mutant mtDNA but does not exhibit a mitochondrial disease is called a carrier. When a woman is a carrier, she can use typical screening methods such as preimplantation genetic diagnosis to see if she has passed on mutant mtDNA to her baby. Preimplantation genetic diagnosis can identify genetic abnormalities in an embryo, but it is only a diagnostic tool, not a treatment. These screening methods may not be able to accurately identify whether the mutant mtDNA has led to a mitochondrial disease.[69] If a woman is a carrier for a mitochondrial disease and does not want to risk passing the condition on to a child, the only current options are adopting or using an egg donor.[70] While a treatment to address the problem of potentially passing on mitochondrial diseases is developing rapidly, it is not approved in the United States at this time. Currently, there is no way for a carrier of mtDNA diseases in the United States to have a child to whom she is biologically related without risking mitochondrial disease.

II. United States Regulation Of Gene, Cell, And Embryo Therapies

In the United States, research on mitochondrial diseases and potential treatments have stalled because of federal regulations. The regulatory landscape is controlled by the Dickey-Wicker Amendment and the Food, Drug, and Cosmetic Act (FDCA), both of which have created substantial roadblocks to the progression of research and clinical trials.[71]

A. *Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps)*

The FDA regulates Cell and Gene Therapies (CGT) under the Center for Biologics Evaluation and Research (CBER) in the Office of Tissues and

68. Lyndsey Craven et al., *Pronuclear Transfer in Human Embryos to Prevent Transmission of Mitochondrial DNA Disease*, 465 NATURE 82, 84 (2010).

69. Annelien L. Bredenoord et al., *PGD to Reduce Reproductive Risk: The Case of Mitochondrial DNA Disorders*, 23 HUM. REPROD. 2392, 2392 (2008).

70. Gretchen Vogel, *For Boys Only? Panel Endorses Mitochondrial Therapy, but Says Start with Male Embryos*, SCIENCE (Feb. 3, 2016, 2:00 PM), https://www.sciencemag.org/news/2016/02/boys-only-panel-endorses-mitochondrial-therapy-says-start-male-embryos.

71. Balanced Budget Downpayment Act, I, Pub. L. No. 104-99, § 128, 110 Stat. 26, 34 (1996); 21 U.S.C. §§ 301–399i (2018).

Advanced Therapies.[72] The CBER mission is, "to protect and enhance the public health through the regulation of biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies."[73] CBER's statutory authority comes from the Public Health Service (PHS) Act[74] and the Food, Drug and Cosmetic Act (FDCA).[75] Under the FDCA and PHS Act, the FDA has the authority to regulate genetically manipulated cells and their derivatives.[76]

For MRT, the pertinent type of biological products are Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps). There are two types of HCT/Ps: 351 HCT/Ps and 361 HCT/Ps. 361 HCT/Ps are only regulated under § 361 of the PHS Act[77] and 21 C.F.R. § 1271. 361 HCT/Ps are not a class of products; § 361 gives the FDA authority to make and enforce regulations that prevent the introduction, transmission, and spread of communicable diseases from foreign countries into the United States.[78] 361 HCT/Ps are not subject to premarket approval.[79] In order to be a 361 HCT/P, the product must meet the criteria outlined in 21 C.F.R. § 1271.10(a). These criteria are:

> (1) the HCT/P is minimally manipulated, (2) intended for homologous use only . . . (3) the manufacture does not involve the combination of the cells or tissues with another article . . . and, (4) either: (i) the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or (ii) the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: (a) is for autologous use; (b) is for allogeneic use in a first-degree or second-degree blood relative; or (c) is for reproductive use.[80]

In its draft guidance for industry, the FDA says that reproductive cells and tissues such as embryos, semen, and oocytes are 361 HCT/Ps that meet

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72. Michael Mendicino et al., *Current State of U.S. Food and Drug Administration Regulation for Cellular and Gene Therapy Products: Potential Cures on the Horizon*, 21 CYTOTHERAPY 699, 699 (2019).

73. *About CBER*, FDA (Feb. 6, 2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/about-cber.

74. *See* 42 U.S.C. § 262(a)(2) (2018).

75. *See* 21 U.S.C. §§ 301–399i (2018).

76. *Therapeutic Cloning and Genome Modification*, FDA (Mar. 16, 2018), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/therapeutic-cloning-and-genome-modification.

77. *See* 42 U.S.C. § 264 (2018).

78. 21 C.F.R. § 1271.1(a) (2020).

79. *See* 42 U.S.C. § 264 (2012); 21 C.F.R. § 1271 (2020); CTR. BIOLOGICS EVALUATION & RSCH., FDA, REGULATION OF HUMAN CELLS, TISSUES AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/PS) – SMALL ENTITY COMPLIANCE GUIDE: GUIDANCE FOR INDUSTRY (2007) [hereinafter FDA HCT/PS GUIDE].

80. 21 C.F.R. § 1271.10(a) (2020).

the criteria outlined in § 1271.10(a).[81] On this basis, it may seem that MRT products qualify as 361 HCT/Ps. However, the egg or embryo resulting from MRT does not meet §1271.10(a)'s minimal manipulation requirement because it combines portions of two different eggs. "Minimal manipulation" is defined as "processing that does not alter the relevant biological characteristics."[82] As the nuclear DNA is replaced in the embryo, the biological characteristics are altered, so MRT embryos fail to meet all of the 361 HCT/P requirements.

There are exceptions listed in 21 C.F.R. § 1271.15 whereby certain HCT/Ps are exempt from regulatory requirements. Only exception (e) is relevant to MRT, which says, "you are not required to comply with the requirements of this part if you are an establishment that only recovers reproductive cells or tissues and immediately transfers them into a sexually intimate partner of the cell or tissue donor." Normal IVF procedures qualify under this exemption, however MRT does not qualify because the cell that is implanted into the mother contains more than just cells from her intimate sexual partner, it also contains a cell fragment from an egg donor.

