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# Striking a Balance: Policy Considerations for Human Germline Modification

Joshua D. Seitz

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# Striking a Balance: Policy Considerations for Human Germline Modification

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**ABSTRACT:**

*Human Germline Modification (HGM) involves the alteration of genes in a human subject, thereby creating changes to physical traits that can be passed on to the subject's offspring. Recent developments in genetic engineering, including the discovery of the CRISPR/Cas9 gene editing tool, have made HGM a realistic possibility in the near future. Currently, HGM in the United States is regulated by a rider on the Appropriations Act that prevents federal funding from being used for FDA review of any treatment options involving HGM. The rider therefore precludes the clinical development of any potential treatment that utilizes HGM – even those designed to cure or prevent severe inheritable diseases. This paper reviews the current state of the science and law surrounding HGM, as well as the various ethical principles that underlie current U.S. and international policy. After careful consideration of these principles, this paper suggests a middle path forward for the development of HGM in the near future: an amendment to the current rider that allows the development of HGM therapies to treat severe genetic diseases that have no better alternative treatment.*

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## I. INTRODUCTION

Until recently, the prospect of altering the genetics of our children has been speculative and remote, relegated to science fiction and theoretical debate. However, with the advent of new techniques in genetic engineering, mankind may soon have the ability to introduce targeted mutations during in vitro fertilization (IVF). These embryos may soon be implanted into a womb, where they will develop into a baby and eventually be born into this world: the first genetically engineered human beings in history. No longer merely hypothetical, reproduction using human germline modification (HGM)<sup>1</sup> has become a pressing international policy issue with serious implications for the future of medicine.

This paper will begin by exploring various aspects of HGM in its present state: (1) relevant advances in scientific understanding and bioengineering technology; (2) the potential clinical applications of HGM; and (3) the current international and domestic landscape for regulation of HGM. In discussing domestic HGM regulation, an emphasis is placed on the U.S. rider on the 2016 Consolidated Appropriations Act that effectively prevents the clinical development of HGM in the U.S. Additionally, the legislative purpose of the rider will be discussed, highlighting specific ethical concerns that have guided U.S. policy.

Lastly, this paper will propose an amendment to the current rider, which would allow the development of HGM as a preventative therapy for severe genetic diseases. In making the case for this amendment, this paper will explore three policy options regarding the future of HGM for reproduction in the U.S.: (1) failure to renew the rider for the following year; (2) renewal of the rider in its intact form; and (3) adoption of the proposed amendment to the current rider. Allowing the clinical development of HGM for the treatment of severe monogenic diseases may prevent unnecessary pain and suffering, reduce the costs associated with these diseases, and ensure that the U.S. remains an ethical and responsible leader in the field of bioengineering.

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<sup>1</sup> Although HGM has potential research and development applications in many biomedical fields, the exclusive focus of this paper is the use of HGM for reproduction.

## II. BACKGROUND

### A. *Genetic Diseases and Inheritance*

Before discussing the potential applications of HGM, it is critical to understand some of the basic science underlying inherited diseases, which are typically caused by mutations in the DNA that are passed from parent to offspring.<sup>2</sup> Mutations in the DNA may cause the production of defective proteins, which can lead to genetic diseases.<sup>3</sup> As opposed to the proteins encoded by the wild-type gene<sup>4</sup>, these defective proteins either remain in the cell, unable to properly function, or are detected by the cell and destroyed.<sup>5</sup> In either of these cases, the body is left unable to perform a basic, yet highly important process, leading to the symptoms of the disease.<sup>6</sup> When a genetic disease is caused by mutations in a single gene, they are known as *monogenic* diseases, whereas those caused by the combined influence of multiple genes are *polygenic*.<sup>7</sup>

Like physical traits, genetic diseases can be inheritable.<sup>8</sup> This relationship is particularly evident in monogenic diseases. For example, in an autosomal dominant disorder such as Huntington's disease, one chromosome carrying a mutated copy of the gene is enough to cause the disease.<sup>9</sup> In this case, if one parent carries the mutation, there is a 50% chance of the child being affected by the disease. In an autosomal recessive disorder, both chromosomes must carry the afflicted gene. If both parents carry the gene but are otherwise healthy, the child has a 25% chance of being born with the disease.<sup>10</sup> For this reason,

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<sup>2</sup> See generally NEIL A. CAMPBELL & JANE B. REECE, *BIOLOGY* (Beth Wilbur et al. eds., 7th ed. 2005).

