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Fixing the Powerhouse of the Cell: Challenging the FDA's Prohibition of Mitochondrial Replacement Therapy

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I. INTRODUCTION

Many women long to be mothers one day. Motherhood can take different forms; it can be adopting children, birthing biological children, or nurturing a stepchild, to name a few options.[1] All mothers, however, want their children to lead healthy lives.

Some women who want biologically related children run a high risk of their children being born with an incurable disease, endangering their chance for biological children to lead healthy lives. One woman, Jane,[2] suffered such a fate. Jane miscarried four times, and her two children died young from Leigh's syndrome,[3] a mitochondrial disease that progressively degrades the central nervous system and typically results in death within several years.[4] To avoid watching another child slowly die or endure the pain of another miscarriage, she decided to undergo mitochondrial replacement therapy (MRT).[5] Dr. John Zhang, an American doctor, conducted the MRT procedure in Mexico.[6] She gave

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[1] For the purpose of this Comment, the author uses gendered phrases such as "women" and "mother" to describe a potential parent who may desire to use mitochondrial replacement therapy (MRT). The author recognizes this language is not all-inclusive of those who desire to be a parent, have mutated mtDNA, or who may utilize MRT. The author also recognizes such gendered language does not encompass all identities.

[2] Jane is a pseudonym to protect the woman's privacy.

[3] *See* Marybeth Pompei & Francesco Pompei, *Overcoming Bioethical, Legal, and Hereditary Barriers to Mitochondrial Replacement Therapy in the USA*, 36 J. ASSISTED REPROD. & GENETICS 383, 385 (2019).

[4] *What is Leigh Syndrome?*, LEIGH SYNDROME INT'L CONSORTIUM, https://leighsyndrome.org/leigh-syndrome/ [https://perma.cc/5AU3-VPJJ] (last visited Oct. 23, 2021).

[5] Pompei & Pompei, *supra* note 3, at 385.

[6] *Id.*

birth to a healthy baby boy in 2016, and he received regular checkups to monitor his health after his birth.[7]

Women like Jane are carriers[8] for mitochondrial diseases. Mitochondria are organelles located within human cells.[9] They produce over 90 percent of our energy,[10] making them critical to our survival and earning them the nickname "the powerhouse of the cell."[11] Mitochondria contain their own DNA, which is referred to as mitochondrial DNA (mtDNA).[12] mtDNA compromises an extremely small proportion of DNA in our cells—less than 0.1 percent[13]—and is not associated with commonly thought of heritable traits, such as physical features, which are housed in nuclear DNA (nDNA).[14] mtDNA mainly regulates mitochondria's energy production.[15] When mtDNA contains mutations that disrupt energy production, individuals may develop mitochondrial disease.[16] Mitochondria and mtDNA are passed down from mother to child.[17] Carriers for a mitochondrial disease have some mutated

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[7] John Zhang et al., *Live Birth Derived from Oocyte Spindle Transfer to Prevent Mitochondrial Disease*, 34 REPROD. BIOMED. ONLINE 361, 367 (2017).

[8] Donna Krasnewich, *Carrier*, NAT'L HUM. GENOME RSCH. INST., https://www.genome.gov/genetics-glossary/Carrier [https://perma.cc/M8TH-ZSFZ] (last visited Feb. 27, 2022) (defining carrier as "an individual who carries and is capable of passing on a genetic mutation associated with a disease and may or may not display disease symptoms").

[9] William Gahl, *Mitochondria*, NAT'L HUM. GENOME RSCH. INST., https://www.genome.gov/genetics-glossary/Mitochondria [https://perma.cc/DZN3-AM53] (last visited Feb. 23, 2022).

[10] *Facts About Mitochondria*, CHILD.'S HOSP. OF PHILA., https://www.chop.edu/mitochondria-facts#:~:text=Mitochondria%20function%20as%20batteries%20that,are%20made%20up%20of%20mitochondria [https://perma.cc/5B3C-7ZQJ] (last visited Oct. 16, 2022).

[11] *Mitochondria: The Powerhouse of the Cell*, PBS LEARNINGMEDIA IL., https://illinois.pbslearningmedia.org/resource/tdc02.sci.life.cell.mitochondria/the-powerhouse-of-the-cell/ [https://perma.cc/SN95-NPQW] (last visited July 26, 2022).

[12] Catherine Weiner, *Mitochondrial Transfer: The Making of Three-Parent Babies*, SCI. NEWS (Aug. 22, 2018), https://sitn.hms.harvard.edu/flash/2018/mitochondrial-transfer-making-three-parent-babies/?web=1&wdLOR=c2B065E78-17A8-454D-A16C-362E84349A7B [https://perma.cc/JYQ7-DHTS].

[13] Rosa J. Castro, *Mitochondrial Replacement Therapy: The UK and US Regulatory Landscapes*, 3 J. L. & BIOSCIENCES 726, 727 (2016).

[14] Radhika Viswanathan, *3 Biological Parents, 1 Child, and an International Controversy*, VOX (July 28, 2018), https://www.vox.com/2018/7/24/17596354/mitochondrial-replacement-therapy-three-parent-baby-controversy [https://perma.cc/3MFS-S8K4] ("[O]ur mitochondria contain just 37 genes [and t]hese genes only code for proteins involved in making ATP); *see also What Are the Characteristics or Properties of DNA?*, MOD. BIOLOGY, INC., https://modernbio.com/blog/what-are-the-characteristics-or-properties-of-dna/ [https://perma.cc/TG33-JGEC] (last visited Dec. 19, 2021) (explaining how genes are inherited from both parents through nDNA and "genes dictate a person's eye color, IQ level, personality traits, and body type).

[15] *See Understanding & Navigating Mitochondrial Disease*, UNITED MITOCHONDRIAL DISEASE FOUND., https://www.umdf.org/what-is-mitochondrial-disease-2/ [https://perma.cc/QHL5-C6YJ] (last visited Feb. 23, 2022).

[16] Zhang et al., *supra* note 7, at 362.

[17] Masahito Tachibana et al., *Mitochondrial Replacement Therapy and Assisted Reproductive*

mtDNA but do not suffer from the condition themselves. However, female carriers then pass this mtDNA on to their biological children, who may inherit the mitochondrial disease. While many women are unaware of their carrier status, research from England indicates at least one in two hundred healthy individuals are carriers for mtDNA mutations associated with mitochondrial diseases.[18] Women carrying mutated mtDNA are at risk of passing on a mitochondrial disease to their offspring, and the Boston Children's Hospital estimates mitochondrial diseases affect one in every six thousand to eight thousand births.[19]

A carrier who wants a child genetically related to her will not find a solution in conventional assisted reproductive technologies (ART).[20] Conventional ART methods all utilize the intended mother's egg, which contains her mutated mtDNA.[21] Therefore, women predisposed to pass on a mitochondrial disease to their children can only safely experience motherhood through two methods: utilizing a donated egg or adopting a child.[22] Neither option allows these women to have biological children.

Fortunately, scientists developed a new ART method in recent years that allows carriers to safely have biological children: mitochondrial replacement therapy (MRT). In MRT, non-mutated mtDNA is secured using a donor egg.[23] In one method for performing MRT, physicians replace the nucleus of a donor egg with that of the intended biological mother but leave the mitochondria of the donor egg undisturbed.[24] This effectively creates an egg with the nDNA of the intended biological mother but the healthy mtDNA of the donor.[25] The resulting child will have no risk of mitochondrial disease while retaining the genetics for nDNA traits, like hair color, dimples, and peanut allergies, of the intended mother. Moreover, the line of mutated mtDNA is ended by this procedure. MRT thus opens the door for carriers of mitochondrial disease to feel secure in having biological children.

Technology: A Paradigm Shift Toward Treatment of Genetic Diseases in Gametes or in Early Embryos, 17 REPROD. MED. & BIOLOGY 421, 422 (2018)

[18] Hannah R. Elliott et al., *Pathogenic Mitochondrial DNA Mutations Are Common in the General Population*, 83 AM. J. HUM. GENETICS 254, 254 (2008).

[19] *Mitochondrial Disease*, BOS. CHILD.'S HOSP., https://www.childrenshospital.org/conditions-and-treatments/conditions/m/mitochondrial-disease [https://perma.cc/69SE-5DT4] (last visited Feb. 23, 2022).

[20] Conventional ART methods include intrauterine insemination (IUI), in vitro fertilization (IVF), and gestational surrogacy. These will be discussed further in the scientific background section.

[21] *See* Weiner, *supra* note 12.

[22] Tachibana et al., *supra* note 17, at 422.

[23] Viswanathan, *supra* note 14.

[24] *Id.*

[25] *Id.*

Use of this marvel of modern medicine has been largely stopped in the U.S. since 2016, when Congress placed a rider amendment banning research on genetic modification in the Food and Drug Administration's (FDA) appropriations bill in 2016.[26] Congress has kept this rider in subsequent appropriations bills.[27] This rider amendment prohibits any "research in which a human embryo is intentionally created or modified to include a heritable genetic modification."[28] The FDA has interpreted this rider amendment to prohibit any future MRT procedures, including applications for MRT clinical trials.[29]

The FDA's advisory banning MRT was a unilateral decision by the agency and did not undergo notice-and-comment rulemaking, as required by the Administrative Procedure Act (APA). While the FDA would likely argue the APA does not apply because this rule is within a safe-harbor exemption from the notice-and-comment rulemaking requirements, this Comment argues otherwise. Two factors from *American Mining Congress v. Mine Safety & Health Administration*[30] point to the FDA's advisory not belonging to this exemption from notice-and-comment rulemaking.

Additionally, the FDA may have been incorrect to conclude MRT is completely prohibited due to this rider amendment. The FDA would likely say that courts should completely defer to their decision through *Chevron* deference.[31] However, in this situation, *Chevron* deference does not apply. Instead, courts are not required to defer to the FDA's decision to ban all MRT because most factors point against deferring to the FDA. Courts will then be able to assess whether MRT does, in fact, fall under this rider amendment.