Because the embryo created by MRT does not qualify as a 361 HCT/P under § 1271.10(a), nor does it qualify for a § 1271.15 exemption, an embryo created by MRT would be a 351 HCT/P if MRT was legally allowed in the United States (as discussed in Part III). 351 HCT/Ps are biological drugs under § 351 of the PHS Act,[83] regulated under 21 C.F.R. § 1271.20, and qualify as "drugs" under the Food, Drug, and Cosmetic Act (FDCA).[84] This means that if MRT were legal, it would be subject to the premarket and post-market requirements of biological drugs. For a 351 HCT/P, a Biologics License Application (BLA) is required. The BLA requests permission to introduce a biologic product into interstate commerce and sets out the requirements for filing.[85] Before a clinical trial can proceed on a 351 HCT/P, the sponsor must submit an Investigational New Drug (IND) application to the FDA.[86] The same as any other IND application, it must comply with the regulations set forth in Title 21 of the Code of Federal Regulations (CFR), parts 50, 56, and 312.[87]

81. FDA HCT/Ps GUIDE, *supra* note 79, at 4.
82. 21 C.F.R. § 1271.3 (2020).
83. *See* 42 U.S.C. § 262(i) (2018).
84. *See* 21 U.S.C. § 321(g)(1)(B) (2018) (defining "drugs" as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals").
85. 21 C.F.R § 601.2 (2019).
86. FDA, *supra* note 76.
87. *Id.*

B. *The Congressional Ban of MRT*

In 2014, the FDA held a meeting of the Cellular, Tissue and Gene Therapy Advisory Committee (CGTAC) to consider the permissibility of oocyte and embryo modification as a treatment for infertility or a method of preventing the inheritance of mitochondrial diseases.[88] This meeting concluded that there was insufficient evidence to prove that the technique was safe enough for research to proceed in humans.[89] The FDA concluded that there was insufficient animal data for MRT to move on to clinical trials in humans.[90]

In 2015, the FDA requested that the Institute of Medicine (IOM) write a consensus report on the ethical and social concerns related to genetic modification of embryos as a treatment for mitochondrial diseases.[91] In 2016, the IOM published a report on the ethical concerns of MRT concluding that MRT is ethically permissible as long as specific conditions and principles are met, as discussed below.[92] The report emphasized the benefits in terms of reproductive options that MRT provides to women who are carriers of mtDNA diseases.[93] The report recommended limiting MRT to women who are at risk of transmitting an mtDNA disease that is likely to manifest in a way that is severely pathological to their child.[94]

The report also recommended limiting MRT to male[95] embryos.[96] MRT resulting in male embryos would not be classified as a therapy that produces a heritable genetic modification because males do not pass on their mtDNA

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88. *Id.*

89. FDA, BRIEFING DOCUMENT, OOCYTE MODIFICATION IN ASSISTED REPRODUCTION FOR THE PREVENTION OF TRANSMISSION OF MITOCHONDRIAL DISEASE OR TREATMENT OF INFERTILITY (2014), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM385461.pdf [https://wayback.archive-it.org/7993/20170405194935/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM385461.pdf].

90. Sharon Begley, *U.S. FDA Weighs Evidence on Producing 'Three-Parent' Embryos,* REUTERS (Feb. 25, 2014), https://www.reuters.com/article/usa-health-ivf/u-s-fda-weighs-evidence-on-producing-three-parent-embryos-idUSL1N0LU1OI20140225.

91. FDA, *supra* note 76.

92. NAT'L ACADS. SCIS., ENG'G & MED., MITOCHONDRIAL REPLACEMENT TECHNIQUES: ETHICAL, SOCIAL, AND POLICY CONSIDERATIONS 117 (2016) [hereinafter NAT'L ACADS. CONSIDERATIONS].

93. *Id.* at 118.

94. *Id.* at 119.

95. The report refers to "male" embryos and "female" embryos, however, the distinction is actually between XY and XX embryos. XY embryos are genotypically male and XX embryos are genotypically female, and the report's suggestion is that XY embryos will develop into people who cannot pass on mtDNA to their children. This is not true in all cases. Discussed below.

96. NAT'L ACADS. CONSIDERATIONS, *supra* note 92, at 120.

to their offspring.[97] Limiting MRT to male embryos eliminates the risk of passing on an unexpected pathology resulting from MRT to future offspring. The report notes that such limitation would be valuable in the early experimental stage because unforeseen consequences of the therapy may present in the first generation of patients, and these issues can be addressed before impacting a second generation.[98] This raises ethical concerns surrounding female embryos and whether the FDA can require parents to select the sex of their child.[99] Additionally, the report itself acknowledges that if preclinical research is only carried out to produce male offspring, the risks associated with female offspring resulting from MRT cannot be resolved.[100] In making this recommendation, the committee reasoned that the tradeoffs of only conducting preclinical MRT research with male embryos are both necessary and justified in order to eliminate the risk of passing on detrimental heritable genetic modifications to a second generation.[101]

The Chair of the CGTAC Committee, Jeffrey Kahn, said, "in examining the ethical, social, and policy issues associated with mitochondrial replacement techniques, we concluded that the most germane issues could be avoided if the use of these techniques were restricted by certain conditions, rather than prohibiting them altogether."[102]

While the Committee cautiously recommended that MRT testing could proceed, Congress halted any progress. In 2016, Congress passed the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, which contained a rider barring the FDA from considering requests to approve clinical trials in which a human embryo is intentionally created to include a heritable genetic modification.[103] Because of this rider, the FDA cannot accept INDs that involve germline modifications. The final version of the rider, which has been incorporated into the annual appropriations bill in every subsequent year, states:

> None of the funds made available by this Act may be used to notify a sponsor or otherwise acknowledge receipt of a submission for an exemption for investigational use of a drug or biological product under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) or section 351(a)(3) of the Public Health Service Act (42 U.S.C. 262(a)(3)) in research in which a human embryo is

97. *Id.* at 119.
98. *Id.*
99. Castro, *supra* note 19, at 732.
100. NAT'L ACADS. CONSIDERATIONS, *supra* note 92, at 120.
101. *Id.* at 121.
102. NAT'L ACADS. *Report, supra* note 17.
103. Jocelyn Kaiser, *Update: House Spending Panel Restores U.S. Ban on Gene-Edited Babies*, SCIENCE (June 4, 2019, 1:45 PM), https://www.sciencemag.org/news/2019/06/update-house-spending-panel-restores-us-ban-gene-edited-babies#:~:text=It%20bars%20the%20Food%20and,human%20germline%20editing%E2%80%94or%20the.

> intentionally created or modified to include a heritable genetic modification. Any such submission shall be deemed to have not been received by the Secretary, and the exemption may not go into effect.[104]

The rider barring FDA review of clinical trials involving genetic modification of human embryos was briefly repealed in 2019. A draft of the 2020 spending bill that was approved by the Democrat-led House appropriations subcommittee did not contain the rider. After the draft was released a Democratic aide, speaking with *Science Insider*, said that the rider was dropped because, "it was inserted in private 3 years ago and has never been subject to public debate. We believe this provision could limit important scientific research and, if Congress chooses to prohibit such research, that should be done in the light of day."[105] Only a few months later, the rider was reinstated by the full Appropriations Committee of the U.S. House of Representatives as the request of the Republicans.[106] The only member who did not vote in favor of restoring the rider was Democrat Debbie Wasserman-Schultz.[107] Some Democrats were reluctant to reinstate the rider and some lawmakers on both sides agree that the issue should be subject to fuller debate and analysis by congressional health committees.[108]

III. Research And Clinical Trials On Mitochondrial Replacement Therapy Should Be Allowed in the United States

The rider in the Agriculture, Rural Development, and Food and Drug Administration and Related Agencies Appropriations Bill has never been fully and publicly debated. It has not been subject to notice and comment, and a full and thoughtful debate amongst lawmakers with perspectives from experts and regulatory agencies to which this ban applies.

