**POLICY MEMORANDUM**

**Congressional Appropriations and Human Germline Modifications**

Submitted by Katherine Drabiak, JD

Assistant Professor

College of Public Health and College of Medicine

University of South Florida HEALTH

kdrabiak@health.usf.edu

**AUTHOR BACKGROUND**

Katherine Drabiak, JD

Assistant Professor

College of Public Health and College of Medicine

University of South Florida HEALTH

kdrabiak@health.usf.edu

Drabiak is Assistant Professor in the Colleges of Public Health and Medicine at the University of South Florida HEALTH in the United States. Her teaching and research focuses in health law, bioethics, and the regulation of emerging technology. She is the author of several articles[[1]](#endnote-1) relevant to human genome editing and Mitochondrial Replacement Therapy, a signatory to the Civil Society Statement to the Organizers of the Second International Summit on Human Genome Editing,[[2]](#endnote-2) and a working group member of the Brocher Accord,[[3]](#endnote-3) an international consortium of scientists, academics, policymakers and ethicists dedicated to responsible governance of genomics technologies involving modifications to the human germline.

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Additional Resources:

Katherine Drabiak, *Untangling the Promises of Human Genome Editing*, 46 Journal of Law, Medicine & Ethics 991-1009 (2018).

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**BRIEF SUMMARY**

***Background:***

On June 4, the House Appropriations Committee cast a bipartisan vote to reinstate a rider to the Consolidated Appropriations Act that prohibits the FDA from reviewing clinical applications in which a human embryo would be intentionally created or modified to include a heritable genetic modification. Prior to this vote, there was debate about whether to remove this provision to permit clinical trials to move forward for embryos that have germline modification in the form of Mitochondrial Replacement Therapy (MRT). There have been calls by scientists and policymakers to provide an exception to permit MRT and potentially permit other forms of “therapeutic” genome editing for human embryos.

***ACTION REQUESTED:***

**The Congressional Appropriations Committee should retain the rider that prohibits FDA from reviewing clinical applications for “research in which a human embryo is intentionally created or modified to include a heritable genetic modification.” Congress should not permit any exceptions for MRT or “therapeutic” applications of genome editing on human embryos.**

1. Removing or altering Sec. 733 to exempt Mitochondrial Replacement Therapy would in effect permit human genome modification technologies to move forward into clinical application. This constitutes a substantial policy modification that should not be undertaken without full and transparent public debate before U.S. Congress.
2. Strong policymaking requires accuracy, transparency, and honest deliberation of available evidence. Public discussions should include the limitations of experimental technology, alternatives, and risks.
3. Scientists have already conducted experiments to create infants through Mitochondrial Replacement Therapy and Human Genome Editing. There is no independent evidence showing these infants are healthy; and evidence in fact demonstrates the procedure of genome editing embryos to create infants in China did not work as intended.

1. Unlike other potential clinical trials where the FDA determines calculations of safety and efficacy for the intended patient, the research subject – a future child – would be *created* using the proposed methodology.
2. In recognition of risks, ethical concerns, and principled objections, modification of the human germline (whether by Mitochondrial Replacement Therapy or Human Genome Editing) has prohibited by International Bioethics Committee of the United Nations, The Council of Europe’s Convention on Human Rights and Biomedicine, and the European Union’s 2001 directive on clinical trials. [[4]](#endnote-4)
3. Public framing of human germline modification technologies (Mitochondrial Replacement Genome Therapy and Genome Editing) contains misleading rhetoric designed to engineer acceptance. These procedures are not curative, but rather highly experimental with significant risks. Using misleading descriptions undermines the authenticity and integrity of the policymaking process.
4. The U.S. will not “fall behind” in science and technology. Dozens of other nations and international agreements unequivocally prohibit human germline modifications as a bright line that should not be crossed.
	1. Globally, approximately forty countries[[5]](#endnote-5) including Canada,[[6]](#endnote-6) Germany,[[7]](#endnote-7) France,[[8]](#endnote-8) Switzerland,[[9]](#endnote-9) Sweden,[[10]](#endnote-10) and Italy[[11]](#endnote-11) have adopted legislation prohibiting germline intervention on embryos for implantation.[[12]](#endnote-12)
5. The U.S. should not permit any exception for MRT. Appropriate policymaking looks not only at the conclusion or recommendations of expert reports, but at whether the evidence supports such conclusion.
6. The U.K.’s policy stance permitting MRT should not serve as model to the U.S. because it lacked public consensus and summarily dismissed substantial concerns with safety and efficacy.
7. There are serious scientific risks involved with human germline modifications through Mitochondrial Replacement Therapy and Human Genome Editing.
	1. Risks of Mitochondrial Replacement Therapy
		1. There are problems determining efficacy and whether the procedure works as intended.
		2. Even if it initially appears that the procedure worked, the modification may not work as more time passes.
		3. There are severe health risks involving in disrupting Mitochondrial DNA.
		4. A live birth does not equate to a healthy child.