<sup>3</sup> See Campbell & Reece, *supra* note 2.

<sup>4</sup> Wild-type genes are typically defined as the gene that encodes for the phenotype that is the most common gene in a natural population. Here, it is used to refer to any gene that codes for a phenotype that naturally occurs in a substantial portion of the healthy population.

<sup>5</sup> See Peter Bross, et al., *Protein misfolding and degradation in genetic diseases*, 14 *HUM. MUTATION* 186 (Sep. 2, 1999), available at <http://www.els.net/WileyCDA/ElsArticle/refId-a0006016.html>.

<sup>6</sup> *Id.*

<sup>7</sup> See generally Campbell & Reece, *supra* note 2.

<sup>8</sup> See *id.*; see also U.S. Nat'l Library of Med., *What are the different ways in which a genetic condition can be inherited?*, NIH GENETICS HOME REFERENCE (Dec. 19, 2017), <https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns> [hereinafter NIH Genetics].

<sup>9</sup> See NIH Genetics, *supra* note 8.

<sup>10</sup> *Id.*

autosomal recessive diseases do not always present themselves in every generation of a family.<sup>11</sup> Diseases carried solely on the X or Y sex chromosomes are known as X-linked<sup>12</sup> and Y-linked<sup>13</sup> diseases. In addition, some mitochondrial disorders are inheritable genetic conditions caused by mutations in the mitochondrial DNA.<sup>14</sup>

Although a monogenic disease is caused by a mutation in only one gene, the resulting disease may still be complex.<sup>15</sup> For example, PKU is caused by a mutation that results in faulty PAH enzymes, which metabolize the amino acid phenylalanine.<sup>16</sup> However, symptoms of PKU are complex. They include heart problems, small head, and low birth weight.<sup>17</sup> Different mutations on different parts of the gene can cause some symptoms of PKU to be more severe than others.<sup>18</sup> Additionally, the severity of these symptoms are dependent on non-genetic, environmental factors, such as a patient's diet.<sup>19</sup> Polygenic diseases are even more complicated than monogenic diseases in both their symptoms and inheritance patterns.<sup>20</sup>

### ***B. Clinical Applications of Genomic Screening and Genetic Engineering***

Generally speaking, there are three primary methods for preventing inherited diseases at the stage of embryo formation using advanced IVF techniques: (1) preimplantation genetic diagnosis; (2) mitochondrial replacement therapy; and (3) human

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<sup>11</sup> *Id.*

<sup>12</sup> *See id.* (explaining that X-linked diseases are caused by mutations in genes on the X chromosome and can be also be both recessive and dominant. In X-linked recessive diseases, the male children are more frequently affected because they only carry one X chromosome).

<sup>13</sup> *Id.*

<sup>14</sup> *See* NIH Genetics, *supra* note 8.

<sup>15</sup> *See* Charles R. Scriver & Paula J. Waters, *Monogenic traits are not simple: lessons from phenylketonuria*, 15 *TRENDS IN GENETICS* 267, 267-70 (Jul. 1999), available at

<http://www.sciencedirect.com/science/article/pii/S0168952599017618>.

<sup>16</sup> *See id.*

<sup>17</sup> *Id.*

<sup>18</sup> *See* Yoshiyuki Okano, et al., *Molecular Basis of Phenotypic Heterogeneity in Phenylketonuria*, 324 *N. ENGLAND J. MED.* 1232 (May 2, 1991), available at <http://www.nejm.org/doi/full/10.1056/NEJM199105023241802#t=article>.

<sup>19</sup> *See* Charles R. Scriver, *supra* note 15.