In order to accomplish Congress's goal of prohibiting gene editing, the rider should be amended. This note suggests amending the language of the rider as follows:

> None of the funds made available by this Act may be used to notify a sponsor or otherwise acknowledge receipt of a submission for an exemption for investigational use of a drug or biological product under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) or section 351(a)(3) of the Public Health Service Act (42 U.S.C. 262(a)(3)) *for research in which a heritable genetic*

104. H.R. 648, 116th Cong. § 733 (2019).
105. Kaiser, *supra* note 103.
106. *Id.*
107. *Id.*
108. *Id.*

> *modification is achieved by creating an artificial DNA sequence*. Any such submission shall be deemed to have not been received by the Secretary, and the exemption may not go into effect.

This modification to the rider would allow the FDA to review and approve INDs for MRT. MRT does not alter the DNA sequence of mtDNA or nuclear DNA—it simply combines different parts of two separate eggs, each with their respective mtDNA or nuclear DNA completely unaltered.

A. *MRT is Legal in Other Countries and Has Produced Positive Results*

While the United States is debating the legality and ethics of this innovate therapy, a few other countries are making great advancements in MRT research. The United Kingdom, Greece, and Ukraine are leading the field. Each of these countries have clinics at which MRT is performed for women who wish to have a genetically related child but have had difficulty because the mother is either a carrier for a mitochondrial disease or struggles with infertility. Other countries such as Spain, Singapore, and Mexico are exploring MRT, but are in the preliminary research phase and have not yet moved to the clinical stage. There is support across the globe for progression of this therapy.

1. MRT Is Legal in the United Kingdom as a Clinical Procedure for Assisted Reproduction

In the United Kingdom, the Human Fertilization Act (HFE Act) governs regulations of mitochondrial replacement therapy and all other reproductive technologies.[109] The regulatory body, Human Fertilization and Embryology Authority (HFEA), which was created in 1990, oversees reproductive technology.[110] HFEA regulates assisted reproduction and embryo research.[111] HFEA has the power to determine and regulate what is "permitted" assisted reproduction.[112] The 2015 amendments to the 1990 HFE Act expanded to include mitochondrial replacement therapy as a permitted reproduction technique and allowed for "mitochondrial donor-conceived person[s]."[113]

The 2015 amendment to the HFE Act allowed MRT as part of an *in vitro* fertilization technique, and subsequently, clinical trials on MRT began.[114] The amendment also declared that mitochondrial donors do not have

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109. Castro, *supra* note 19, at 728.
110. *Id.*
111. Vogel, *supra* note 70.
112. Castro, *supra* note 19, at 728.
113. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, SI 2015/572, pt. 2.
114. *See id.*

parental rights.[115] A child born from MRT is allowed limited access to information about the mitochondrial donor, but this information will not identify the donor, and the child is not provided any information about other children from the same donor.[116] Similarly, the donor can access a limited amount of non-identifying information about children born from their donation.[117] This amendment also declared that once the egg or embryo is produced with the donor's egg, with informed consent, it is no longer considered the egg or embryo of the mitochondrial donor for consent purposes, and at this point consent can no longer be withdrawn.[118] HFEA granted a patient license in 2017, and now MRT can be done outside of clinical trials.[119] HFEA now allows fertility clinics to offer MRT on a case-by-case basis with close HFEA oversight.[120] HFEA ensures that patients for all types of assisted reproduction provide informed consent and carefully weigh their options prior to making a decision.[121]

Prior to the implementation of the 2015 amendment, HFEA undertook a public and stakeholder consultation to "review the ethical, social and regulatory issues involved in the clinical use of techniques for mitochondrial replacement."[122] This consultation informed the advice HFEA gave the legislature for consideration when amending the HFE Act.[123] HFEA continuously meets throughout the year to evaluate and modify policies and practices for assisted reproduction.[124] HFEA has committees and panels of members, staff, and the general public.[125]

2. Greece and Ukraine Have Had Successful Births Through MRT

In Greece and Ukraine, MRT is legally used to treat infertility.[126] In Greece, a healthy baby conceived through MRT treatment was born in April

115. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 pt. 3.
116. *Id.*
117. Castro, *supra* note 19, at 728.
118. *Id.*
119. Ian Sample, *UK Doctors Select First Women to Have 'Three-Person Babies*', GUARDIAN (Feb. 1, 2018, 1:48 PM), https://www.theguardian.com/science/2018/feb/01/permission-given-to-create-britains-first-three-person-babies.
120. Vogel, *supra* note 34.
121. *Consent to Treatment*, HUM. FERTILISATION & EMBRYOLOGY AUTH., https://www.hfea.gov.uk/choose-a-clinic/consent-to-treatment (last visited Feb. 17, 2021).
122. Diane Warburton, *Tracing the Impacts of Public Dialogue Projects Supported by Sciencewise: Mitochondrial Replacement*, SCIENCEWISE (Mar. 2016).
123. *Id.*
124. *About Us*, HUM. FERTILISATION & EMBRYOLOGY AUTH., https://www.hfea.gov.uk/about-us/our-authority-committees-and-panels (last visited Feb. 17, 2021).
125. *Id.*
126. *E.g.*, Mullin, *supra* note 4.

2019. A maternity clinic in Athens is licensed by the National Medically Assisted Reproduction Authority to perform clinical trials on MRT.[127]

In Kiev, Ukraine, a private fertility clinic called the Nadiya Clinic performs MRT.[128] Since the Clinic opened, Dr. Valery Zukin has performed twenty-one MRT procedures.[129] Fourteen of these procedures were unsuccessful in implanting the embryo into the mother; however, the clinic believes that this was due to the age of the mother and the increased difficulty of getting pregnant as a woman gets older.[130] The seven remaining MRT procedures performed at the Nadiya Clinic resulted in four successful and healthy births, and three more pregnancies were in progress when Dr. Zukin reported his success in June 2018. No further information on the success of these pregnancies has been reported.[131]

3. Other Countries, Including Spain and Singapore, Are Considering Legalizing MRT

Spanish researchers are investigating MRT as a treatment for infertility. Clinical trials are being carried out in Greece in collaboration with a Spanish company.[132] Singapore is considering legalizing MRT.[133] Currently, Singapore does not allow human germline modifications in the clinical setting, but it allows gene editing for research, and so MRT can be done as a part of a research study.[134]

B. *MRT is Distinct from the Types of Therapies That Have Been Met with the Most Vehement Societal Opposition*

There are a variety of therapies that involve genetic modifications, and they all raise unique ethical questions. There are particularly strong concerns regarding "new eugenics" and "designer babies," which are multifac-

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127. *MST Research*, INST. LIFE, https://www.iolife.eu/en/us/mst-research (last visited Apr. 2, 2021).