* 1. Risks of Human Genome Editing Human Embryos
		1. There are problems determining efficiency and whether the procedure worked.
		2. Genome editing results in unpredictable effects on human development.
		3. In animal models, germline modifications induced multiple devastating effects, ranging from latent health deficits, inducing tumor growth, and producing developmental abnormalities.[[13]](#endnote-13)
		4. Genome editing may result in mosaicism, where some cells contain genetic modification and other cells do not demonstrate the intended modification.[[14]](#endnote-14) Mosaicism can result in gross structural abnormalities, major Mendelian disorders, cell and tissue degeneration associated with aging, and death.[[15]](#endnote-15)
		5. Genome editing also produces off target effects, which impacts the functioning of the whole genome.
			1. Identifying off target effects poses considerable challenges; not being able to identify off target effects does not mean they do not exist.[[16]](#endnote-16)
1. The available evidence demonstrates germline modification technologies could not effectively address genetic disease or infertility.
	1. MRT would not effectively and sustainably address causes of mitochondrial dysfunction.
		1. MRT is not designed to address most cases of mitochondrial disease.
	2. It may not be feasible to use Human Genome Editing as a method to address genetic disease and infertility.
		1. Genome editing presumes that scientists can properly identify and classify which variants are pathogenic and cause disease: this is a misleading oversimplification.
	3. Disease does not occur simply because of a “genetic flaw” or “faulty genes,” but genetic variants appear as one of many causal factors in multifactorial diseases. Many people have a harmful mutation, but never develop the disease.
	4. Even genome editing may not be able to fix monogenic (single gene diseases) like Huntington’s Disease or Cystic Fibrosis.
	5. Scientific evidence does not support using MRT or Genome Editing as means to treat infertility.

***CONCLUSION:***

Based on global legal consensus against germline modification of human embryos and scientific evidence demonstrating serious risks of Mitochondrial Replacement Therapy and Human Genome Editing, the Congressional Appropriations Committee should retain Section 733 without modification.

**DESCRIPTIVE POLICY BRIEF**

***Background:***

On June 4, the House Appropriations Committee cast a bipartisan vote to reinstate a rider to the Consolidated Appropriations Act that prohibits the FDA from reviewing clinical applications in which a human embryo would be intentionally created or modified to include a heritable genetic modification. Prior to this vote, there was debate about whether to remove this provision to permit clinical trials to move forward for embryos that have germline modification in the form of Mitochondrial Replacement Therapy (MRT). There have been calls by scientists and policymakers to provide an exception to permit MRT and potentially permit other forms of “therapeutic” genome editing for human embryos.

***ACTION REQUESTED:***

**The Congressional Appropriations Committee should retain the rider that prohibits FDA from reviewing clinical applications for “research in which a human embryo is intentionally created or modified to include a heritable genetic modification.” Congress should not permit any exceptions for MRT or “therapeutic” applications of genome editing on human embryos.**

1. **Removing or altering Sec. 733 to exempt Mitochondrial Replacement Therapy would in effect permit human genome modification technologies to move forward into clinical application. This constitutes a substantial policy modification that should not be undertaken without full and transparent public debate before U.S. Congress.**
2. **Strong policymaking requires accuracy, transparency, and honest deliberation of available evidence. Public discussions should include the limitations of experimental technology, alternatives, and risks.**
3. **Scientists have already conducted experiments to create infants through Mitochondrial Replacement Therapy and Human Genome Editing. There is no independent evidence showing these infants are healthy; and evidence in fact demonstrates the procedure of genome editing embryos to create infants in China did not work as intended.**