<sup>20</sup> *See* Kelly Frazer, et al., *Human genetic variation and its contribution to complex traits*, 10 *NATURE REV. GENETICS* 241 (April, 2009), available at <http://www.nature.com/nrg/journal/v10/n4/full/nrg2554.html>.

germline engineering. The basics of these three methods are discussed below.

### 1. *Pre-implantation Genetic Diagnosis*

At the moment, some parents already attempt to avoid inheritable diseases by using a technique called preimplantation genetic diagnosis (PGD).<sup>21</sup> PGD is accomplished by growing several embryos during the IVF process, removing a cell from each embryo or blastocyst, and sequencing each genome to assess which embryos carry the inheritable disease.<sup>22</sup> Those that do not carry the disease are then implanted into the mother and brought to term.<sup>23</sup> This practice is widely employed in countries across the world, including the U.S., to increase the chance that people afflicted with genetic diseases will have healthy offspring.<sup>24</sup>

### 2. *Mitochondrial Replacement Therapy*

When the mutated gene causing the disease is located on the mitochondrial DNA (mtDNA) and not the nuclear DNA (nDNA), mitochondrial replacement therapy (MRT) might be able to prevent the passage of the disease to children.<sup>25</sup> MRT is predominantly accomplished using one of two techniques, both of which involve the use of a donor's mtDNA and the mother's nDNA.<sup>26</sup> As the donor's mtDNA does not carry the affected gene, a child born from a successful MRT procedure should not develop the disease.<sup>27</sup> However, MRT may result in inheritable changes

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<sup>21</sup> See ASRM Ethics Committee, *Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion*, 100 FERTILITY & STERILITY 54 (Jul. 2013), available at <http://www.sciencedirect.com/science/article/pii/S0015028213003427>.

<sup>22</sup> See Joyce C. Harper & Sioban B. Sengupta, *Preimplantation genetic diagnosis: State of the ART 2011*, 131 HUMAN GENETICS 175 (Feb. 2012), available at <http://link.springer.com/article/10.1007/s00439-011-1056-z>.

<sup>23</sup> See *id.*

<sup>24</sup> See *id.*

<sup>25</sup> Klaus Reinhardt, et al., *Mitochondrial Replacement, Evolution, and the Clinic*, 341 SCIENCE 1345 (Sep. 20, 2013), available at <http://science.sciencemag.org/content/341/6152/1345.full>.

<sup>26</sup> First, pronuclear spindle involves the transfer of nuclear DNA from a fertilized zygote to an enucleated donor zygote. Alternatively, in maternal spindle transfer, the nuclear material of an unfertilized oocyte can be transferred to an enucleated donor oocyte. See P. Amato, et al., *Three-parent in vitro fertilization: gene replacement for the prevention of inherited mitochondrial diseases*, 101 FERTILITY & STERILITY 31, 32 (Jan. 2014), available at <https://www.ncbi.nlm.nih.gov/pubmed/24382342>.

<sup>27</sup> Reinhardt, et al., *supra* note 25.

to DNA, particularly in female offspring.<sup>28</sup> Because MRT has the potential to create inheritable genetic changes, its use has been controversial.<sup>29</sup> Nevertheless, the United Kingdom has recently become the first country to permit the clinical evaluation of MRT.<sup>30</sup>

*a. Somatic Cell Engineering and Human Germline Modification*

There are two major clinical applications of gene editing: somatic cell engineering (SCE) and human germline modification (HGM). SCE typically entails editing copies of the affected gene in the differentiated cells of an adult or child.<sup>31</sup> In theory, the patient's germ cells are not affected during SCE, so the genetic changes are not passed down to the next generation.<sup>32</sup> Somatic gene therapies are legal in the U.S., with many undergoing clinical evaluation.<sup>33</sup> The first somatic gene therapy achieved market approval in the EU in 2012; however, commercial use has thus far been limited.<sup>34</sup>

In reproductive HGM<sup>35</sup> the DNA of either an embryo or gametes is edited and the modified embryos or gametes are used

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<sup>28</sup> If the child is a female, she will pass the donor mtDNA to her progeny via her eggs. While a male child would carry the donor's mtDNA, it would not pass the DNA down the germline because a father's mtDNA is lost during fertilization. See Anne Claiborne, et al. *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, NAT'L ACADEMIES PRESS, 6-7 (2016), available at <https://www.nap.edu/catalog/21871/mitochondrial-replacement-techniques-ethical-social-and-policy-considerations>.