128. Rob Stein, *Clinic Claims Success in Making Babies with 3 Parents' DNA*, NPR (Jun. 6, 2018, 5:11 AM), https://www.npr.org/sections/health-shots/2018/06/06/615909572/inside-the-ukrainian-clinic-making-3-parent-babies-for-women-who-are-infertile.

129. *Id.*

130. *Id.* A study conducted by the Nadiya Clinic doctors and presented at a Philadelphia meeting of the American Society of Reproductive Medicine concluded that MRT was not effective at increasing the fertility of women age thirty-seven and older. *See* Pavlo Mazur et al., *Mitochondrial Replacement Therapy Give No Benefits to Patients of Advanced Maternal Age*, 112 FERTILITY & STERILITY, Sept. 2019, at e193, e193.

131. Stein, *supra* note 128.

132. *See* Mullin, *supra* note 4.

133. Sandy Ong, *Singapore Could Become the Second Country to Legalize Mitochondrial Replacement Therapy*, SCIENCE (June 6, 2018, 1:00 PM), https://www.sciencemag.org/news/2018/06/singapore-could-become-second-country-legalize-mitochondrial-replacement-therapy.

134. *Id.*

eted.[135] The process and potential applications of these types of therapies are distinct from MRT, as discussed below. Handpicking traits is not something that can be achieved through MRT. The result of the rider is that it encompasses and prevents progress on a broader array of reproductive technologies. MRT has been classified as germline therapy by some experts,[136] and not germline therapy by others.[137] This inconsistency calls into question whether the ban should apply to MRT. MRT is a substantially different process from gene editing technologies such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR).[138] The methods and potential future applications of CRISPR are different from those of MRT. Gene editing technologies alter the actual DNA sequence. This modifies the genes that are expressed, and the proteins coded from these genes, which ultimately affects physical traits. With MRT, the nuclear and mitochondrial DNA sequences are completely unaltered. The goal of gene editing therapies such as CRISPR is to alter the expression or presence of certain heritable traits by targeting the DNA sequences encoding specific characteristics. The goal of MRT is to replace the entire mutated mitochondrial DNA sequence of the parent with a healthy, normal mtDNA sequence from a donor.

The plain language of the rider does not specifically ban editing of gametes,[139] as the rider uses the language "embryo," not "gamete," "sperm," or "egg." Looking at the plain language, the rider banning intentional modification of human embryos may not strictly apply to techniques such as MRT that do not modify an embryo, but a precursor. University of Illinois at Urbana-Champaign law professor Jacob S. Sherkow says:

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135. *See* Michael R. Dohn, *Preventing an Era of "New Eugenics": An Argument for Federal Funding and Regulation of Gene Editing Research in Human Embryos*, 25 RICH. J.L & TECH. 1, 21–22 (2018); *see also* Peter H. Huang, *Herd Behavior in Designer Genes*, 34 WAKE FOREST L. REV. 639, 640 (1999); Alexandra M. Franco, *Transhuman Babies and Human Pariahs: Genetic Engineering, Transhumanism, Society and the Law*, 37 CHILD LEGAL RTS. J. 185, 185–86, 190 (2017).

136. NUFFIELD COUNCIL ON BIOETHICS, NOVEL TECHNIQUES FOR THE PREVENTION OF MITOCHONDRIAL DNA DISORDERS: AN ETHICAL REVIEW 58 (2012) (stating that MRT is not intended to modify nuclear genes or change the donor's mitochondrial DNA, but to replace the mother's mitochondria).

137. NAT'L ACADS. CONSIDERATIONS, *supra* note 92, at 6–7, 62 (stating that "genetic modification" means "changes to the genetic material within a cell." However, the report defined germline modification as that entailing "heritable modifications" and so the process of MRT to create a male offspring is not germline modification).

138. CRISPRs are DNA sequences from prokaryotic organisms such as bacteria. These DNA sequences are associated with an enzyme, Cas9, which cuts DNA at a specific sequence. The CRISPR-Cas9 system can be used to cut out and replace specific DNA sequences in a human's DNA sequence. This has the potential to cure a genetic disease or disorder. Aparna Vidyasagar, *What Is CRISPR?*, LIVE SCI. (Apr. 21, 2018), https://www.livescience.com /58790-crispr-explained.html.

139. Sperm and egg cells.

> The debate was firmly centered on the editing of embryos, but no legislator considered whether the language also applied to the editing of sperm and eggs . . . and there are strong arguments to be made that the plain text of the rider does not apply to sperm and eggs.[140]

Religious and political opposition to gene editing are less vehement when it comes to the modification of sperm and egg cells, as opposed to embryos.[141] The Dickey-Wicker Amendment took on the issue of destroying human embryos for research and clinical settings.[142] Parallel objections to the destruction of sperm and egg cells have not been raised.[143] According to Sherkow, "the current federal funding ban is predicated on a concept of bioethics that focuses on the embryo, and that's because there's widespread recognition in U.S. society that embryos have a certain moral salience that other biological components don't."[144]

Much of the opposition to gene editing technology, and precursory procedures such as embryonic stem cell therapy, was based on the fact that in order to pursue this research and the resulting clinical procedures, an embryo needs to be destroyed. Those who believe in embryonic personhood claim that personhood begins when the sperm and egg combine to form a zygote.[145] Forms of MRT, such as maternal spindle transfer, that modify the egg or sperm prior to fertilization, and so occur before the formation of the embryo. MRT therefore precedes personhood from the embryo personhood perspective. A sperm or egg alone cannot become a viable human, and this makes them analytically and biologically distinct from embryos.

C. *Removing the Rider Simply Enables the FDA to Perform Its Job and Evaluate Applications for Clinical Trials*

Some researchers and scientific advocacy groups oppose the rider because Congress made the decision, not scientific and regulatory experts.[146] Sean Tipton, chief advocacy, policy, and development officer at the Ameri-

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140. Univ. of Ill. at Urbana-Champaign, News Bureau, *Paper: Congress Must Clarify Limits of Gene-Editing Technologies*, EUREKALERT! (Oct. 21, 2020), https://www.eurekalert.org/pub_releases/2020-10/uoia-pcm102120.php.