* 1. In 2016, Dr. John Zhang (U.S.) used Mitochondrial Replacement Therapy (MRT) to create an infant, who he declared is healthy but there has been no independent follow up.
	2. In 2018, Dr. He Jiankui (China) used genome editing to modify the CCR5 gene aiming to reduce risk of HIV infection. This experiment produced two twin girls. Multiple reports suggest He’s experiment did not produce the intended modification:[[17]](#endnote-17) the infants have a new, unknown mutation, which creates uncertain health risks. A recent article in Nature Medicine suggests inducing this mutation may *increase risk* of mortality.[[18]](#endnote-18)
1. **Unlike other potential clinical trials where the FDA determines calculations of safety and efficacy for the intended patient, the research subject – a future child – would be *created* using the proposed methodology**.
	1. Mistakes in the process when MRT and Human Genome Modifications do not work as expected are both inevitable and irreversible, which means these procedures could potentially not only create a congenitally impaired child, but introduce those deficits into the germline of all subsequent offspring.
	2. It is unethical to proceed with experiments knowing the risk of potential “mistakes.”
	3. No person has the moral authority to purposefully alter the human germline or expose future children to such serious risks.
2. **In recognition of risks, ethical concerns, and principled objections,** **modification of the human germline (whether by Mitochondrial Replacement Therapy or Human Genome Editing) has** **prohibited by International Bioethics Committee of the United Nations, The Council of Europe’s Convention on Human Rights and Biomedicine, and the European Union’s 2001 directive on clinical trials**. [[19]](#endnote-19)
3. **Public framing of human germline modification technologies (Mitochondrial Replacement Therapy and Human Genome Editing) contains misleading rhetoric designed to engineer acceptance. These procedures are not curative, but rather highly experimental with significant risks.** **Using misleading descriptions undermines the authenticity and integrity of the policymaking process.**
	1. Misleading statements about Mitochondrial Replacement Therapy
		1. Media has referred to mitochondria as mere batteries of the cell and ethicists have compared MRT to a “micro-organ transplantation,” alleging there is “no sound basis to oppose MRT” because it constitutes a “cure” so infants can be born without mitochondrial disease.[[20]](#endnote-20)
		2. MRT is highly risky, experimental, and not a curative method to prevent mitochondrial disease or treat infertility.
		3. Touting MRT as a cure for mitochondrial disease is misleading because it will not address most cases. Most instances of mitochondrial disease arise from de novo mutations and mutations in nDNA.[[21]](#endnote-21) Approximately 80% of mitochondrial disease arises from nDNA mutations, which MRT does not address.[[22]](#endnote-22)
	2. Misleading statements about Human Genome Editing
		1. Both media and scientific articles have described genome editing as method for scientists to make precise corrections, to eliminate mutant genes, correct genetic flaws and efficiently treat or even cure disease.
		2. Human genome editing has been described as a “search and replace” mechanism to specifically as a mechanism to address monogenic diseases such as Huntington’s Disease and Cystic Fibrosis. This is not scientifically feasible or accurate because even single gene disorders involve many areas on the human genome.[[23]](#endnote-23)