<sup>29</sup> See Robert Kiltzman, et al., *Controversies concerning mitochondrial replacement therapy*, 103 FERTILITY & STERILITY 344-45 (Feb. 2015), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4505924/pdf/nihms-648296.pdf>.

<sup>30</sup> Ewen Callaway, *UK moves closer to allowing 'three-parent' babies*, NATURE NEWS (Nov. 30, 2016), <http://www.nature.com/news/uk-moves-closer-to-allowing-three-parent-babies-1.21067>.

<sup>31</sup> W.F. Anderson, *Prospects for human gene therapy*, 226 SCIENCE 402 (Oct. 25, 1984), available at <http://science.sciencemag.org/content/226/4673/401>.

<sup>32</sup> *Id.*

<sup>33</sup> See Luigi Naldini, *Gene therapy returns to centre stage*, 526 NATURE 351 (Oct. 15, 2015), available at <http://www.nature.com/nature/journal/v526/n7573/full/nature15818.html>.

<sup>34</sup> See Antonio Regalado, *The World's Most Expensive Medicine Is a Bust*, MIT TECH. REV. (May 4, 2016), <https://www.technologyreview.com/s/601165/the-worlds-most-expensive-medicine-is-a-bust/>.

<sup>35</sup> For the purposes of this paper HGM refers to the reproductive use of germline modification, not research on germline modifications that are done

for reproduction via IVF.<sup>36</sup> The edit is made at the earliest possible stage of embryonic development; therefore, every cell of the resulting person carries the edited gene, including the germ cells.<sup>37</sup> As a result, the altered gene will be propagated down the germline to the offspring.<sup>38</sup>

*b. Therapy and Enhancement using  
HGM*

There are two general purposes for HGM treatment of embryos: (1) the correction of genetic diseases to produce a healthy child (therapy); and (2) the selection of specific desired traits in an otherwise healthy child (enhancement).<sup>39</sup> The use of HGM for therapy would include the replacement of mutated genes with their functional, wild-type counterparts.<sup>40</sup> This can be accomplished by deleting the former and inserting the latter, or by directly editing the mutated genes, resulting in a functional variant.<sup>41</sup> Similarly, enhancement could be accomplished by adding new genes, deleting unwanted genes, and editing existing genes to create the desired phenotype.<sup>42</sup> Both applications of HGM would create heritable changes to the patient's genome. Accordingly, HGM has become extremely controversial and its

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with no intention of implanting the embryo. Germline modification for research, while exceedingly important, is beyond the scope of this paper.

<sup>36</sup> See Tetsuya Ishii, *Germline genome-editing research and its socioethical implications*, 21 TRENDS IN MOLECULAR MED. 473-80 (Aug. 2015), available at [http://www.cell.com/trends/molecular-medicine/pdf/S1471-4914\(15\)00107-0.pdf](http://www.cell.com/trends/molecular-medicine/pdf/S1471-4914(15)00107-0.pdf).

<sup>37</sup> *Id.*

<sup>38</sup> See, e.g., Pradeep Reddy, *Selective Elimination of Mitochondrial Mutation in the Germline by Genome Editing*, 161 CELL 45 (Apr. 23, 2015), available at [http://www.cell.com/cell/abstract/S0092-8674\(15\)00371-2?\\_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867415003712%3Fshowall%3Dtrue](http://www.cell.com/cell/abstract/S0092-8674(15)00371-2?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867415003712%3Fshowall%3Dtrue).

<sup>39</sup> The distinction between therapy and enhancement is not always crystal clear due to ambiguities in the meaning of "healthy" and "genetic diseases." For the purposes of this paper, "therapy" refers to the treatment of serious genetic diseases that are caused by known genetic mutations and "enhancement" refers to the selection of traits for non-therapeutic purposes, including but not limited to selection of cosmetic features and the augmentation of intellectual capacity.