141. I. Glenn Cohen et al., *Gene Editing Sperm and Eggs (not Embryos): Does it Make a Legal or Ethical Difference?*, 48 J.L MED. & ETHICS 619, 619 (2020).

142. *See id.*

143. *See id.*

144. Univ. of Ill. at Urbana-Champaign, News Bureau, *supra* note 140.

145. *Id.* Many states have introduced "personhood" initiatives which have attempted to equate an embryo with a person who has legal rights. These laws have all been rejected by voters and legislatures, however, they continue to be filed and debated. Editorial, *The "Personhood" Initiative*, N.Y. TIMES (Oct. 27, 2011), http://www.nytimes.com/2011/10/28/opinion/the-personhood-initiative.html.

146. Kaiser, *supra* note 103.

can Society for Reproductive Medicine says "[the provision was] an anti-science rider" and that "[removing it] allows the FDA to do its job."[147]

The current rider prevents scientists from conducting the research that is necessary to determine if it may one day be safe and effective to genetically modify embryos to prevent inherited genetic diseases.[148] In 2018, the FDA and National Institutes of Health (NIH) said that "[i]n the view of the senior leaders of the FDA and NIH, there is no longer sufficient evidence to claim that the risks of gene therapy are entirely unique and unpredictable—or that the field still requires special oversight that falls outside our existing framework for ensuring safety."[149]

If the rider were modified so that the ban does not encompass MRT, this therapy would be considered a 351 HCT/P and would be regulated by the FDA the same as other biological drugs. It would be subject to pre-market and post-market approval, a sponsor for a clinical trial would need to submit a biologics license application and an investigational new drug application, and the biologic would be subject to all of the safeguards the FDA has in place to ensure safety and efficacy. Modifying the rider would not mean that MRT would be available immediately. It would mean that researchers who wish to perform clinical trials would be able to apply to the FDA for approval and begin the process of investigating the safety and efficacy of this therapy.

D. *Political and Legislative Resistance is Based on Past Therapies that are Unrelated to MRT*

Congressman Jeff Fortenberry (R-NE) opposes removing the FDA rider barring embryo modification, and said "starting in 2016, the subcommittee acted to prevent an emerging science that would allow for the permanent modification of an individual's genetics and those of future offspring. This is a prohibition that is accepted by nearly every nation in the world due to the unknown risks."[150] Congresswoman Kay Granger (R-TX) also supported the ban, saying "it would be irresponsible for us to fund FDA's review of this very risky research."[151] Congressman Robert Aderholt (R-AL) said, "There are just too many unknowns . . . . Many of us believe it's just a step too far too soon."[152] There is some credence in this fear of the unknown because of unrelated experimental gene therapies which did not result in via-

147. *Id.*

148. Rob Stein, *House Committee Votes to Continue Ban on Genetically Modified Babies*, NPR (June 4, 2019, 4:38 PM), https://www.npr.org/sections/health-shots/2019/06/04/729606539/house-committee-votes-to-continue-research-ban-on-genetically-modified-babies.

149. Francis S. Collins & Scott Gottlieb, *The Next Phase of Human Gene-Therapy Oversight*, 379 NEW. ENG. J. MED. 1393, 1393 (2018).

150. Kaiser, *supra* note 103.

151. Stein, *supra* note 148.

152. *Id.*

ble treatment procedures. Even so, scientific progress and valuable medical advances such as MRT can only be achieved by researching what its unknown. This is the foundation of scientific discovery.

1. Issues with Past Unrelated Gene Therapies

Gene therapies have a complicated history that is distinct from the merits of new therapies. Earlier gene therapies came under scrutiny for safety concerns and unknown efficacy. In the 1990s, the United States conducted research on cytoplasmic transfer in an attempt to improve a woman's chances of successful IVF after numerous failed implantations attempts.[153] This technique involved injecting cytoplasm from a donor egg into the mother's egg prior to IVF.[154] Research into cytoplasmic transfer was stopped after two children born through this process had chromosomal anomalies and one child had a serious developmental disorder.[155] Because of the chromosomal abnormalities and birth defects the FDA, which has regulated gene therapy since 1990,[156] banned cytoplasmic transfer due to safety concerns.[157]

In 1999, an eighteen-year-old volunteer died in a Phase I clinical trial for a gene therapy designed to treat ornithine transcarbamylase deficiency, a rare and fatal X-linked disease.[158] Although mitochondrial replacement therapy is not strictly a gene therapy in the sense that genes are not modified, it has been associated with gene therapy and the accompanying concerns.

Compared to other countries such as the United Kingdom, the United States has not consulted the public.[159] This may be in part due to fears over the controversial nature of therapies involving human embryos. Discussions in the United States relating to MRT and other assistive reproductive technologies have been conflated with abortion and the surrounding controversy.[160] Reproductive rights in the United States have a long history of scrutiny based on political and religious values, often making these conversations unproductive.

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153. Castro, *supra* note 19, at 727.

154. *Id.*

155. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 136.

156. The first human gene therapy clinical trial the FDA oversaw was a pediatric study on adenosine deaminase deficiency, carried out in Bethesda, Maryland at the NIH Clinical Center. Collins & Gottlieb, *supra* note 149, at 1393.

157. Tachibana et al., *supra* note 16, at 424.

158. Jesse Geslinger is the first person reported to have died in an FDA approved clinical trial for a gene therapy. Nikunj V. Somia & Inder M. Verma, *Gene Therapy: Trials and Tribulations*, NATURE REVS. GENETICS (2000).

159. I. Glenn Cohen et al., *Transatlantic Lessons in Regulation of Mitochondrial Replacement Therapy*, 348 SCIENCE 178, 180 (2015).

160. *Id.* at 179.

2. The Fight Over Stem Cell Research

The policy and ethical issues that MRT currently faces are similar to those of human embryonic stem cells (hESC). In the early 2000s, legislation prohibited American researchers for investigating hESC, which set back the scientific community and slowed the progression of a valuable therapy. The current ban on MRT puts this therapy in the same standstill. In 2001, President George W. Bush banned federal funding for research using hESC.[161] Private funding was still eligible for use on this type of research, but this put researchers in a difficult position and some resorted to dividing staff, equipment, and laboratory space for private and federally funded research.[162] The Bush Administration policy prevented research using embryonic stem cells because of the belief that using these cells required the destruction of human life.[163] This policy reflected an entire movement of thought supporting the notion that life begins in the embryo. In order to isolate embryonic stem cells, an embryo must be destroyed. However, scientists extract stem cells from the extra embryos created for couples undergoing IVF, and these unused embryos would be destroyed by the IVF clinics regardless.[164] This ban stifled progress for many researchers. In 2009, President Obama signed an executive order that revoked President Bush's order on embryonic stem cells, allowing researchers to proceed with embryonic stem cell research.[165] This allowed researchers to use the extra embryos created from IVF to derive embryonic stem cells.[166]

State and private funding allowed continued research of embryonic stem cells, but while the federal ban was in place progress was slowed. When President Obama issued his executive order, he remarked, "(m)edical miracles do not happen simply by accident. They result from painstaking

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161. Varnee Murugan, *Embryonic Stem Cell Research: A Decade of Debate from Bush to Obama*, 82 YALE J. BIOL. & MED. 101, 101 (2009).