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[26] Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2242, 2283 (2015).

[27] *See, e.g.*, Consolidated Appropriations Act, 2022, Pub L. No. 117-103, § 737, 136 Stat. 49, 94 (2022).

[28] Consolidated Appropriations Act, 2016 § 749.

[29] *Advisory on Legal Restrictions on the Use of Mitochondrial Replacement Techniques to Introduce Donor Mitochondria into Reproductive Cells Intended for Transfer into a Human Recipient*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/advisory-legal-restrictions-use-mitochondrial-replacement-techniques-introduce-donor-mitochondria [https://perma.cc/MZN5-H3XQ] (last visited July 25, 2021).

[30] 995 F.2d 1106 (D.C. Cir. 1993).

[31] *See* Chevron U.S.A., Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837 (1984).

II. SCIENTIFIC BACKGROUND

Mitochondria, small organelles located in all of our cells, are critical to our survival. Without mitochondria, our cells would be starved of energy and die.[32] Thankfully, mitochondria are plentiful in our cells; a single human cell can contain around 5,000 mitochondria.[33]

Each mitochondrion contains its own set of DNA, referred to as mtDNA.[34] mtDNA is critical to a mitochondrion's cellular functions.[35] Despite its important function, mtDNA makes up a miniscule portion of the human genome. For reference, mtDNA contains approximately thirty-seven genes while the entire human genome contains somewhere between 20,000 to 25,000 genes.[36] mtDNA is not associated with conventional heritable traits, such as physical features and personality features, while nDNA is associated with these traits.[37] mtDNA can also mutate—scientists have identified at least 700 possible mtDNA mutations.[38] While some of these mutations are harmless, others can result in a mitochondrial disease.[39]

Since mitochondrial diseases disrupt the body's energy production, they are associated with negative effects on tissues and organs, with the heart, muscles, and brain the most affected.[40] Mitochondrial diseases can present a wide array of symptoms including dementia, seizures, strokes, muscle weakness and failure, nerve pain, diabetes, and renal tube failure.[41]

Even if the mitochondrial disease is not fatal, it can significantly reduce a person's enjoyment of life. Lauren Quinn, a young woman from

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[32] *See Understanding & Navigating Mitochondrial Disease*, *supra* note 15.

[33] *What Are Mitochondria?*, MITOCANADA, https://mitocanada.org/understand/#:~:text=there%20are%20about%2010%20million,second%20throughout%20a%20person's%20life [https://perma.cc/X754-KRBL] (last visited Feb. 24, 2022).

[34] Weiner, *supra* note 12.

[35] *Mitochondrial DNA*, MEDLINE PLUS, https://medlineplus.gov/genetics/chromosome/mitochondrial-dna/#:~:text=This%20genetic%20material%20is%20known,essential%20for%20normal%20mitochondrial%20function [https://perma.cc/56K2-79B4] (last visited Oct. 11, 2022).

[36] *Id.*; *What Is a Gene?*, MEDLINE PLUS, https://medlineplus.gov/genetics/understanding/basics/gene/#:~:text=In%20humans%2C%20genes%20vary%20in,between%2020%2C000%20and%2025%2C000%20genes. [https://perma.cc/5WH3-AKAS] (last visited Feb. 24, 2022).

[37] *See* Viswanathan, *supra* note 14 ("[O]ur mitochondria contain just 37 genes [and t]hese genes only code for proteins involved in making ATP.").

[38] 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 [https://perma.cc/VJ94-PX2V].

[39] Heidi Chial & Joanna Craig, *mtDNA and Mitochondrial Diseases*, 1 NATURE EDUC. 217 (2008).

[40] *Understanding & Navigating Mitochondrial Disease*, *supra* note 15.

[41] *Id.*

Florida, recounted how her mitochondrial disease has affected her life.[42] When her disease first presented itself in late elementary school, she had to give up her athletic hobbies, and her classmates stopped inviting her to events because they did not understand her exhaustion.[43] She was exhausted to the point where simple tasks, such as making a moderate commute to school and walking from class to class, sapped her energy reserves.[44] Countless doctors could not identify what was wrong with her, and it took more than a decade for her to receive treatment she was satisfied with.[45] While Lauren's new treatment with the Mayo Clinic improved her quality of life, her story highlights the difficulties and confusion those with a mitochondrial disease face.

There are currently no approved cures for mitochondrial diseases, and the few available treatments merely treat symptoms and slow disease progression.[46] Individuals suffering from a mitochondrial disease are plagued by various ailments, generally have a limited life expectancy, and currently have little hope for a cure.[47]

Mitochondria and its DNA are passed down mother to child.[48] The mother's egg, which is fertilized by sperm and develops into a fetus, contains thousands of mitochondria, each with its own copy of mtDNA that the child inherits.[49] The assortment of mitochondria a mother passes to her child is unpredictable.[50] If she is a carrier of mutated mitochondria, her child may inherit only healthy mitochondria, a mix of healthy and mutated mitochondria, or mainly mutated mitochondria.[51] For most mitochondrial diseases, the egg the child originated from must contain at least sixty percent mutated mitochondria in order for the child to develop mitochondrial disease.[52] If a woman knows she is a carrier for a mitochondrial disease, then at least some of her mitochondria contain mutated mtDNA. Due to the unpredictability of which mitochondria are passed on to the child, it is up to fate whether a woman

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[42] Cynthia Weiss, *How the Right Diagnosis and a New Approach Changed My Life*, MAYO CLINIC (Feb. 3, 2022), https://sharing.mayoclinic.org/2022/02/03/how-the-right-diagnosis-and-a-new-approach-changed-my-life/?fbclid=IwAR0ZKv4-PA-B6QdvWvUppXeqUNBD9pvsqku_0Myy3dQs0HaXNRjmdpJ0vyw [https://perma.cc/R7Y2-649Q].

[43] *Id.*

[44] *Id.*

[45] *Id.*

[46] Tachibana et al., *supra* note 17, at 422.

[47] *Id.*

[48] *Id.*

[49] Dorothy R. Haskett, *Mitochondrial DNA (mtDNA)*, THE EMBRYO PROJECT ENCYCLOPEDIA (Dec. 19, 2014), https://embryo.asu.edu/pages/mitochondrial-dna-mtdna [https://perma.cc/5J8Y-YS9B].

[50] Tachibana et al., *supra* note 17, at 422–24.

[51] *Id.*

[52] *Id.* at 426.

who is a carrier for mitochondrial disease passes on the threshold amount of mutated mitochondria to her child.

A woman who wants a biological child but is concerned about passing on a mitochondrial disease will not find a solution with conventional assisted reproductive technologies (ARTs). Conventional ART methods that result in a biological child of both intended parents utilize the intended mother's egg.[53] If only conventional ARTs were available, women carrying mutated mtDNA could only safely experience motherhood through two avenues: adopting a child or using a donated egg. The use of an egg donor or adoption, though, may not satisfy a woman's desire to have biological children.

Thankfully, scientists developed a new ART technique that allows these women to feel secure in having biological children: mitochondrial replacement therapy (MRT). MRT can be thought of as IVF with an additional step. First, a scientist extracts an egg from both the intended mother and an egg donor.[54] Then, the scientist removes the nucleus from the egg donor's egg.[55] She places the intended mother's nucleus into the remaining donor egg.[56] The resulting egg contains all the cellular organelles, including healthy mitochondria, from the egg donor but the nucleus of the intended mother.[57] This ensures the resulting child has healthy mitochondria but inherits the nDNA, which is the DNA containing desirable heritable traits such as physical features, from the intended mother. The scientist then fertilizes the egg with the intended father's sperm and implants the resulting embryo in the intended mother, who then experiences a normal pregnancy.[58]

Studies of MRT in animals demonstrate its success in producing healthy offspring with no mitochondrial diseases.[59] While it is possible for there to be some carryover of mtDNA from the intended carrier mother's egg to the healthy egg, studies show the carryover ranges from undetectable to three percent of mtDNA.[60] Since a minimum of sixty percent mutated mitochondria is necessary for a child to develop most

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[53] *See Assisted Reproductive Technology (ART)*, U.S DEP'T OF HEALTH & HUM. SERVS., https://www.nichd.nih.gov/health/topics/infertility/conditioninfo/treatments/art [https://perma.cc/A45F-YSC5] (last visited Oct. 23, 2021) (comparing intrauterine insemination (IUI) and in vitro fertilization (IVF) with third party-assisted ART).

[54] Viswanathan, *supra* note 14.

[55] *Id.*

[56] *Id.*

[57] *See* Viswanathan, *supra* note 14.

[58] *Id.*

[59] Tachibana et al., *supra* note 17, at 425.

[60] *Id.* at 426.

mitochondrial diseases, MRT's miniscule carryover of mtDNA is very unlikely to result in mitochondrial disease.[61]

Women who have a mitochondrial disease or know they are carriers of mutated mtDNA can now feel safe in having biological children through MRT. However, through a rider amendment to an appropriations bill and the Food and Drug Administration's (FDA) subsequent actions, MRT is currently banned in the United States.

III. THE GOVERNMENT'S SHIFTING STANCE ON MRT

A. The United States Approach to MRT Prior to Congress's Rider Amendment in 2016

The FDA was considering the benefits of MRT in 2014; it called together the Cellular, Tissue, and Gene Therapy Committee to determine whether MRT was a viable reproductive treatment method for preventing mitochondrial diseases.[62] At that time, this committee determined there was too little animal study data to move forward in human subjects.[63] However, this was not an outright ban on moving forward with MRT. Instead, the FDA commissioned the Institute of Medicine to generate a report regarding the ethical implications of MRT.[64]

The Institute of Medicine released its report in early 2016.[65] It stated that clinical research investigations for MRT in humans are ethically permissible as long as certain requirements are met.[66] There were two particularly significant conditions. The first requirement was that the clinical trials be restricted to women who are at risk of passing on severe mitochondrial disease to their children.[67] The goal of MRT is to eliminate the risk of passing on mitochondrial diseases, but the data regarding how MRT affects human children was slim; therefore, the Institute of Medicine concluded that clinical trials in MRT should be limited to those who certainly stand to benefit from it to ensure the rewards

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[61] *See id*. at 426.