<sup>40</sup> See Naldini, *supra* note 33.

<sup>41</sup> See Jeffrey D. Sander & J. Keith Joung, *CRISPR-Cas systems for editing, regulating and targeting genomes*, 32 NATURE BIOTECH. 347 (Jan. 31, 2014), available at <http://www.nature.com/nbt/journal/v32/n4/full/nbt.2842.html>.

<sup>42</sup> See *id.*

use is heavily regulated or banned in many countries around the world.<sup>43</sup>

### **C. *HGM Made Possible – CRISPR Genomic Editing Technology***

CRISPR, (Clustered Regularly Interspaced Short Palindromic Repeats) is a gene-editing technique that has revolutionized the field of genetic engineering.<sup>44</sup> The CRISPR/Cas9 system is composed of two parts: (1) the Cas9 nuclease, which is the enzyme responsible for cutting DNA, allowing it to be edited; and (2) the guide RNA, which directs the Cas9 nuclease to the target site by binding to the corresponding sequence in the DNA.<sup>45</sup> The CRISPR/Cas9 system is significantly more efficient than previous gene editing methods.<sup>46</sup> Using automated RNA synthesis, new guide RNAs can be produced quickly and cheaply, making it possible to target and edit essentially any gene.<sup>47</sup> The same nuclease can be used with two or more guide RNAs to edit multiple genes simultaneously.<sup>48</sup> Moreover, the Cas9 nuclease can be deactivated and combined with different enzymes, allowing for additional site-specific manipulation of DNA, including the conversion of a single nucleotide to a different nucleotide,<sup>49</sup> nucleotide deletions<sup>50</sup> and demethylation of target nucleotides.<sup>51</sup> CRISPR's modular

<sup>43</sup> See Ishii, *supra* note 36.

<sup>44</sup> See *id.*

<sup>45</sup> See Martin Jinek, et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 *SCIENCE* 816 (Aug. 17 2012), available at <http://science.sciencemag.org/content/337/6096/816.full>.

<sup>46</sup> See, e.g., Prashant Mali, et al., *RNA-Guided Human Genome Engineering via Cas9*, 339 *SCIENCE* 823, 825 (Feb. 15, 2013), available at <http://science.sciencemag.org/content/339/6121/823.long>.

<sup>47</sup> See Elizabeth Pennisi, *The CRISPR Craze*, 341 *SCIENCE* 833 (Aug. 23, 2013), available at <http://science.sciencemag.org/content/341/6148/833>.

<sup>48</sup> See, e.g., Le Cong, et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 *SCIENCE* 6121 (Feb. 15, 2013), available at <http://science.sciencemag.org/content/339/6121/819>.

<sup>49</sup> See, e.g., Alexis C. Komor, et al., *Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage*, 533 *NATURE* 420, 420-21 (May 19, 2016), available at <http://www.nature.com/nature/journal/v533/n7603/full/nature17946.html>.

<sup>50</sup> See, e.g., Keiji Nishida, et al., *Targeted nucleotide editing using hybrid prokaryotic and vertebrate adaptive immune systems*, 353 *SCIENCE* 1248 (Aug 4, 2016), available at <http://science.sciencemag.org/content/early/2016/08/03/science.aaf8729.full>.

<sup>51</sup> See, e.g., Samrat Roy Choudury, et al., *CRISPR-dCas9 mediated TET1 targeting for selective DNA demethylation at BRCA1 promotor*, 7 *ONCOTARGET* 29 (Jun. 23, 2016), available at

versatility, unprecedented accuracy, ease of use, and low cost have opened the door to opportunities in genetic engineering that were considered fiction less than ten years ago.