162. *Id.*

163. President Bush was quoted as saying, "at its core, this issue forces us to confront fundamental questions about the beginnings of life and the ends of science . . . . My position on these issues is shaped by deeply held beliefs . . . I also believe human life is a sacred gift from out creator." Alice Park, *George W. Bush and the Stem Cell Research Funding Ban*, TIME (Aug. 20, 2012), https://healthland.time.com/2012/08/21/legitimate-rape-todd-akin-and-other-politicians-who-confuse-science/slide/bush-bans-stem-cell-research/print.

164. *Id.*

165. Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 11, 2009).

166. Park, *supra* note 163. A few months later, a lawsuit was filed alleging that President Obama's Executive Order Violated the Dickey-Wicker amendment. The court ruled for the plaintiffs and issued a preliminary injunction that blocked federal funding of human embryonic stem cell research. On appeal, the U.S. Court of Appeals for the D.C. Circuit reversed on August 24, 2012, and the plaintiffs appealed to the Supreme Court, who denied to grant *certiorari*. In the 2012 presidential election, this was a point of contention, President Obama intended to allow embryonic stem cell research to continue if reelected and Mitt Romney would have banned it. *See* Allen M. Spiegel, *The Stem Cell Wars: A Dispatch from the Front*, 124 TRANSACTIONS AM. CLINICAL & CLIMATOLOGICAL ASS'N 94, 105 (2013).

and costly research . . . and from a government willing to support that work."[167]

The issues concerning MRT are similar to those faced by embryonic stem cell researchers. Political and religious opposition to these techniques are in complete opposition to researchers who see an opportunity for progress and to alleviate suffering caused by disease. Studies have concluded that the ban on stem cell research set back the scientific community in the United States substantially.[168] One study estimates that as a result of the Bush administration's 2001 policy, "U.S. production of hESC [human embryonic stem cell research] lagged 35 to 40 percent behind anticipated levels."[169] Once President Obama lifted the ban, the stem cell policy was subject to notice and comment, and regulations were issued by the NIH, the governing regulatory body. MRT has not been provided the benefits of these procedures.

E. *Without FDA Regulation and the Opportunity for Approval, Researchers and Patients Will Look Abroad or Conduct MRT Illegally and Dangerously*

There is currently no federal funding in the US for gene editing in human embryos. This has led American researchers to go to other countries.[170] In Mexico, MRT is only allowed in research to "solve sterility problems that cannot be solved otherwise."[171] In 2016, an American doctor crossed the border and implanted an embryo created through MRT into a Jordanian woman who was a carrier for Leigh syndrome.[172] This resulted in a successful birth.[173] Some researchers argue that this procedure was in violation of Mexican law because the mother did not technically have unsolvable fertility problems,[174] but no legal action was taken.

The Dickey-Wicker rider hinders the development of potentially helpful therapies, including MRT.[175] Federal funding would allow the government oversee regulation and monitor any ethical concerns stemming from this

167. Barack Obama, President, United States, Remarks of the President: Signing of Stem Cell Executive Order and Scientific Integrity Presidential Memorandum (Mar. 9, 2009), https://obamawhitehouse.archives.gov/the-press-office/remarks-president-prepared-delivery-signing-stem-cell-executive-order-and-scientifi.

168. *See* Jason Owen-Smith & Jennifer McCormick, *An International Gap in Human ES Cell Research*, 24 NATURE BIOTECH. 391, 392 (2006).

169. Jeffrey L. Furam et al., *Growing Stem Cells: The Impact of Federal Funding Policy on the U.S. Scientific Frontier*, 31 J. POL'Y ANALYSIS & MGMT. 661, 661 (2012).

170. *See* Dohn, *supra* note 135, at 25.

171. Bartha Maria Knoppers et al., *Mitochondrial Replacement Therapy: The Road to the Clinic in Canada*, J. OBSTET. GYNAECOL. CAN. 916–17 (2017).

172. *Id.*

173. Mullin, *supra* note 4.

174. Knoppers et al., *supra* note 171, at 117.

175. Kaiser, *supra* note 103.

technology.[176] In addition to researchers going abroad, there is a substantial risk of "medical tourism" whereby Americans will travel to other countries, such as the United Kingdom, in order to have this procedure.[177] If the procedure occurs in a different country than the child's birth, the rights of the egg donor may be in question. If an American woman has MRT in the United Kingdom, and the child is born in America, the United Kingdom's parental rights laws would not apply.[178] Further, medical tourism makes clinical follow-ups difficult or impossible, limiting the ability of researchers and clinicians' to identify and assess any long-term risks a child born from MRT may face.[179]

F. *Ethical Considerations Counsel in Favor of Allowing Parents to Choose Whether to Pursue MRT*

Research and clinical trials of MRT can be conducted ethically, as is already happening in other countries such as the United Kingdom, as discussed above. Considerations such as the rights of the egg donor, the impact on the child, and the scope of the therapy are valid but ultimately counsel in favor of continuing to pursue MRT.

1. Rights of the Egg Donor

There are concerns about whether the egg donor would be considered a parent of the child,[180] what information about the egg donor should be available to the child, and what information about the child should be available to the donor.[181] In the United Kingdom, MRT egg donors do not have parental rights.[182] This is appropriate because the genetic contribution from the egg donor is only mtDNA, which is less than one tenth of one percent of the child's entire DNA sequence. Concern over whether an egg donor wants parental rights are not pressing due to the small number of prospective parents who are candidates for MRT and the high number of people who are willing to donate their eggs for studies in the United Kingdom.[183] As long as the terms are clearly outlined and egg donors provide informed consent, any issues with egg donors will be minimal.

mtDNA makes up a very small fraction of the genome in terms of unique DNA sequences, however, every somatic cell has thousands of cop-

176. Dohn, *supra* note 135, at 3.
177. *See* Castro, *supra* note 19, at 734.
178. *See id.*
179. *Id.*
180. *See, e.g.*, *id.* at 728.
181. *Id.* at 733
182. *Id.* at 728.
183. Rebecca Dimond, *Social and Ethical Issues in Mitochondrial Donation,* 115 BRIT. MED. BULL. 173, 179 (2015).

ies of mtDNA and only two copies of nuclear DNA.[184] Mitochondria are essential to energy production in the cell and to programmed cell death.[185] This makes mtDNA very important to cellular function, which is why mtDNA diseases are so severe and devastating.[186] The question of how much DNA a child inherits from the oocyte donor is complicated and can be answered best if scientists are free to research the process. The role of the oocyte donor is complex and ambiguous given the current state of knowledge, but with more research it could become clearer, and policy decisions would be better informed.