[62] Sabrina K. Glavota, *Mitochondrial Replacement Therapy: Let the Science Decide*, 27 MICH. TECH. L. REV. 345, 357 (2021).

[63] *Id.*

[64] *Id.*

[65] *Clinical Investigations of Mitochondrial Replacement Techniques Are 'Ethically Permissible' if Significant Conditions Are Met, Says New Report*, NAT'L ACADS. OF SCI., 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 [https://perma.cc/P6ZK-M6MU].

[66] *Id.*

[67] *Id.*

outweigh the risks of this experimental procedure.[68] The second requirement was to limit resulting offspring to the male sex.[69] Since men cannot pass on mitochondria to succeeding generations, this requirement ensures any negative consequences of MRT are not inherited by succeeding generations.[70] This report signaled that limited MRT clinical trials could be pursued in the future.

B. Congress's Rider Amendment to Consolidated Appropriations Act

The Consolidated Appropriations Act of 2016[71] placed a major obstacle in the path of MRT clinical trials and therapeutic use. Congress embedded a rider amendment within this FDA appropriations bill contained the following language:

> 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 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.[72]

This amendment prohibits the FDA from considering any research or clinical trials where the embryo contains a heritable genetic modification.

The rider amendment was placed in this appropriations bill shortly after researchers in China edited the nDNA of human embryos[73] using clustered regularly interspaced short palindromic repeats (CRISPR) technology, which is a novel tool that allows scientists to easily edit nDNA.[74] At least one scientist has since gone even further: He Jiankui, another Chinese scientist, announced that the first babies with edited

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[68] *Id.*

[69] *Id.*

[70] *Id.*

[71] Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, 129 Stat. 2242 (2015).

[72] Consolidated Appropriations Act, 2016 § 749.

[73] Sara Reardon, *U.S. Congress Moves to Block Human-Embryo Editing*, NATURE (June 25, 2015), https://www.nature.com/articles/nature.2015.17858 [https://perma.cc/X8ME-KNF6].

[74] *What Are Genome Editing and CRISPR-Cas9?*, MEDLINEPLUS, https://medlineplus.gov/genetics/understanding/genomicresearch/genomeediting/ [https://perma.cc/XH35-LVYE] (last visited Oct. 24, 2021).

nDNA using CRISPR were born in November 2018.[75] Scientists and ethicists around the world have identified several concerns regarding heritable genetic modifications. First, because more research is needed regarding the long-term and unintended effects of heritable genetic modifications on impacted individuals, the consensus by the scientific community is to proceed with an abundance of caution when using these new technologies.[76] There is also a concern regarding eugenics; specifically, using technologies to create heritable genetic modifications can "reinforce prejudice and narrow definitions of normalcy," especially when used for personal enhancement rather than treating diseases.[77] Finally, it may widen the inequities within our society because only certain populations will have the means to access this technology, at least initially.[78]

The use of CRISPR to edit embryonic nDNA was major news in 2015,[79] which was also when Congress decided to insert this rider amendment into the appropriations bill. While Congress made no specific statements regarding this rider amendment when it was first inserted in 2015,[80] it is probable that Congress inserted it in response to this major world news and thus did not even consider the impact on MRT. This language has remained in all subsequent Consolidated Appropriations Acts,[81] and Congress reaffirmed it after a Chinese scientist announced he helped bring the first CRISPR baby into the world.[82]

A congressional spending panel's actions further support the conclusion that the rider amendment was in response to editing embryonic

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[75] David Cyranoski, *The CRISPR-Baby Scandal: What's Next for Human Gene Editing*, NATURE (Mar. 11, 2019), https://www.nature.com/articles/d41586-019-00673-1 [https://perma.cc/FT9C-E4V2]; *see also* David Cyranoski, *What CRISPR-Baby Prison Sentences Mean for Research*, Nature (Jan. 3, 2020), https://www.nature.com/articles/d41586-020-00001-y [https://perma.cc/JMJ5-FU8J] (reporting Chinese courts convicted and sentenced He Jiankui and his colleagues who assisted him in creating the first children using MRT for "illegal medical practice").

[76] *See, e.g.*, Kelly E. Ormond et. al., *Human Germline Genome Editing*, 101 AM. J. HUM. GENETICS 167, 169 (2017) (reporting conclusions of the American Society of Human Genetics Workgroup on Human Germline Genome Editing).

[77] *Id.* at 171–72.

[78] *Id.* at 172.

[79] *See, e.g.,* David Cyranoski & Sara Reardon, *Chinese Scientists Genetically Modify Human Embryos*, NATURE (Apr. 22, 2015), https://www.nature.com/articles/nature.2015.17378 [https://perma.cc/5R7X-4E5C].

[80] *See* Jocelyn Kaiser, *Update: House Spending Panel Restores U.S. Ban on Gene-Edited Babies*, SCI. (June 4, 2019), https://www.science.org/content/article/update-house-spending-panel-restores-us-ban-gene-edited-babies [https://perma.cc/YKT8-D66N] (quoting statement by a Democratic aide that "[t]he provision . . . was inserted in private 3 years ago and has never been subject to public debate").

[81] *See e.g.*, Consolidated Appropriations Act, 2022, Pub L. No. 117-103, § 737, 136 Stat. 49, 94 (2022).

[82] Cyranoski, *supra* note 75.

nDNA, not MRT. In 2019, a congressional spending panel voted to drop this amendment from the FDA appropriations bill for the upcoming year.[83] This panel wanted to foster more debate regarding this rider amendment; as one aide aptly put it, "[t]he provision was dropped because it was inserted in private three years ago and has never been subject to public debate."[84] Specifically, while this panel still supported prohibiting some genetic modifications like CRISPR genome modifications on embryos, it was concerned this language was prohibiting less extreme and useful therapies such as MRT.[85] While the amendment was reinserted by the full Appropriations Committee,[86] this action shows this rider amendment can easily be excluded from future appropriations acts.

C. The FDA's Approach to MRT Under the Rider Amendment

The FDA interpreted this rider amendment to prohibit any MRT clinical trials in the United States.[87] Since MRT research in the United States had only been conducted in animal studies before 2015,[88] the next step would be clinical trials.[89] The FDA's current interpretation of the rider amendment prohibits it from considering any applications to conduct MRT clinical research.[90] Therefore, as long as the FDA's interpretation of the rider amendment stands, there is a complete prohibition on MRT in humans in the United States.[91]

The FDA is willing to enforce the ban on MRT. The FDA sent a letter to Dr. John Zhang, the American doctor who performed the MRT procedure in the introductory story, stating he violated various regulations.[92] Specifically, the FDA stated he committed two offenses under the MRT ban. First, he impermissibly created a genetically modified embryo through MRT.[93] Then, he impermissibly exported this embryo

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[83] Kaiser, *supra* note 80.

[84] *Id.*

[85] *Id.*

[86] *Id.*

[87] *Advisory on Legal Restrictions*, *supra* note 29.

[88] Glavota, *supra* note 62, at 357.

[89] *See Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products [https://perma.cc/2A6D-8M6D] (last visited Oct. 11, 2022) ("Following initial laboratory and animal testing that show that investigational use in humans is reasonably safe, biological products . . . can be studied in clinical trials in humans.").

[90] *See Advisory on Legal Restrictions*, *supra* note 29.

[91] *See, e.g.*, Letter from Mary A. Malarkey, Dir. of the Food & Drug Admin.'s Ctr. for Biologics Evaluation and Rsch. to John Zhang (Aug. 4, 2017), https://www.fda.gov/media/106739/download [https://perma.cc/VF9A-CKKW].

[92] *Id.*

[93] *Id.*

to Mexico.[94] It is not clear, however, what penalties Dr. Zhang faced. The FDA's letter only explicitly required Dr. Zhang to address the violation and identify the steps he was taking to prevent it from recurring.[95] His medical license does not seem to have been revoked because he is still a practicing fertility doctor at the New Hope Fertility Clinic.[96]

IV. THE IMPLICATIONS OF THE FDA CONSIDERING MRT TO BE BANNED BY CONGRESS

While the United States currently has a moratorium on MRT, other countries continue to explore practical applications of this therapy. In 2015, the United Kingdom's Parliament decided to expand its permitted eggs and embryos category to include eggs and embryos "where unhealthy mitochondrial DNA is replaced by healthy mitochondrial DNA by a donor," making it the first country to explicitly permit MRT.[97] The United Kingdom's Human Fertilisation and Embryology Authority (HFEA) oversees the various permissible reproductive technologies in the country, including MRT.[98] The HFEA determined MRT is not unsafe and could potentially benefit women who may pass on a severe mitochondrial disease to their children.[99] The HFEA granted the first licenses for MRT procedures in the world in 2017.[100] MRT can now be conducted outside of clinical trials in the United Kingdom.[101] Also, Ukraine and Greece permit MRT as an infertility treatment.[102] A private clinic in the Ukraine has had at least seven successful births with these procedures.[103] Clinicians in Greece also had at least one successful birth with MRT procedures.[104]

Because several countries permit MRT, Americans could potentially engage in medical tourism, especially if they are desperate to have a healthy child. Americans engaging in medical tourism for MRT is not

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[94] *Id.*

[95] *Id.*

[96] *See John Zhang, MD, MSc, PhD*, NEW HOPE FERTILITY, https://www.newhopefertility.com/about-us/fertility-doctor/john-zhang/ [https://perma.cc/8M9G-WUCD] (last visited Feb. 24, 2022).