In the three years since Jennifer Doudna and Emmanuel Charpentier's landmark publication on CRISPR for gene editing, research in the field has expanded at a breakneck pace.<sup>52</sup> The technique has led to rapid advances in the development of genetically-modified plants<sup>53</sup> and customized animal models of diseases.<sup>54</sup> In 2014, scientists used CRISPR to edit two genes in cynomolgus monkey embryos, leading to the birth of the first two genetically-modified monkeys.<sup>55</sup> Earlier this year, the National Institutes of Health (NIH) approved a proposal for the clinical use of the technology to edit human T-cells as part of a cancer immunotherapy.<sup>56</sup> Feng Zhang, MIT professor and CRISPR pioneer, told the MIT Technology Review that the actual gene editing of humans is only about "10 to 20 years away."<sup>57</sup>

In fact, we may be much closer to HGM than anyone had originally anticipated. Earlier this year, researchers at the

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<http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path%5B%5D=10234>.

<sup>52</sup> See Heidi Ledford, *CRISPR: gene editing is just the beginning*, 531 NATURE NEWS (Mar. 7, 2016), <http://www.nature.com/news/crispr-gene-editing-is-just-the-beginning-1.19510>; Heidi Ledford, *CRISPR, the disruptor*, 522 NATURE NEWS (Jun. 3, 2015), <http://www.nature.com/news/crispr-the-disruptor-1.17673>; Addison V. Wright, et al., *Biology and Applications of CRISPR Systems: Harnessing Nature's Toolbox for Genome Engineering*, 164 CELL 29 (Jan., 2016), available at [http://www.cell.com/cell/abstract/S0092-8674\(15\)01699-2](http://www.cell.com/cell/abstract/S0092-8674(15)01699-2).

<sup>53</sup> See, e.g., Shigeo S. Sugano, et al., *CRISPR/Cas9-mediated targeted mutagenesis in the liverwort *Marchantia polymorpha* L.*, 55 PLANT & CELL PHYSIOL. 475 (Jan. 18, 2014), available at <http://pcp.oxfordjournals.org/content/55/3/475.long>.

<sup>54</sup> See, e.g., Zhuchi Tu, et al. *CRISPR/Cas9: a powerful genetic engineering tool for establishing large animal models of neurodegenerative diseases*, 10 MOLECULAR NEURODEGENERATION 35 (Aug. 4, 2015), available at <https://molecularneurodegeneration.biomedcentral.com/articles/10.1186/s13024-015-0031-x>.

<sup>55</sup> See Yuyu Niu, et al., *Generation of Gene-Modified Cynomolgus Monkey via Cas9/RNA-Mediated Gene Targeting in One-Cell Embryos*, 156 CELL 836 (Feb. 13, 2014), available at [http://www.cell.com/abstract/S0092-8674\(14\)00079-8](http://www.cell.com/abstract/S0092-8674(14)00079-8); see also Helen Shen, *First monkeys with customized mutations born*, NATURE NEWS (Jan. 30, 2014), available at <http://www.nature.com/news/first-monkeys-with-customized-mutations-born-1.14611>.

<sup>56</sup> Sara Reardon, *First CRISPR clinical trial gets green light from US panel*, NATURE (Jun. 22, 2016), available at <http://www.nature.com/news/first-crispr-clinical-trial-gets-green-light-from-us-panel-1.20137>.

<sup>57</sup> See Antonio Regalado, *Engineering the Perfect Baby*, MIT TECH. REV. (Mar. 5, 2015), <https://www.technologyreview.com/s/535661/engineering-the-perfect-baby/>.

Oregon Health and Science University utilized CRISPR/Cas9 to achieve gene editing that resulted in viable human embryos.<sup>58</sup> The researchers were able to correct mutations in the *MYBPC3* gene that are responsible for hypertrophic cardiomyopathy, a condition that leads to sudden death in young athletes.<sup>59</sup> Gene editing was successful in 42 out of 58 human embryos, with 41 of these embryos containing two healthy, wild-type copies of the *MYBPC3* gene.<sup>60</sup> Importantly, the techniques disclosed in this report appeared to surpass two significant hurdles to utilizing HGM by minimizing off-target gene edits and preventing mosaicism of the embryos.<sup>61</sup>