2. Children Born from MRT

Since germline cell therapy affects embryos, the human recipient of MRT cannot choose whether or not to undergo this treatment, which has led to ethical debates surrounding consent.[187] Since the recipient of MRT is the child resulting from the therapy, the individual who may benefit or harm from MRT is not able to make the decision of whether to have the therapy, as they are not yet in existence at the time the choice is made. It is possible that a child born from this therapy may not have made that decision if they had been able to choose.[188] While this is a valid concern, the people who ultimately make the decision of whether the child will be the recipient of MRT are the child's parents. Parents are legally allowed to make medical decisions for children who are under eighteen, and this parental authority should extend to prenatal decisions as well.[189] Parents are in a difficult decision about whether to have a biological child or not in this situation.[190] Parents already make decisions on which embryos to implant and dispose of based on preimplantation genetic diagnosis when undergoing IVF. During the process of IVF, before embryos are implanted, the embryologist performs a genetic screening to determine which embryos are most likely to result in pregnancy.[191] Typically, embryos which have genetic diseases are not selected.[192] At this stage, parents also have the ability to choose the sex of their child if desired. The concerns surrounding consent of the recipient

184. Tachibana et al., *supra* note 16, at 422.
185. *Id.*
186. *See id.*
187. *What Are the Ethical Issues Surrounding Gene Therapy?*, MEDLINEPLUS (Sept. 17, 2020), https://medlineplus.gov/genetics/understanding/therapy/ethics.
188. *See id.*
189. *See* Marybeth Pompei & Francesco Pompei, *Overcoming Bioethical, Legal, and Hereditary Barriers to Mitochondrial Replacement Therapy in the USA*, 36 J. ASSISTED REPROD. & GENETICS 383, 387 (2018).
190. *Id.*
191. Nikhil Swaminathan, *Better Baby-Making: Picking the Healthiest Embryo for IVF*, SCI. AM. (May 14, 2008), https://www.scientificamerican.com/article/better-baby-making-pickin.
192. *Id.*

embryo of MRT are similar to those posed by regular IVF. The decision-making authority that parents have over the fetus created through MRT is not so dissimilar to that of the parents to an embryo created by IVF.

Some scientists and legislators have suggested that MRT should be performed to produce exclusively male XY embryos in order to prevent the altered mtDNA from being passed on to future generations, in case there are any long-term side effects that are unknown at the time of the procedure. This is not an acceptable course of action because it denies future female children equal access to a procedure that would prolong their lives and vastly improve the quality of life. Allowing MRT to be performed to produce female XX embryos would provide a better chance that future female offspring benefit from MRT research. Additionally, the distinction between XY and XX embryos does not guarantee that XY embryos will develop into people who cannot pass on mtDNA to their children. Some XY embryos become children who are phenotypically female (46,XY females). One study reports that 6.4 per 100,000 live born females are 46,XY females.[193] Another source reports that one in 15,000 XY embryos results in a phenotypically female child.[194] According to current medical knowledge, 46,XY females usually have female external genitalia, a uterus, and fallopian tubes, but usually do not have functional ovaries and do not produce oocytes.[195] However, there have been reported cases of 46,XY females who have functional ovaries and have had biological children.[196] This suggests that the recommendation to limit MRT to XY embryos does not accomplish the goal of eliminating the risk that a child born from MRT passes on their mtDNA to their offspring.

The choice should be in the hands of the parents, who already have a large amount of choice and control in the typical IVF process. During IVF, doctors often implant multiple embryos in the hopes that at least one will be viable. Implanting multiple embryos increases the chance of pregnancy, but also leaves the door open to multiple viable embryos. In this case, it is common to "selectively reduce" the number of embryos. When this happens, parents can choose which embryos are brought to term based on genetics, including gender. It is possible that informed couples undergoing

193. Agenthe Berglund et al., *Incidence, Prevalence, Diagnostic Delay, and Clinical Presentation of Female 46,XY Disorders of Sex Development*, J. CLINICAL ENDOCRINOLOGY & METABOLISM 4532, 4535 (2016).

194. Morten Busch, *More Women than Expected Are Genetically Men*, NOVO NORDISK FOUND. (Oct. 25, 2016), https://novonordiskfonden.dk/en/news/more-women-than-expected-are-genetically-men.

195. *Swyer Syndrome*, MEDLINEPLUS (Aug. 18, 2020), https://medlineplus.gov/genetics/condition/swyer-syndrome; *see also Swyer Syndrome*, NAT'L ORG. FOR RARE DISEASES, https://rarediseases.org/rare-diseases/swyer-syndrome (last visited Feb. 17, 2021).

196. *See* Miroslav Dumic et al., *Report of Fertility in a Woman with a Predominantly 46,XY Karyotype in a Family with Multiple Disorders of Sexual Development*, J. CLINICAL ENDOCRINOLOGY & METABOLISM 182, 182 (2008).

MRT will make the decision to have male children because of the increased risk of passing on any genetic abnormalities through a female embryo. If the gender of a child is chosen in advance of implantation, this choice should belong to the parents, not the government. This type of legislation would also intrude on the physician-patient relationship, which many believe should be free of governmental interference.[197] There are many factors at play when deciding which embryos to implant during IVF or MRT, and the person in the best position to make this very personal and very difficult decision is the parent, with the expertise and guidance of the medical professional providing the procedure.[198]

3. Limits on MRT's Therapeutic Scope

There are questions about what the limits on the use of MRT should be. In other countries, MRT has been used to treat infertility, though it may not be an effective infertility treatment for older mothers,[199] and it can be used to prevent the inheritance of deadly mitochondrial diseases. Some have argued that legislation should only permit MRT as a treatment for deadly mitochondrial diseases for which there is no effective treatment. In the early experimental stage, the study population can permissibly be limited to potential parents who are carriers of mtDNA diseases. Then, if proven to be safe on this population, the experimental group should be expanded for further tests of safety and efficacy. In other countries such as Greece and Spain, MRT is used to treat infertility when all other options have been exhausted. Women in this position, who have no other recourse but want to have a child, should be allowed to participate in later stage studies. If MRT can be proven effective for both preventing mitochondrial diseases and treating infertility, the therapy should be provided to women on both groups.