[97] Castro, *supra* note 13, at 728.

[98] *Id.*

[99] *Id.* at 734.

[100] Glavota, *supra* note 62, at 361.

[101] *Id.*

[102] *Id.*

[103] Hitika Sharma et al., *Development of Mitochondrial Replacement Therapy: A Review*, 6 HELIYON 1, 4 (2020).

[104] Beatrice Christofaro, *A Baby in Greece Was Born with 3 Parents After Doctors Used an Experimental Technique to Make 'Medical History'*, INSIDER (Apr. 11, 2019), https://www.insider.com/3-parent-baby-born-in-greece-experimental-ivf-treatment-2019-4 [https://perma.cc/9NMB-EQMP].

a hypothetical: the American woman introduced at the beginning of this Comment went to Mexico with Dr. Zhang, an American fertility doctor, to implant an embryo created through MRT.[105] While Dr. Zhang was cited for violating various regulations, this situation illustrates how desperate women may leave the country to access MRT.

While there are many high-quality care facilities outside of the United States for medical tourists,[106] women who travel abroad for MRT may face greater risks than if they received the procedure at home. Specifically, the CDC cautions that other countries may have lower requirements for maintaining licensure, credentialing, and accreditation for healthcare procedures.[107] The CDC also cautions it is possible these women will receive counterfeit medicines.[108] If a woman travels to a country where English is not the official language, such to Ukraine or Greece, for MRT, she may face language barriers during the course of her treatment, which could lead to misunderstandings about the treatment.[109] If MRT were permitted in the United States, these women would not have to weigh the risks associated with medical tourism against their desire for a healthy biological child.

The effective ban on MRT also places limitations on the scientific community in the United States. While other countries' scientists are tentatively engaging in MRT research with humans, researchers in the United States must restrict themselves to animal studies. Yet research using animal studies may have reached its limit.[110] By restricting the progression of MRT studies, the United States may be missing out on a beneficial technology that could improve its citizens' lives.

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[105] Pompei & Pompei, *supra* note 3, at 384.

[106] *See* James E. Dalen & Joseph S. Alpert, *Medical Tourists: Incoming and Outgoing*, 132 AM. J. MED. 9, 10 (Jan. 1, 2019) (discussing accreditation of over 800 hospitals abroad).

[107] *Medical Tourism: Travel to Another Country for Medical Care*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://wwwnc.cdc.gov/travel/page/medical-tourism [https://perma.cc/7DNF-LYGX] (last visited Oct. 11, 2022).

[108] *Id.*

[109] *Id.*

[110] *See* Zhang et al., *supra* note 7, at 362.

V. THE FDA'S RULE THAT THE RIDER AMENDMENT PROHIBITS MRT SHOULD HAVE UNDERGONE NOTICE-AND-COMMENT RULEMAKING

A. The Administrative Law Background on Agency Rules and Rulemaking

While Congress is the nation's legislator,[111] governmental actions other than bills can have the force of law.[112] For example, federal agencies can promulgate rules, which also have the force of law.[113] Agencies can promulgate these rules because Congress passed legislation delegating their rulemaking authority.[114]

Congress delegates rulemaking authority to agencies for practical purposes. Congress is more of a generalist body and is focused on establishing the country's big-picture policy objectives.[115] Agencies, on the other hand, are experts on a narrow range of topics and can fill in the technical details of Congress's big-picture policy.[116] By having experts in a field fill in these details, Congress does not waste its time and resources figuring out the details of implementing every policy.[117]

However, agencies do not have carte blanche when promulgating rules—Congress retains some measure of control over agencies delegated rulemaking authority. First, when Congress delegates rulemaking authority to agencies, it must include an intelligible principle that directs what actions the agency can take.[118] The intelligible principle can be broad, though, to permit the agency to retain flexibility. Consequently, the intelligible principle requirement is not a major constraint on agencies. Congress also enacted the Administrative Procedure Act

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[111] *See* U.S. CONST. art. I, § 1.

[112] *See What Is an Executive Order?*, AM. BAR ASS'N (Jan. 25, 2021), https://www.americanbar.org/groups/public_education/publications/teaching-legal-docs/what-is-an-executive-order-/ [https://perma.cc/7GMF-W2L2]; *Types of Rules and Agency Statements*, U.S. LEGAL, https://administrativelaw.uslegal.com/administrative-agency-rulemaking/types-of-rules-and-agency-statements/#:~:text=An%20administrative%20agency's%20rules%20can,the%20form%20of%20a%20rule. [https://perma.cc/5RS8-4LM5] (last visited Feb. 26, 2022).

[113] *An Overview of Federal Regulations and the Rulemaking Process*, CONG. RSCH. SERV. (Mar. 19, 2021), https://sgp.fas.org/crs/misc/IF10003.pdf [https://perma.cc/MB7X-DPXD]; 5 U.S.C. § 551 ("'[R]ule' means the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy . . . .").

[114] *Id*113. at 113.

[115] *Id.*

[116] *See, e.g., What We Do*, FOOD & DRUG ADMIN. (Mar. 28, 2018), https://www.fda.gov/about-fda/what-we-do#responsibilities [https://perma.cc/8N6W-YJTJ].

[117] *An Overview of Federal Regulations*, *supra* note 113.

[118] *See* Indus. Union Dep't, AFL-CIO v. Am. Petroleum Inst., 448 U.S. 607 (1980) (standing for the intelligible principle doctrine); *but see* Gundy v. United States, 139 S.Ct. 2116, 2139 (2019) (Gorsuch, J., dissenting) ("This mutated version of the 'intelligible principle' remark has no business in the original meaning of the Constitution, in history, or even in the decision from which it was plucked.").

(APA),[119] which requires agencies to follow strict procedures when making a legally binding rule.[120] Additionally, Congress can use its "power of the purse" to prohibit agencies from using appropriated funds to promulgate certain rules.[121] While Congress has additional mechanisms to control agencies,[122] these are the most pertinent to this Comment.

Agencies can promulgate four types of rules: legislative rules, interpretive rules, procedural rules, and general statements of policy.[123] A rule's classification is important; for example, a legislative rule must undergo more rigorous requirements than an interpretive rule. If an agency states it promulgated an interpretive rule and thus did not pursue a legislative rule's requirements, but a court later determines the rule is a legislative rule, then the agency violated the APA.

Legislative rules have the force of law and implement a general statutory provision passed by Congress.[124] They create changes in the existing law, grant new rights, impose new obligations, or otherwise substantially impact people to whom the rule applies.[125]

The APA delineates how an agency can promulgate a legislative rule. First, the agency must give notice of the proposed rule in the Federal Register.[126] This notice must include the time, place, and nature of the rulemaking proceedings; the legal authority under which the rule is proposed; and either the substance of the proposed rule or a description of the subjects involved.[127] Then, the agency must permit interested parties to participate in the rulemaking process by submitting "written data, views, or arguments," about the proposed rule.[128] These submissions are typically referred to as "comments."[129] The agency must then review these comments, as held by *United States v. Nova Scotia Food*

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[119] 5 U.S.C. §§ 551–559.

[120] 5 U.S.C. § 553.

[121] *An Overview of Federal Regulations*, *supra* note 113.

[122] *Id.* (explaining how Congress can use traditional tools of congressional oversight, such as committee hearings, and the Congressional Review Act (CRA) to control agencies).

[123] *Types of Rules and Agency Statements*, *supra* note 112.

[124] *Legislative Rules*, U.S. LEGAL, https://administrativelaw.uslegal.com/administrative-agency-rulemaking/legislative-rules/#:~:text=A%20legislative%20rule%20is%20a,concurrence%20with%20the%20legislature's%20intention [https://perma.cc/M2E9-2UUG] (last visited Feb. 26, 2022).

[125] *Id.*

[126] 5 U.S.C. § 553(b).

[127] *Id.* § 553(b)(1)–(3).

[128] *Id.* § 553(c).

[129] *A Guide to the Rulemaking Process*, OFF. OF THE FED. REG., https://www.federalregister.gov/uploads/2011/01/the_rulemaking_process.pdf [https://perma.cc/C43H-LGJY] (last visited Feb. 26, 2022).

Products Corporation.[130] *Nova Scotia* also requires the agency to respond to comments that raise questions of cogent materiality and to include all of the evidence it is relying on to make the rule in the rule's preamble.[131] *Nova Scotia*'s requirements ensure the agency considers expert knowledge on the topic, on-the-ground experiences, and potential alternatives.[132] These requirements may also serve the interests of democracy because interested parties feel their voices are heard, at least to some extent, by the agency.[133]

Interpretive rules, on the other hand, do not undergo notice-and-comment rulemaking.[134] Interpretive rules are "rules or statements issued by an agency to advise the public of the agency's construction of the statutes and rules which it administers."[135] They do not, however, create a new law or modify existing ones.[136] Agencies make interpretive rules when there is "confusion and disagreement" over the statute and when "the ambiguity should be clarified."[137] Agencies promulgating interpretive rules can act unilaterally—they do not have to consider comments nor explain what evidence they relied on when making the rule.[138]

If an agency promulgates a legislative rule under the guise of an interpretive rule and did not subject it to notice-and-comment rulemaking, then the agency violated the APA.[139] However, it can be difficult distinguishing a genuine interpretive rule from a legislative rule. Thankfully, *American Mining Congress v. Mine Safety & Health Administration* articulates a commonly used multi-factor test to determine whether a rule is interpretive or legislative in nature.

American Mining Congress's test contains four factors.[140] If the answer to any of these factors is yes, then the rule is a legislative rule that

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[130] 568 F.2d 240, 251–52 (2d Cir. 1977).