		3. Human genome editing is also highly risky, experimental, and it not a curative therapy.
4. **The U.S. will not “fall behind” in science and technology. Dozens of other nations and international agreements unequivocally prohibit human germline modifications as a bright line that should not be crossed.**
	1. This constitutes alarmist rhetoric that is not based on the current climate of law internationally.
	2. **Globally, approximately forty countries[[24]](#endnote-24) including Canada,[[25]](#endnote-25) Germany,[[26]](#endnote-26) France,[[27]](#endnote-27) Switzerland,[[28]](#endnote-28) Sweden,[[29]](#endnote-29) and Italy[[30]](#endnote-30) have adopted legislation prohibiting germline intervention on embryos for implantation.[[31]](#endnote-31)**
		1. Laws enacted in the aforementioned nations not only prohibit germline or heritable modification, but such actions constitute criminal violation subject to fines and or imprisonment.
		2. Unequivocally prohibiting and criminalizing an action communicates the egregiousness, potential for harm, and social unacceptability of such an action in these nations.
		3. These laws demonstrate many countries acknowledge the lure of technology, but renounce risky experiments that cross the historical bright line of manipulating future generations.[[32]](#endnote-32)
		4. Prohibitions do not stem from “irrational fear” but instead affirm longstanding precedent based on reasoned deliberation.
5. **The U.S. should not permit any exception for MRT. Appropriate policymaking looks not only at the conclusion or recommendations of expert reports, but at whether the evidence supports such conclusion**.
	1. In 2016, The National Academies stated it is ethically permissible for the FDA to conduct clinical investigations subject to a set of conditions.
	2. However, this conclusion dismissed extensive concerns of multiple experts present at the 2014 Cellular, Tissue, and Gene Therapies Advisory Committee of the FDA (described below in #10).
		1. Participants at the 2014, the FDA’s Cellular, Tissue, and Gene Therapies Advisory Committee reiterated *there are less risky alternatives to having children, and the current evidence falls “far short” of showing MRT would be potentially safe and effective.[[33]](#endnote-33)*
6. **The U.K.’s policy stance permitting MRT should not serve as model to the U.S. because it lacked public consensus and summarily dismissed substantial concerns with safety and efficacy.**
	* 1. Key shortcomings with the U.K’s policymaking process:[[34]](#endnote-34)
			1. During the initial proposal, bioethicists, scholars, and scientists voiced dissent because MRT would breach the broad global consensus against germline modifications and urged the government to reconsider.
			2. During the consultation process, numerous scientists provided testimony and correspondence at length relating to safety and efficacy.
			3. Scientists objected to HFEA’s conclusions based on available evidence, finding not merely a lack of consensus pertaining to safety and efficacy, but that the available scientific evidence demonstrated how unsafe MRT is.
			4. Despite objections based on international governance, evidence demonstrating insufficient safety and efficacy, and lack of public consensus, British Parliament passed the amendment that would permit HFEA to license fertility clinics to offer MRT.
7. **There are substantial scientific risks involved with human germline modifications through Mitochondrial Replacement Therapy and Human Genome Editing.**
	1. Risks of Mitochondrial Replacement Therapy