Long-term follow up of any resulting children, as is required in the United Kingdom, should be part of the agreement for women who want to undergo MRT. Because MRT does not affect the woman who carries the embryo, but the child born from the therapy, any effects MRT may have on the subject cannot be known until the child is born.[200] To conclusively determine the safety and efficacy of MRT, children born from MRT must be monitored.

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197. Bratislav Stankovic, *"It's a Designer Baby!": Opinions on Regulation of Preimplantation Genetic Diagnosis*, 9 UCLA J.L. & TECH. 1, 5 (2005).

198. NAT'L ACADS. CONSIDERATIONS, *supra* note 92, at 81.

199. Mazur et al., *supra* note 130, at e193.

200. *See* Dimond *supra* note 183, at 176.

G. *The Health Risks of MRT are Unproven and Can Only be Discovered Through Further Research*

Some who oppose MRT argue against the therapy because safer alternatives exist.[201] The executive director of the Center for Genetics and Society, Marcy Darnovsky, has said, "there is no compelling medical argument for heritable genome editing, and no need to subject our children to the risks it would entail, because we already have ways to prevent transmission of inheritable disease."[202] These ways are not sufficient for a carrier woman who wants a biological child.

Germline cell therapy may affect the development of a fetus in unanticipated ways, or it may have unknown long-term side effects.[203] Little is known about whether the interaction of mtDNA and nuclear DNA might cause adverse effects in the child.[204] Although there have been some children born through MRT, the number is so small it is statistically insignificant. The only way to find out is to further carefully monitored testing. For a carrier woman who does not want to adopt or use an egg donor, her options are either to not have a child, to have a child who will inherit mutated mtDNA who may suffer and die at a young age, or to try MRT. Of these three options, MRT is the best chance for a healthy, genetically related child. Even if there may be side effects, that arguably is the best-case scenario for the child.

Furthermore, research teams are refining MRT to alleviate this concern entirely. One team has conducted experiments using polar bodies rather than the mother's oocyte as the source of the mother's nuclear DNA, as discussed above.[205]

H. *MRT Provides Benefits Carriers of Mitochondrial Diseases*

The benefits that MRT provides cannot be achieved by other means. If a woman who is a carrier for a mitochondrial disease wants to have a child and does not want to risk passing on mutant mtDNA, her only options are to use an egg donor or adopt.

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201. Castro, *supra* note 19, at 733; *see also* Taylor Philippa, *Three Parent Babies: Unethical, Unnecessary, Unsafe*, BIONEWS (Feb. 16, 2015), https://www.bionews.org.uk/page_94923.

202. Stein, *supra* note 148.

203. MEDLINEPLUS, *supra* note 187.

204. Dimond, *supra* note 183, at 176.

205. Wang et al., *supra* note 6, at 1593.

1. MRT Provides Carriers with the Potential to Have a Healthy Baby to Whom they are Biologically Related

Currently, American women who are carriers of mtDNA diseases have no process by which they can have healthy babies to whom they are genetically related. Adoption and egg donation are options, but this does not provide the woman the chance to have a biological child. Additionally, if the woman chooses to attempt a pregnancy without an egg donor, the child will likely have a severe disease and die at a young age. The trauma of losing a child has lifelong impact. CGTAC Committee Chair Jeffrey Kahn said:

> Although MRT would not treat a person with a mitochondrial disease, its pursuit could satisfy prospective parents' desire to bear genetically related offspring with a significantly reduced risk of passing on mitochondrial disease. The limitations on MRT that we propose focus on protecting the health and well-being of children born as a result of the techniques.[206]

One of the first women to have a baby as a result of MRT, giving an interview with NPR under the pseudonym Tamara, was thrilled to have undergone the process.[207] She struggled with infertility for years and went through many rounds of IVF without success, "I was quite sad. And at some moments I even lost my hope."[208] Tamara underwent MRT at the Nadiya Clinic in Kiev and now has a son who is currently completely healthy.[209] Once she was finally pregnant, she said, "it was a lot of smiles. A lot of tears of happiness. I can't describe it . . . It's how happiness feels."[210] This couple was able to have a biological child, which is especially important to many couples. Tamara says, "I'm so excited. I have a child. And he's so beautiful. He smiles to me. He's so cute. He's so smart. He looks like my mom."[211]

2. MRT Has the Potential to Eradicate Heritable Mitochondrial Diseases

Inherited genetic diseases cause over 10,000 medical conditions.[212] Mutations in mtDNA directly cause diseases such as Leigh syndrome,[213] and

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206. NAT'L ACADS. *Report*, *supra* note 17.
207. Rob Stein, *Her Son Is One of the Few Children to Have 3 Parents' DNA*, NPR (June 6, 2018, 5:47 PM), https://www.npr.org/sections/health-shots/2018/06/06/616334508/her-son-is-one-of-the-few-children-to-have-3-parents.
208. *Id.*
209. *Id.*
210. *Id.*
211. *Id.*
212. Dohn, *supra* note 135, at 20.
213. Tachibana et al., *supra* note 16, at 424.

now mtDNA mutations are being associated with cancer,[214] Alzheimer's disease, Huntington's disease, and Parkinson's disease.[215] With further research and support from the scientific community, MRT has the potential to drastically reduce the pain and suffering that both a child with MRT and others face. With further research, MRT could also open the door to treatment of other diseases for which there is currently no cure.

CONCLUSION

MRT is an innovative therapy that has the potential to prevent mitochondrial disease before it can ever cause harm to a child. This provides women who thought they could not have biological children an incredible opportunity with immense emotional value. Concerns about the safety and ethics of conducting this therapy are based on fear, rather than scientific evidence, and should not prevent the progression of this research. Currently, we do not know if there are health effects on children born from MRT, though results in other countries suggest this therapy is safe. We cannot know if there are effects unless further research is conducted. MRT is no different from other cutting-edge therapeutic treatments because trials must be conducted in order to learn. The rider which bans clinical trials of MRT should be modified to allow the FDA to do its job and evaluate applications for clinical trials. The ban is not based in science, nor was the public or the expert scientific agency who regulates such therapy consulted in the implementation of the ban. The decision on whether to pursue MRT should be made on the merits of the therapy, and these merits can only be evaluated if the ban is lifted.

214. *See* Marty Brandon et al., *Mitochondrial Mutations in Cancer*, 25 ONCOGENE 2647 (2006).

215. Damien J. Keating, *Mitochondrial Dysfunction, Oxidative Stress, Regulation of Exocytosis and Their Relevance to Neurodegenerative Diseases*, 104 J. NEUROCHEM 298, 300–01 (2008).