[131] *Id.*

[132] *See Why Public Comments Matter*, HARV. L. SCH. CTR. FOR HEALTH L. & POL'Y INNOVATION, https://chlpi.org/wp-content/uploads/2013/12/Why-Public-Comments-Matter-CHLPI-Branded.pdf [https://perma.cc/K6K6-B7NM] (last visited Feb. 26, 2022).

[133] *See id.*

[134] 5 U.S.C. § 553(b)(A).

[135] *Agency Guidance Through Interpretive Rules*, ADMIN. CONF. OF THE U.S. (Aug. 8, 2019), https://www.acus.gov/recommendation/agency-guidance-through-interpretive-rules [https://perma.cc/DM3G-NB68].

[136] *Types of Rules and Agency Statements*, *supra* note 112.

[137] *Types of Rules and Agency Statements*, *supra* note 112.

[138] *See* 5 U.S.C. § 553(b)(A); *see also Nova Scotia*, 568 F.2d at 251–52.

[139] *See, e.g.*, Child.'s Hosp. of the King's Daughters, Inc. v. Azar, 896 F.3d 615, 617 (4th Cir. 2018) (concluding the rule was a legislative rule and thus must go through the APA's notice-and-comment rulemaking before being enforced).

[140] *Am. Mining Cong.*, 995 F.2d at 1112.

should have gone through notice-and-comment rulemaking.[141] The first factor looks to "whether in the absence of the rule there would not be an adequate legislative basis for enforcement or other agency action to confer benefits or ensure the performance of duties."[142] The second factor examines "whether the agency has explicitly invoked its general legislative authority."[143] The third factor is "whether the rule effectively amends a prior legislative rule."[144] Finally, the fourth factor is "whether the agency has published the rule in the Code of Federal Regulations,"[145] although this factor is only a "snippet of evidence"[146] rather than determinative.

B. The FDA's Advisory for MRT's Status Is a Legislative Rule and Thus Needs to Undergo Notice-and-Comment Rulemaking

A potential plaintiff could argue the FDA violated the APA by not subjecting the advisory banning MRT to notice-and-comment rulemaking. Specifically, the plaintiff could argue the advisory is a legislative, rather than interpretive, rule, and 5 U.S.C. § 553 requires it to undergo notice-and-comment rulemaking.

A court only needs to determine whether one *American Mining Congress* factor is met for a rule to be classified as a legislative rule in substance.[147] A court should look to the first and third factors to determine that the rule prohibiting MRT is a legislative rule rather than an interpretive rule in substance. Once a court makes this conclusion, it will determine the FDA violated the APA by not subjecting the advisory banning MRT to notice-and-comment rulemaking. A court will not find the second or fourth factors useful in determining that this is a legislative rule rather than an interpretive rule.

The first factor, which examines "whether in the absence of the rule there would not be an adequate legislative basis for enforcement or other agency action to confer benefits or ensure the performance of duties,"[148] can be satisfied here. The FDA could argue there is another adequate legislative basis for banning MRT: the rider amendment. However, a plaintiff could counter this argument by stating Congress did not intend for MRT to be swept under this rider amendment's umbrella. The plaintiff could use two pieces of evidence to support this argument.

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[141] *Id.*

[142] *Id.*

[143] *Id.*

[144] *Id.*

[145] *Id.*

[146] Health Ins. Ass'n of Am. v. Shalala, 23 F.3d 412, 423 (D.C. Cir. 1994).

[147] *Am. Mining Cong.*, 995 F.2d at 1112.

[148] *Id.*

First, the plaintiff could point to the text of the rider amendment itself. The rider amendment only prohibits the FDA from considering applications for research involving "a human embryo [that] is intentionally created or modified to include a heritable genetic modification."[149] It makes no mention of MRT, which many scientists consider not to include a heritable genetic modification when only male embryos are gestated.[150] Second, the plaintiff could argue that the legislative intent of this rider amendment was to prohibit modifying embryonic nDNA. While there is no legislative history regarding the amendment, a Chinese scientist using CRISPR to modify embryonic nDNA was major news immediately preceding the insertion of this amendment.[151] As stated in Part III.B, Congress likely inserted this amendment in response to this worldwide news. The plaintiff arguably has both the text and legislative intent on his side, so a court should find this factor is satisfied and this rule is legislative in substance.

The third factor, which examines "whether the rule effectively amends a prior legislative rule,"[152] can also be satisfied here. The FDA has a complex regulatory scheme in place for submitting and approving investigational new drug applications.[153] The FDA must approve an investigational new drug application before any clinical trials can begin.[154] Biologics products, such as MRT,[155] require approval of an investigational new drug application prior to the commencement of clinical trials.[156] The FDA's advisory decided it could not accept, let alone approve, investigational new drug applications.[157] However, prior to this advisory, the FDA was considering MRT clinical trials in humans and appointed the Institute of Medicine to determine the ethics surrounding human MRT clinical trials.[158] Plaintiffs can argue the FDA's current advisory for MRT carves out a prohibition within this complex regulatory scheme. By flatly prohibiting even accepting investigational

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[149] Consolidated Appropriations Act, 2022, Pub L. No. 117-103, § 737, 136 Stat. 49, 94 (2022).

[150] *See Clinical Investigations of Mitochondrial Replacement Techniques*, *supra* note 65.

[151] Cyranoski & Reardon, *supra* note 79.

[152] *Am. Mining Cong.*, 995 F.2d at 1112.

[153] *See* 21 C.F.R. § 312 (2022).

[154] *Investigational New Drug Applications (INDs) for CBER-Regulated Products*, FOOD & DRUG ADMIN. (Apr. 21, 2021), https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/investigational-new-drug-applications-inds-cber-regulated-products [https://perma.cc/684K-NPFL].

[155] *See Letter to John Zhang*, *supra* note 91.

[156] *Investigational New Drug Applications*, *supra* note 154.

[157] *Advisory on Legal Restrictions*, *supra* note 29.

[158] Glavota, *supra* note 62, at 357.

new drug applications for MRT, the FDA effectively amended this regulatory scheme as applied to MRT. Therefore, a court should find the third factor is satisfied as well.

On the other hand, courts will find the second and fourth factors clearly fail in this situation. The second factor, which examines "whether the agency has explicitly invoked its general legislative authority,"[159] does not apply here because the FDA did not explicitly state it promulgated this advisory through its legislative authority.[160] Instead, the advisory states, "the clinical use of MRT . . . falls within FDA's *regulatory* authority,"[161] rather than legislative authority. Also, the FDA's advisory states that Congress's rider amendment prevents the FDA "from accepting applications for clinical research using MRT."[162] When compiled, these facts indicate the second factor is not satisfied. The fourth factor, which states that a rule published in the Federal Register points in the direction of it being a legislative rule, is also not satisfied here. The Federal Register did not contain any reference to this FDA advisory.[163] Therefore, this fourth factor is not satisfied either.

Thankfully, a court only needs to find one factor is met to satisfy *American Mining Congress*'s test that the rule is legislative in substance.[164] Since there are strong arguments that the first and third factor are satisfied in this case, a court should find one of these factors was satisfied and thus determine this advisory is a legislative rule. When a court determines this, then the FDA violated the APA by not subjecting this legislative rule to notice-and-comment rulemaking.

C. Parties Interested in MRT Will Benefit from the FDA's Advisory Undergoing Notice-and-Comment Rulemaking

Several benefits will flow from subjecting the FDA's ban on MRT to notice-and-comment rulemaking. First, interested parties can submit comments about MRT to the FDA.[165] Scientists and fertility doctors can register their opinions with the FDA, and they may bring up many good points. They may point to MRT's effectiveness by pointing to the successful births from MRT.[166] They can point to other countries' practices,

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[159] *Am. Mining Cong.*, 995 F.2d at 1112.

[160] *See Advisory on Legal Restrictions*, *supra* note 29.

[161] *Id.*

[162] *Id.*

[163] This Commentor searched the terms "MRT" and "mitochondria replacement therapy" in the Federal Register and found no documents relevant to this Comment.

[164] *Am. Mining Cong.*, 995 F.2d at 1112.

[165] 5 U.S.C. § 553(c).

[166] *See, e.g.*, Sharma et al., *supra* note 103, at 4.

such as practices in the United Kingdom, and the Institute of Medicine's report concluding that MRT clinical trials are permissible.[167] Scientists and fertility doctors may raise important scientific points as well. For example, some scientists analogize MRT more to a transplant,[168] which is a legal practice in the United States,[169] than to a heritable genetic modification. If their comments convince the FDA that MRT is more like a transplant than a heritable genetic modification, then the rider amendment undoubtedly would not apply to MRT. Even if this argument and the fact that Congress almost certainly included this rider amendment to prohibit manipulating embryonic nDNA does not entirely convince the FDA that this rider amendment excludes MRT, scientists could comment that male-only embryos should still be permissible, at least while scientists gather more data on the long-term effects of MRT. Specifically, they could explain that mtDNA is only passed down from mother to child,[170] so limiting MRT to male embryos in clinical trials would ensure this genetic modification is not heritable. Women who have a mitochondrial disease or women who know they are carriers of mutated mtDNA may also be interested in submitting comments to this rule. These women could explain their various experiences: the pain of watching their current children develop a mitochondrial disease, the difficulties associated with living with a mitochondrial disease themselves, and their petrified fear in having any more children.

Nova Scotia requires the FDA to read these comments and take them into consideration when formulating their final rule.[171] The FDA would have to directly address whether MRT is more analogous to an organ transplant than a heritable genetic modification. Even if the FDA found it was more like a heritable genetic modification, it would then have to address limiting MRT to male embryos. If forced to consider this, the FDA would be forced to confront the science and determine MRT is permissible as long as it is limited to male offspring. Finally, the FDA would have to address the impact its decision has on women's lives.

Nova Scotia also requires the FDA to provide the evidence it relied on in the preamble of the final rule.[172] Interested parties would benefit from this transparency in the FDA's final decision. They will know how

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[167] *Clinical Investigations of Mitochondrial Replacement Therapies*, *supra* note 65.