In 2014, the Cellular, Tissue, and Gene Therapies Advisory Committee of the FDA convened meetings to discuss MRT for both the prevention of mitochondrial disease and the treatment of infertility.[[35]](#endnote-35) Participants discussed an extensive list of scientific concerns:

* + 1. **There are problems determining efficacy and whether the procedure works as intended.**
			1. Testing the blastomere for viability is not indicative of the health of the child and subsequent offspring.[[36]](#endnote-36) One scientist also noted that testing a sample is not indicative of the rest of the inner cell mass, meaning different levels of heteroplasmy may exist, and even subsequently develop at varied rates in different tissues though stages of development and the child’s life.[[37]](#endnote-37)
		2. **Even if it initially appears that the procedure worked, the modification may not work as more time passes**.
			1. Segregation and replication of mtDNA occurs according to its own evolutionary system, so predicting subsequent levels of heteroplasmy is difficult.[[38]](#endnote-38) Even if segregation initially demonstrates favorable drift toward the donor’s mtDNA, these levels may jump unpredictably, or segregate at different levels in tissues throughout the body.[[39]](#endnote-39)
			2. Levels of mtDNA in the child’s blood may reflect a low percent of heteroplasmy, but genetic drift can cause segregation toward the mother’s mutated mtDNA in specific tissues or organs, wherein the child may experience diseases arising in those systems.[[40]](#endnote-40)
			3. Segregation occurs throughout the lifespan of the individual which means low levels of the mother’s mtDNA in the child’s blood or partial tissue testing would also not reflect the possibility of increasing levels of heteroplasmy later in life resulting in latent presentation of mitochondrial disease.[[41]](#endnote-41)
		3. **There are serious health risks involving in disrupting Mitochondrial DNA.**
			1. Some scientific evidence suggests that segregation appears affected by genetic distance between haplotypes and when haplotypes of maternal mtDNA and donor mtDNA are mixed, reversion toward maternal mtDNA occurs.[[42]](#endnote-42)
			2. In animal models, mixed mtDNA has resulted in immune rejection, susceptibility to diseases of metabolism, and deficits in performance and learning capabilities.[[43]](#endnote-43)
			3. MRT would disrupt crucial cross-talk between mtDNA and nDNA. Mitochondrial DNA not only functions as a source of energy, but affects a wide range of cellular functioning and how nDNA is expressed.[[44]](#endnote-44)
			4. Current research suggests interference in the communication between mtDNA and nDNA can negatively affect individual development, behavior, susceptibility to disease, and fertility.[[45]](#endnote-45)
		4. **A live birth does not equate to a healthy child.**
			1. Initial positive results (or even a live birth) in Animal and In Vitro Models does not mean human offspring would be “healthy.”
			2. Some studies relied on a small sample and may miss problems that would arise with a larger sample; they did not perform extensive testing for heteroplasmy throughout tissues; the studies did not test germ cells for heteroplasmy or assess the health of subsequent generations; and using sample tests for heteroplasmy as a proxy for health may miss other dysfunction.[[46]](#endnote-46)
	1. Risks of Human Genome Editing Human Embryos
		1. **There are problems determining efficiency and whether the procedure worked.**
			1. Scientific claims that genome editing is highly efficient and make the targeted changes requires close qualification:
			2. Midic and colleagues demonstrated potential efficiency at 80-100% using rhesus monkey embryos, but despite such “high efficiency” in animal models, they also reported only 52% efficiency in human embryos.
			3. The National Academies recognize it is not possible to accurately infer the developmental events in human embryos by studying animal models.[[47]](#endnote-47)
			4. In animal models using rhesus monkey zygotes, less than 10% of embryos resulted in a full term birth.[[48]](#endnote-48) Midic and colleagues noted a high rate of pregnancy loss and developmental arrest.[[49]](#endnote-49)
			5. Although the National Academies *assumes* the genome editing process does not interfere with development. However, some scientists have suggested the opposite: diminishing survival rate suggests that embryos that do survive germline modifications may develop subtle latent health deficits.[[50]](#endnote-50)
		2. **Genome editing results in unpredictable effects on human development.**
			1. Although the National Academies presumes that embryo survival equates to health, this conclusion does not account for the highly significant impact of the process of genome editing on the subsequent developmental trajectory.[[51]](#endnote-51)
			2. In 2015, the Office of Science Policy of the National Institutes of Health published a report in which it described the risks associated with genome editing, including the potential for the extra chromosomal DNA to become trapped into the double strand break where the genome editing technology interacts within the gene.[[52]](#endnote-52)
			3. Available research provides support for the proposition that the impact on the organism as a whole is highly risky and unpredictable.[[53]](#endnote-53)
			4. Evolutionary biologist Stuart Newman describes the serious risks, stating genome modification:
				1. Is “fraught with potential error” precisely because germline interventions impact every cell in the body and will affect every cell’s subsequent growth and development.[[54]](#endnote-54)
				2. Is risky because “there is no such thing as engineering an organism” because interactions between genes are highly integrated, designed to achieve stability and balance, and manipulation of one location risks disrupting the biological equilibrium.[[55]](#endnote-55)
		3. **In animal models, germline modifications induced multiple devastating effects, ranging from latent health deficits, inducing tumor growth, and producing developmental abnormalities**.[[56]](#endnote-56)
			1. Biologist Xiangjin Kang and colleagues explicitly warn even modifying a target to a naturally occurring allele requires scrutiny:
				1. We are unable to predict the genome wide effect of changing a single allele and disrupting the pre-existing genome.[[57]](#endnote-57) This may result in creating a child who may be congenitally impaired, facing biological complications and irreversible health harms.[[58]](#endnote-58)
				2. **Effects of genome editing may not be immediately visible, but may create latent health risks to the child.** The impact of germline modifications may only become apparent during the growth and development of the future child, as the embryo grows into specific cells and tissues, during the unfolding of the nervous system, the organs, the brain, and over the course of the child’s life.[[59]](#endnote-59)
				3. **Animal models that appeared to be growing and developing according to prediction suffered tumor development later in life and encountered unexpected developmental abnormalities** not previously anticipated by scientists.[[60]](#endnote-60)
		4. **Genome editing may result in mosaicism, where some cells contain genetic modification and other cells do not demonstrate the intended modification**.[[61]](#endnote-61) **Mosaicism can result in** **gross structural abnormalities, major Mendelian disorders, cell and tissue degeneration associated with aging, and death**.[[62]](#endnote-62)
			1. Animal models demonstrate “substantial” genetic mosaicism because the editing mechanism may occur during different stages of cell division or exert residual influence on cells after division.[[63]](#endnote-63)
			2. In one study using early human embryos, the rates of mosaicism in the developing cells exceeded the measured percent of efficiency to induce the desired modification.[[64]](#endnote-64)
			3. Testing for embryos for mosaicism cannot predict the child’s future health.
			4. Testing a single cell of the embryo with Preimplantation Genetic Diagnosis does not reflect the rest of the cells in the embryo, and there are no effective methods to predict the organism’s growth and development.[[65]](#endnote-65)
		5. **Genome editing also produces off target effects, which impacts the functioning of the whole genome.**
			1. The editing nucleases make cuts to unintended locations rather than the target, modifies the target sequence but continues making modifications after the initial target, or the guide RNA may bind to nontarget sequences.[[66]](#endnote-66)
			2. Insertions, deletions, or translocations can activate or deactivate crucial sequences in the genome, which **could activate oncogenes related to tumor development or produce unexpected outcome such as advanced aging**.[[67]](#endnote-67)
			3. **Identifying off target effects poses considerable challenges; not being able to identify off target effects does not mean they do not exist**.[[68]](#endnote-68)
				1. Some studies only examine a few sites.[[69]](#endnote-69) Some insertions or deletions may be so small that they escape detection, leading researchers to report no off target effects occurred.[[70]](#endnote-70)
				2. Off target effects may not be phenotypically apparent, so preliminary appearances would likely suggest normal development.[[71]](#endnote-71)
				3. Kosicki and colleagues found both on target and significant off target damage, such as large deletions and complex rearrangements at areas they had not anticipated.[[72]](#endnote-72)
1. **Appealing to parental suffering relies on a false dilemma fallacy: Proponents for MRT and Human Genome Editing argue it will prevent incurable genetic disease, fix infertility, save families needless misery, and prevent medical progress. In fact, the** **available evidence demonstrates germline modification technologies could not effectively address genetic disease or infertility.**
	1. Less risky alternatives already exist to have children, include Preimplantation Genetic Diagnosis to screen embryos for genetic disease, or adoption.
	2. **MRT would not effectively and sustainably address causes of mitochondrial dysfunction.**
		1. **MRT is not designed to address most cases of mitochondrial disease.**
		2. Mitochondrial dysfunction may result from either mtDNA mutations or nDNA mutations. 80% of mitochondrial dysfunction arises from nDNA mutations for which MRT would not address.
		3. Recent evidence suggests that a variety of environmental factors induce de novo (new) mutations. Mitochondrial dysfunction is not only a cause of rare fatal disease, but also has been implicated as a factor in the development of common diseases, such as neurodegenerative disease, cancer, diabetes, cardiovascular disease.[[73]](#endnote-73)
		4. Public health research suggests a variety of environmental agents, including pesticides,[[74]](#endnote-74) heavy metals,[[75]](#endnote-75) antibiotics,[[76]](#endnote-76) pharmaceutical drugs,[[77]](#endnote-77) environmental toxicants such as dioxin[[78]](#endnote-78) and Bisphenol A[[79]](#endnote-79) can all exert changes to mitochondrial integrity and development.
	3. **It may not be feasible to use Human Genome Editing as a method to address genetic disease and infertility.**
		1. **Genome editing presumes that scientists can properly identify and classify which variants are pathogenic and cause disease: this is a misleading oversimplification**.
		2. In 2016, *Nature* published an article stating that the average person has an average of 54 mutations classified as pathogenic, but that 41 occur so frequently in the human population that they are not likely to cause severe disease.[[80]](#endnote-80)
		3. Many genetic mutations have been misclassified as harmful, and not all variants are pathogenic that could cause disease. [[81]](#endnote-81)
	4. **Disease does not occur simply because of a “genetic flaw” or “faulty genes,” but genetic variants appear as one of many causal factors in multifactorial diseases. Many people have a harmful mutation, but never develop the disease.**
		1. *Cancer*:
			1. Inherited mutations that contribute to the cause of cancer account for only 5-10% of all cases of cancer, with a substantial percent of remaining risk attributed to environmental and lifestyle factors.[[82]](#endnote-82)
			2. Even genetic variants such as BRCA1 and BRCA2 (which occur in .2% of the general population) are not 100% penetrant: a person may carry a BRCA1 variant that predisposes her to risk of breast and ovarian cancer, but never develop the disease.[[83]](#endnote-83)
		2. *Parkinson’s Disease:*
			1. 90% Parkinson’s Disease patients do not report a family history of the disease and the most common genetic variant associated with Parkinson’s Disease only accounts for fewer than 2% of all cases.[[84]](#endnote-84) This variant only correlates to a lifetime penetrance of 30-40%” this means the majority of individuals who have the variant will never develop Parkinson’s Disease.[[85]](#endnote-85)
			2. Physician Samuel Goldman states: genetic variation is involved in the development of Parkinson’s Disease, but the vast majority of cases cannot be ascribed to genetic factors but appear to be linked with exposure to environmental factors such as pesticides, solvents, and air pollutants.[[86]](#endnote-86)
	5. **Even genome editing may not be able to fix monogenic (single gene diseases) like Huntington’s Disease or Cystic Fibrosis.**
		1. Not all individuals with a particular disease causing mutation will develop the disease, which geneticists refer to as reduced or incomplete penetrance.[[87]](#endnote-87)
		2. Medical geneticist David Cooper: “The traditional view of genetic disorders as being either monogenic or multifactorial is no longer supported and requires a change in focus toward factors that modify gene expression and disease course.”[[88]](#endnote-88)
			1. Many mutations are conditionally pathogenic.
			2. The mutation alone is insufficient to cause the disease but interaction between modifier genes and the environment are key components that result in pathogenicity.[[89]](#endnote-89)
		3. Individuals may carry hundreds of potentially disadvantageous variants without adverse health effects, which further undermines the presumption that one variant alone causes the disease, and that modifying one variant constitutes a sufficient solution.[[90]](#endnote-90)
	6. **Scientific evidence does not support using MRT or Genome Editing as means to treat infertility.**
		1. Infertility is indeed a health problem, affecting both females and males and impacting 12-25% of the population.[[91]](#endnote-91)
		2. Rising rates of impaired fertility are likely due to a variety of complex environmental and lifestyle causes including aging, not inherent genetic flaws.[[92]](#endnote-92) Research suggests a connection between infertility and rising rates of other diseases such as reproductive abnormalities, endocrine disorders, and cancer in both males and females.[[93]](#endnote-93)
		3. In addition to the impact of lifestyle factors[[94]](#endnote-94) such as level of activity, exercise, diet, sleep and stress, research implicates chemical exposures as a factor contributing to both the decline in fertility and reproductive disorders. A variety of environmental toxicants including pesticides, PCBs, phthalates, parabens, and Bisphenol A present in our daily environment may adversely affect our health, including fertility.[[95]](#endnote-95)
		4. MRT and Genome Editing does not address the fundamental causes of infertility and increases in endocrine disorders and cancer. Population level increases in infertility constitutes a warning, signaling lifestyle and environmental factors are threatening both human reproduction and health outcomes, which cannot be addressed by modifying a particular gene or manipulating an embryo.

***CONCLUSION:***

**Based on global legal consensus against germline modification of human embryos and scientific evidence demonstrating serious risks of Mitochondrial Replacement Therapy and Human Genome Editing, the Congressional Appropriations Committee should retain Section 733 without modification.**

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