[168] *See* Pompei & Pompei, *supra* note 3, at 384.

[169] *See Organ Donation Legislation and Policy*, HEALTH RES. & SERVS. ADMIN. (Apr. 2021), https://www.organdonor.gov/about-us/legislation-policy [https://perma.cc/J8DR-MXK8].

[170] Tachibana et al., *supra* note 17, at 422.

[171] *Nova Scotia*, 568 F.2d 252–53.

[172] *Id.*

the FDA came to its final determination, what is motivating its decision, and the potential avenues for expanding access to MRT in the future.

While subjecting this rule to notice-and-comment does not definitely mean MRT will be permitted in the United States, it requires the FDA to engage with the public and fully consider all alternatives, such as limiting MRT to male embryos. Since the current FDA advisory flatly prohibits any consideration of MRT,[173] this would be, at the very least, a step towards women having access to this useful therapeutic.

VI. COURTS CAN LIKELY LOOK TO THE RIDER AMENDMENT'S CONSTRUCTION ITSELF TO DETERMINE WHETHER IT BANS MRT

A. The Administrative Law Background of *Chevron* Deference

In addition to evaluating whether a rule is legislative in substance, courts can evaluate whether an agency's interpretation of a statute is permissible.[174] Historically, courts grant these interpretations varying levels of deference. If the agency interpretation satisfies the test articulated in *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*,[175] then courts will completely defer to the agency's action.[176] If an agency's interpretation does not satisfy *Chevron*, though, it can still obtain some level of deference. Courts can then analyze the agency action under *Skidmore v. Swift*'s[177] test despite the agency interpretation failing *Chevron*'s test. Based on its evaluation under the *Skidmore* test, a court can determine how much deference to give the agency action in a case.[178]

However, in recent years, some commentators have questioned whether these deference doctrines are dead,[179] especially since some of the current Justices have previously indicated they disagreed with courts deploying *Chevron* analysis.[180] In recent decisions, the Court did not use *Chevron* deference when determining whether agency action

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[173] *Advisory on Legal Restrictions*, *supra* note 29.

[174] Chevron *Deference*, LEGAL INFO. INST., https://www.law.cornell.edu/wex/chevron_deference#:~:text=The%20scope%20of%20the%20Chevron,made%20by%20the%20administrative%20agency. [https://perma.cc/G4P2-5QWB] (last visited Feb. 27, 2022).

[175] 467 U.S. 837 (1984).

[176] *See id.* at 865–66.

[177] 323 U.S. 134 (1944).

[178] *See id.* at 140.

[179] *See, e.g.*, Evan Zoldan, *Another Round of Speculation about Chevron?*, REGUL. REV. (Sept. 26, 2022), https://www.theregreview.org/2022/09/26/zoldan-another-round-of-speculation-about-chevron/ [https://perma.cc/7GEE-VQE8].

[180] *See, e.g.*, Ilya Somin, *Gorsuch Is Right About Chevron Deference*, WASH. POST (Mar. 25, 2017), https://www.washingtonpost.com/news/volokh-conspiracy/wp/2017/03/25/gorsuch-is-right-about-chevron-deference/ [https://perma.cc/GN7B-ZSHY] (noting Justice Gorsuch opposed *Chevron* deference while a nominee for the Supreme Court).

was appropriate—instead, it ignored *Chevron* and used statutory interpretation to come to its decision.[181] As of now, though, these deference doctrines have not been overturned by the Court.[182]

When courts do use Chevron to analyze an agency's interpretation of a statute, they break *Chevron* deference into three distinct inquiries: *Chevron* step zero, *Chevron* step one, and *Chevron* step two.[183] All three steps must be satisfied in order for a court to grant *Chevron* deference.[184]

Chevron step zero determines whether courts can even consider applying *Chevron* deference to an agency's action.[185] Two cases compose *Chevron* step zero's inquiry. The first case is *United States v. Mead Corp.*[186] The *Mead* test requires two prongs to be satisfied. First, Congress must have "delegated authority to the agency generally to make rules carrying the force of law."[187] Second, "the agency interpretation claiming deference was promulgated in the exercise of that authority."[188] The Court lists some examples of the delegation of such authority, such as notice-and-comment rulemaking and formal adjudication,[189] as well as "some other indication of a comparable congressional intent."[190] If the *Mead* test is not satisfied in a case, courts will turn to the multi-factor test in *Barnhart v. Walton*[191] to determine if *Chevron* step zero is satisfied.[192] *Barnhart*'s factors are the interstitial nature of the legal question, or how much the administering agency is stitching together the statute rather than determining a major question; the related expertise of the agency; the importance of the question to the administration of the statute; the complexity of that administration; and whether the agency carefully considered the question for a long period of time.[193] Courts will move on to *Chevron* step one if they determine either the *Mead* or *Barnhart* tests are satisfied.[194]

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[181] *See, e.g.*, West Virginia v. Env't Prot. Agency, 142 S. Ct. 2587, 2610 (2022) (applying major questions doctrine).

[182] *See id.* (not referencing *Chevron*); *see also* Am. Hosp. Ass'n v. Becerra, 142 S. Ct. 1896 (2022) (same).

[183] Cass R. Sunstein, Chevron *Step Zero*, 92 VA. L. REV. 187, 191 (2005).

[184] *See id.*

[185] *Id.*

[186] 533 U.S. 218 (2001).

[187] *Id.* at 226–27.

[188] *Id.* at 227.

[189] *Id.*

[190] *Id.*

[191] 535 U.S. 212 (2002).

[192] *Id.* at 222.

[193] *Id.*

[194] *See id.*

Chevron step one looks to whether Congress's intent was silent or ambiguous.[195] If congressional intent was clear, then courts must follow Congress's intention rather than granting *Chevron* deference.[196] However, if Congress was silent or its intent was ambiguous, then *Chevron* step one is satisfied, and courts will move on to *Chevron* step two.[197]

Chevron step two examines whether the agency's interpretation and action under the statute is "reasonable" or "permissible."[198] If a court determines it is reasonable or permissible, then *Chevron* step two is satisfied, and courts will defer to the agency's action or interpretation.[199] However, if a court determines an agency's action or interpretation fails at any of *Chevron* steps zero, one, or two, the court will not completely defer to the agency's action.[200] Instead, the court will examine the agency's action or interpretation under the *Skidmore v. Swift* test.[201]

The *Skidmore* test has four factors.[202] The amount of deference a court grants to an agency's action or interpretation depends on how strong these factors point in favor of the agency.[203] These factors are "the thoroughness evident in [the agency's] consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade."[204] The court grants the agency the amount of deference it believes is warranted under the *Skidmore* analysis.

B. Under a Statutory Interpretation Framework, Courts Should Find the Rider Amendment's Statutory Language and Legislative History Do Not Include MRT

If a court does not follow one of the deference doctrines, the court should turn to statutory interpretation to determine whether Congress intended to include MRT in the rider amendment.[205] First, the court will examine the statutory language of the rider amendment. The relevant statutory language at issue here is:

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[195] *Chevron*, 467 U.S. at 847.

[196] *Id.* at 846–47.

[197] *Id.*

[198] *Id.*

[199] *Id.*

[200] *Id.*

[201] *See* Chevron *Deference*, *supra* note 174174.

[202] *See Skidmore*, 323 U.S. at 140.

[203] *Id.*

[204] *Id.*

[205] *See* West Virginia v. Env't Prot. Agency, 142 S. Ct. 2587 (June 30, 2022).

> 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 intentionally created or modified to include a heritable genetic modification.[206]

The FDA will likely make a plain language argument: MRT results in a human embryo that is "intentionally created or modified to include a heritable genetic mutation,"[207] and, therefore, it cannot sanction clinical research for MRT. However, the rider amendment does not specifically mention MRT; instead, it only mentions a "heritable genetic modification."[208] The court therefore should examine what MRT is when determining whether it results in a heritable genetic modification.

While some may argue it does result in a heritable genetic modification, others may argue it is more analogous to an organ transplant on the cellular level than a genetic modification. The National Human Genome Research Institute defines genetic engineering, which creates genetic modifications, as "a process that uses laboratory-based technologies to alter the DNA makeup of an organism" such as "changing a single base pair."[209] One example given is adding genes from one organism to the DNA of another organism to produce a specific trait.[210] MRT, though, does not involve tinkering with the base pairs or cutting and pasting in genes into one mtDNA. Instead, it replaces entire cellular organelles, mitochondria, from one person to another while maintaining the original mtDNA in these organelles, similar to a transplant.

Alternatively, if a court finds MRT is more comparable to a genetic modification than a cellular organelle transplant, it can still deem that MRT is not barred by this rider amendment if limited to male offspring. This argument hinges on the word "*heritable*" in "heritable genetic modification." Heritable is defined as "capable of being inherited or of passing by inheritance,"[211] and inherited is defined as "to receive from a parent or ancestor by genetic transmission."[212] MRT's genetic modifications

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[206] Consolidated Appropriations Act, 2016, § 749.

[207] *See id.*

[208] *See id.*

[209] *Genetic Engineering*, NAT'L HUM. GENOME RSCH. INST. (Oct. 17, 2022), https://www.genome.gov/genetics-glossary/Genetic-Engineering [https://perma.cc/8XCB-EBNC].

[210] *Id.*

[211] *Heritable*, MERRIAM-WEBSTER, https://www.merriam-webster.com/dictionary/heritable [https://perma.cc/B9QY-KVNH] (last visited Oct. 13, 2022).

[212] *Inherit*, MERRIAM-WEBSTER, https://www.merriam-webster.com/dictionary/inherited

could only be inherited by future generations if the resulting child is female because only females can pass on mitochondria to their offspring.[213] Therefore, if MRT was limited to male offspring, they would be the first and only generation with the genetic modification, and thus the modification would not be "heritable."

Additionally, a court examining the rider amendment's legislative history should find MRT was not intended to be included within its scope. As one aide pointed out, this rider amendment was embedded within the Consolidated Appropriations Act of 2016 without any public debate.[214] However, Congress was likely responding to major events when it inserted the rider amendment. Specifically, Congress likely inserted this amendment in response to Chinese scientists using CRISPR technology to genetically modify the nDNA of human embryos in a laboratory setting, which sparked a global outcry.[215] Also, in 2019, a Congressional spending panel initially took this provision out of the Consolidated Appropriations Act of 2020.[216] Some Democrats who removed this provision were concerned this amendment forecloses useful therapies, such as MRT, while they continue to support bans on technologies such as CRISPR.[217] In summation, this evidence indicates Congress wanted to prohibit modifying embryonic nDNA and did not consider MRT.

The FDA will likely argue Congress meant to include MRT under this rider amendment. While the rider amendment does not explicitly mention MRT, the FDA could argue that Congress was responding to reports being generated by the FDA and the Institute of Medicine. Specifically, before this rider amendment, the FDA's Cellular, Tissue, and Gene Therapy Committee determined there was too little information regarding MRT in animal studies to permit human clinical trials to commence.[218] Also, the Institute of Medicine was in the midst of writing a report commissioned by the FDA, which found human clinical trials for MRT could commence if certain strict criteria were met.[219] The FDA may argue Congress was responding to these reports rather than major

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[https://perma.cc/GGH7-GK2B] (last visited Oct. 13, 2022).

[213] *See* Tachibana et al., *supra* note 17, at 422.

[214] Kaiser, *supra* note 80.

[215] *Id.*

[216] *Id.*

[217] *Id.*

[218] Glavota, *supra* note 62, at 357.

[219] *See* Glavota, *supra* note 62, at 357. *Compare* Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2242, 2283 (2015) (first legislation with the rider banning research that generates heritable genetic modifications, passed on December 15, 2015), *with Clinical Investigations of Mitochondrial Replacement Techniques*, *supra* note 65 (press release announcing IOM report, issued February 2016).

world news and thus wanted to prohibit MRT before the FDA could take additional steps.

A court should find the former argument is stronger than the latter. Congress was probably more attuned to the unfolding CRISPR receiving global media coverage than administrative reports regarding a less contentious reproductive procedure.

Based on both the statutory language and the legislative history, a court should find Congress did not intend for the rider amendment to encompass MRT. Therefore, the court should find the FDA's interpretation of the rider amendment to outright ban MRT is incorrect.

C. Under the Deference Doctrines, Courts Should Grant the FDA's Advisory on MRT Little Deference

1. It is a toss-up whether the FDA's prohibition of MRT under Congress's rider amendment satisfies *Chevron* step zero.

A court will first inquire whether the FDA's rule banning MRT satisfies *Chevron* step zero.[220] To accomplish this, the court will determine whether the *Mead* or *Barnhart* tests are met. Courts typically begin by analyzing whether the FDA's rule prohibiting MRT satisfies the *Mead* test.

The first prong of the *Mead* test determines whether Congress "delegated authority to the agency generally to make rules carrying the force of law."[221] Congress delegated authority to the Secretary of Health and Human Services to generally make rules carrying the force of law in the Food, Drug, and Cosmetic Act.[222] Specifically, the Act permits the Secretary to "promulgate regulations for the efficient enforcement of this chapter."[223] The Food, Drug, and Cosmetic Act also established the FDA.[224] The Act states in the FDA's section that the Secretary, through the Commissioner of the FDA, will be responsible for executing this law.[225] Therefore, the FDA satisfies the first prong of *Mead* because the FDA falls under the Secretary of Health and Human Services' purview, and the Secretary can promulgate rules to give the Act effect. *Mead*'s second prong examines whether "the agency interpretation claiming deference was promulgated in the exercise of that authority."[226] The

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[220] Sunstein, *supra* note 183, at 191.

[221] *Mead*, 533 U.S. at 226–27.

[222] 21 U.S.C. §§ 301–399i.

[223] *Id.* § 371(a).

[224] *Id.* § 393.

[225] *Id.* § 393(d)(2).

[226] *Mead*, 533 U.S. at 227.

FDA's advisory clearly fails here because this was not formal rulemaking, notice-and-comment rulemaking, nor a formal adjudication. Therefore, the court will certainly conclude the FDA's rule regarding MRT fails the *Mead* test.

Because the FDA's rule failed the *Mead* test, the court would then examine whether the FDA's rule satisfies enough *Barnhart* factors. If it does, then the FDA's rule survives *Chevron* step zero and qualifies to be considered for *Chevron* deference.

The first *Barnhart* factor is "the interstitial nature of the legal question",[227] or how much the administering agency is stitching together the statute rather than determining a major question. While the FDA's interpretation of Congress's rider amendment bans MRT has effects on advancing scientific research on this subject matter and impacts carrier women's lives, it does not seem to be a major question. A major question is typically something that has "deep economic and political significance."[228] For example, in *King v. Burwell*, the Court determined the ACA's grant of tax credits to qualified individuals was too major a question for the IRS to decide because it was central to the ACA and involved spending billions of dollars each year.[229] The ban on MRT does not implicate such deep economic and political issues. Instead, the FDA simply decided what fell under a "heritable genetic modification,"[230] in a rider amendment and concluded MRT fell under this umbrella.[231] This prong points in favor of *Chevron* deference applying to this situation.

The second *Barnhart* factor examines "the related expertise of the agency."[232] The more expertise an agency has on a subject matter, the more likely a court will find this factor points in favor of the court moving on to *Chevron* step one.[233] Here, the FDA is clearly the administrative agency with the most expertise on this subject matter. First, part of the FDA's overall mission is to "promote the public health by promptly and efficiently reviewing clinical research"[234] and to "protect the public health by ensuring that . . . there is reasonable assurance of the safety and effectiveness of devices intended for human use."[235] The

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[227] *Barnhart*, 535 U.S. at 222.

[228] King v. Burwell, 135 S. Ct. 2480, 2489 (2015).

[229] *Id.*

[230] *See*, Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2242, 2283 (2015).

[231] *Advisory on Legal Restrictions*, *supra* note 29.

[232] *Barnhart*, 535 U.S. at 222.

[233] *See id.*

[234] 21 U.S.C. § 393(b)(1).

[235] *Id.* § 393(b)(2)(C).

FDA also contains the Office of Tissues and Advanced Therapies,[236] which publishes a list of currently approved cellular and gene therapy products.[237] Finally, the Cellular, Tissue, and Gene Therapies Advisory Committee, which was called upon to evaluate whether MRT would be an effective fertility treatment for carrier women of mutated mtDNA before Congress's rider amendment was enacted,[238] is a subsidiary of the FDA.[239] Therefore, this factor also points in favor of analyzing the FDA's rule under the *Chevron* framework.

The third *Barnhart* factor examines "the importance of the question to the administration of the statute."[240] Whether MRT falls under the rider amendment's prohibition on creating embryos with a heritable genetic modification is not critically important to the administration of this rider amendment. Many of the ethical and medical concerns regarding manipulating embryos' genetics concern nDNA manipulation.[241] Congress intended to prohibit manipulation of an embryo's nDNA through technologies such as CRISPR when adding this rider amendment, so the FDA's primary focus when administering this statute is to prohibit manipulation of embryos' nDNA. This factor points against contemplating whether *Chevron* deference should apply to FDA's rule prohibiting MRT.

The fourth *Barnhart* factor examines "the complexity of [the] administration" of the statute.[242] The rider amendment itself is facially complex. Specifically, the rider amendment prohibits the FDA to consider, or even acknowledge, the submission of forms for clinical trials that involve a human embryo intentionally created or modified to have a heritable genetic modification.[243] However, while this implicates the complex process of requesting the FDA's approval for clinical trials, the administration of the rider amendment may not be complex because it

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[236] *OTAT Learn*, FOOD & DRUG ADMIN. (Mar. 23, 2018), https://www.fda.gov/vaccines-blood-biologics/news-events-biologics/otat-learn [https://perma.cc/Q64M-M57C].

[237] *Approved Cellular and Gene Therapy Products*, FOOD & DRUG ADMIN. (Oct. 26, 2021), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products [https://perma.cc/DU28-2LNN].

[238] Glavota, *supra* note 62, at 357.

[239] *Cellular, Tissue, and Gene Therapies Advisory Committee*, FOOD & DRUG ADMIN. (Apr. 26, 2019), https://www.fda.gov/advisory-committees/blood-vaccines-and-other-biologics/cellular-tissue-and-gene-therapies-advisory-committee [https://perma.cc/6YHV-NC9Q].

[240] *Barnhart*, 535 U.S. at 222.

[241] *See, e.g.*, *Gene Editing Technology: Innovation and Impact: Hearing of the Comm. on Health, Educ., Lab., and Pensions: First Session on Examining Gene Editing Technology, Focusing on Innovation and Impact*, 115th Cong. (2017) (examining technologies such as CRISPR thoroughly but failing to mention MRT).

[242] *Barnhart*, 535 U.S. at 222.

[243] *See* Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2242, 2283 (2015).

simply bans the FDA from even acknowledging the receipt of these submissions.[244] Under this rider amendment, the FDA does not have to consider this complex process at all when it implicates procedures the FDA deems to involve an embryo with a heritable genetic modification,[245] and the FDA determined MRT falls within this category.[246] Ultimately, this *Barnhart* factor cuts in both directions for whether to move onto *Chevron* step one.

Finally, the fifth *Barnhart* factor examines "whether the agency carefully considered the question for a long period of time."[247] The FDA considered MRT for several years before the rider amendment went into effect in 2016. In 2014, the FDA convened the Cellular, Tissue, and Gene Therapy Committee to determine whether MRT was a viable reproductive technology to prevent mitochondrial diseases.[248] When this Committee concluded there were too few animal studies to make a definitive determination, the Institute of Medicine was asked to generate a report on MRT.[249] However, it is uncertain whether the FDA considered whether MRT is more analogous to an organ transplant than a heritable genetic modification. It is also uncertain whether the FDA considered that limiting MRT to male embryos would prevent this modification from being inherited by future generations. Therefore, until the FDA shows it considered these details, it is unsettled whether *Barnhart*'s fifth factor points in favor of or against moving forward with *Chevron*'s analysis.

Because two *Barnhart* factors cut in favor of moving forward with the *Chevron* analysis, one factor cuts against moving forward, and two factors are debatable, a court may reach either conclusion based on its interpretation of these factors. If a court determines the FDA's rule prohibiting MRT under Congress's rider amendment satisfied enough *Barnhart* factors, then the court will move forward with analyzing the rule under *Chevron* step one. However, if a court determines the FDA's rule did not satisfy enough *Barnhart* factors, then it failed *Chevron* step zero, and the court would determine the amount of deference this rule deserves by analyzing it under *Skidmore*'s test.

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[244] *Id.*

[245] *See id.* ("None of the funds made available by this Act may be used to . . . acknowledge receipt of a submission for an exemption for investigational use of a drug or biological product.").

[246] *Advisory on Legal Restrictions*, *supra* note 29.

[247] *Barnhart*, 535 U.S. at 222.

[248] Glavota, *supra* note 62, at 357.

[249] *Id.*

2. Even if the FDA's prohibition of MRT under Congress's rider amendment satisfies *Chevron* step zero, it likely fails *Chevron* step one.

Chevron step one examines whether Congress's intention was silent or ambiguous.[250] If congressional intent was clear, then courts must follow Congress's intention rather than granting *Chevron* deference.[251] For the first step, the rider amendment itself does not mention MRT in any capacity, so courts will likely look to legislative history to determine whether Congress unambiguously intended to exclude MRT from this rider amendment.[252]

As mentioned in Part IV.B, while there was no congressional debate regarding this rider amendment when it was inserted, Congress was responding to current events at the time of its insertion—specifically, it was responding to the genetic manipulation of embryonic nDNA via CRISPR. At the time of its insertion, there was a global outcry against a Chinese scientist using CRISPR technology to genetically modify the nDNA of human embryos in the laboratory setting.[253] While the FDA may argue Congress was responding to reports from the FDA's Cellular, Tissue, and Gene Therapy Committee and the Institute of Medicine, these administrative reports did receive much media attention at the time. To further take the wind out of this argument, the Institute of Medicine's report on MRT was published after the rider amendment was inserted into the Consolidate Appropriations Act of 2016.[254]

A court should find Congress did not intend the rider amendment to encompass MRT or, at the very least, was ambiguous on this front. If a court comes to this conclusion, then the FDA's rule fails *Chevron* step one, and the court will move on to analyze it under the *Skidmore* deference test.

3. Under *Skidmore*'s test, courts will probably not grant much deference to the FDA's prohibition of MRT under Congress's rider amendment.

Since a court is likely to determine the FDA's rule either fails at *Chevron* step zero or *Chevron* step one, the court will turn to *Skidmore*'s

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[250] *Chevron*, 467 U.S. at 837.

[251] *Id.*

[252] *See id.*

[253] Kaiser, *supra* note 80.

[254] Reardon, *supra* note 73.

test. The court will use *Skidmore*'s test to determine how much deference the FDA's rule should be given as it determines whether the FDA can outrightly ban MRT under the rider amendment.

Skidmore's first factor is "the thoroughness evident in [the agency's] consideration."[255] The FDA's advisory on the status of MRT does not provide much information regarding how the FDA determined that Congress's rider amendment bans MRT. Instead, the FDA flatly states that "Congress has included provisions in annual federal appropriations laws that prohibit FDA from accepting applications for clinical research using MRT."[256] However, the relevant provision never mentions MRT; it simply states the FDA cannot "acknowledge receipt of submission" for clinical trials involving "research in which a human embryo is intentionally created or modified to include a heritable genetic modification."[257] Therefore, based on this evidence, the FDA did not thoroughly consider whether MRT should fall under this rider amendment's prohibition. This *Skidmore* factor points towards granting less deference to the FDA's rule.

The second *Skidmore* factor examines "the validity of [the agency's] reasoning."[258] As seen in the first *Skidmore* factor, there is not much evidence regarding the FDA's reasoning for determining MRT falls under the rider amendment. Furthermore, the FDA does not address the alternative possibility where MRT is limited to male children, who cannot pass on the genetic modification. The second *Skidmore* factor also points towards giving the FDA's rule less deference because there does not seem to be much validity to its reasoning.

The third *Skidmore* factor examines the rule's "consistency with earlier and later pronouncements."[259] Before this rider amendment was inserted in the Consolidated Appropriations Act of 2016, the FDA was considering whether it should permit MRT clinical trials.[260] Its determination that MRT is flatly prohibited by the rider amendment is inconsistent with this earlier consideration. The FDA will likely argue the rider amendment's language was an intervening circumstance, so it was appropriate for their stance on MRT to change. Based on these two arguments, a court could find this factor goes either way. Therefore, the third *Skidmore* factor cuts in both directions.

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[255] *Skidmore*, 323 U.S. at 140.

[256] *Advisory on Legal Regulations*, *supra* note 29.

[257] *See* Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2242, 2283 (2015).

[258] *Skidmore*, 323 U.S. at 140.

[259] *Id.*

[260] Glavota, *supra* note 62, at 357.

The final *Skidmore* factor examines "all those factors which give [the agency] power to persuade."[261] Courts will likely find the FDA's expertise on this subject matter as a persuasive factor in granting it deference. Therefore, this factor cuts in favor of granting deference.

Because two *Skidmore* factors cut against granting deference, one factor is ambiguous, and the last factor cuts in favor of granting deference, a court will likely grant the FDA a slight to moderate amount of deference when determining whether MRT falls under this rider amendment. However, even with some deference under *Skidmore*, a court may still find MRT is not flatly prohibited by the rider amendment. A court can reach this decision by determining MRT is more analogous to a transplant than a heritable genetic modification. A court that determines MRT is more like a heritable genetic modification than a transplant may still consider it permissible to allow MRT as long as it is limited to male children. Therefore, even with *Skidmore* deference, there is hope that a court will open the door for women with mutated mtDNA to feel safe in having biological children.

VII. CONCLUSION

MRT could prevent future children from being afflicted with debilitating mitochondrial diseases. Several countries, including the United Kingdom, allow MRT to be conducted in their countries, having concluding it is sufficiently safe and effective.[262] The United States was following these countries footsteps in the mid-2010s as the FDA called the Cellular, Tissue, and Gene Therapy Committee to determine the viability of MRT for human clinical trials.[263]

Congress's rider amendment to the Consolidated Appropriations Act of 2016 included language prohibiting the FDA from considering clinical trial applications for anything involving "a human embryo [ ] intentionally created or modified to include a heritable genetic modification."[264] The FDA interpreted this to prohibit all MRT, thus bringing MRT research in the United States to a standstill.[265]

The FDA continues to prohibit any MRT procedures due to Congress's rider amendment. Therefore, women who know they can pass on mutated mtDNA to their children must choose between taking the risk of having biological children, using an egg donor, or adopting a child.

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[261] *Skidmore*, 323 U.S. at 140.

[262] Castro, *supra* note 13, at 735.

[263] Glavota, *supra* note 62, at 357.

[264] Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, § 749, 129 Stat. 2242, 2283 (2015).

[265] *Advisory on Legal Restrictions*, *supra* note 29.

Women who want a biological child cannot achieve this desire when using an egg donor or adoption, but they can through MRT.

While no one has challenged the legality of this prohibition so far, future challenges may arise, especially as other countries progress using this technology. Given the complex interplay between the rider amendment and the FDA, future litigants may attempt to overturn the ban on MRT through administrative procedure arguments. One potential argument they may bring forward is that the FDA's interpretation of the rider amendment is a legislative rule rather than an interpretive rule, so the FDA violated the APA by not subjecting it to notice-and-comment rulemaking. Courts may find this was a legislative rule using the multi-factor test articulated in *American Mining Congress*. The FDA would then be forced to subject this rule to notice-and-comment rulemaking. Because the rule would undergo notice-and-comment rulemaking, the FDA would be required to answer key questions, such as whether MRT is more analogous to a transplant than a heritable genetic mutation and whether MRT would be permissible if limited to male embryos.

Another potential argument is that the FDA acted impermissibly when it determined the rider amendment prohibits MRT. Under a statutory interpretation framework, a court should find the rider amendment's statutory language and legislative history did not intend to include MRT. Thus, under the statutory interpretation framework, the FDA's full ban on MRT does not fall under the rider amendment. The FDA will not succeed under the deference doctrines favorable to administrative agencies, either. While the FDA will likely argue *Chevron* deference applies, a court should find *Chevron* step zero or step one fails in this situation. The court will then determine how much deference to give the agency by analyzing the rule under *Skidmore*'s test. In this case, *Skidmore* indicates the court should give the FDA's rule little deference. A litigant will then be well poised to argue that MRT should not fall under this rider amendment because MRT is more analogous to a transplant. Alternatively, even if the court determines MRT is more like a heritable genetic modification than a transplant, a litigant could argue limiting MRT to male children would ensure this modification is not heritable.

The ban on MRT in the United States has negative consequences for individuals and scientific inquiry. Thankfully, it may not be here to stay based on the above arguments. The FDA may reconsider its stance if forced to undergo notice-and-comment rulemaking. Also, a court may find the FDA's full ban on MRT does not fall under the rider amendment. Either option would progress MRT's status within the United States, thus getting women with mutated mtDNA one step closer to feeling safe in having biological children.