Prior to this report, CRISPR had already been used to edit human embryos. In 2015, the first report used CRISPR to alter the hemoglobin gene (*HBB*) in non-viable zygotes.<sup>62</sup> The authors found that CRISPR/Cas9 system effectively cleaved the gene; however, the inefficiency of repair process and gene incorporation led to mosaicism of the embryo (embryos with cell-to-cell variation in genes).<sup>63</sup> The authors also detected off-target cleavage, indicating that the CRISPR/Cas9 system was not ready for clinical application.<sup>64</sup> In the second paper written prior to the Oregon research, CRISPR was used on non-viable embryos to introduce a naturally-occurring gene involved in HIV resistance.<sup>65</sup> Like the prior study, the authors found that the CRISPR system was not efficient enough to consider clinical applications.<sup>66</sup> Although both of these studies used non-viable embryos that could not develop into a fetus, the news of engineered human embryos generated a significant amount of

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<sup>58</sup> Heidi Ledford, *CRISPR fixes disease gene in viable human embryos*, NATURE NEWS (Aug. 2, 2017), available at <http://www.nature.com/news/crispr-fixes-disease-gene-in-viable-human-embryos-1.22382>.

<sup>59</sup> Hong Ma, et al., *Correction of a pathogenic gene mutation in human embryos*, 548 NATURE 413-19 (Aug. 24, 2017), available at <http://www.nature.com/nature/journal/v548/n7668/full/nature23305.html>.

<sup>60</sup> *Id.* at 416.

<sup>61</sup> *Id.*

<sup>62</sup> Puping Liang, et al., *CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes*, 6 PROTEIN & CELL 363 (Apr. 1, 2015), available at <http://link.springer.com/article/10.1007/s13238-015-0153-5>.

<sup>63</sup> *Id.*

<sup>64</sup> *Id.*

<sup>65</sup> Xiangjin Kang, et al., *Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated editing*, 33 J. ASSIST. REPROD. GENET. 581-88 (Apr. 6, 2016), available at <https://link.springer.com/article/10.1007%2Fs10815-016-0710-8>.

<sup>66</sup> *Id.*

controversy.<sup>67</sup> Scientists in the field have called for a voluntary worldwide moratorium on any application of CRISPR to the human germline.<sup>68</sup> However, discussion is needed about the potential risks and benefits of the various clinical applications of CRISPR.

### III. CURRENT LAWS REGULATING HGM IN THE UNITED STATES

#### A. *FDA Jurisdiction over HGM*

The FDA claims jurisdiction over HGM in the United States.<sup>69</sup> The FDA has jurisdiction over “drugs,”<sup>70</sup> medical “devices,”<sup>71</sup> and “biological products.”<sup>72</sup> In addition, it is the primary agency tasked with the review of applications of gene therapy.<sup>73</sup> Thus, one likely source of the FDA’s jurisdiction over HGM is that modified gametes or embryos may constitute “biological products.”<sup>74</sup> Alternatively, the FDA has the jurisdiction to regulate the use of “human cells or tissues that are intended for implantation . . . into a human,” which could include the modified embryo.<sup>75</sup> Some have challenged the scope of the FDA’s authority to regulate procedures that utilize advanced

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<sup>67</sup> See, e.g., G. Burningham, *We need to talk about human genetic engineering before it’s too late*, NEWSWEEK (Apr. 30, 2016),

<http://www.newsweek.com/human-genome-editing-crispr-454315>.

<sup>68</sup> Antonio Regalado, *Industry Body Calls for Gene-Editing Moratorium*, MIT TECH. REV. (Mar. 12, 2015),

<https://www.technologyreview.com/s/535846/industry-body-calls-for-gene-editing-moratorium/>.

<sup>69</sup> See Francis S. Collins, *Statement on NIH funding of research using gene-editing technologies in human embryos*, U.S. DEPT OF HEALTH & HUMAN SERVICES: NIH (April 28, 2015), <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos>.

<sup>70</sup> 21 U.S.C. § 321(g)(1).

<sup>71</sup> 21 U.S.C. § 321(h).

<sup>72</sup> 42 U.S.C. § 262(a).

<sup>73</sup> See *Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products*, 58 Fed. Reg. 53,248 (Oct. 14, 1993); see also Emily Marden & Dorothy Nelkin, *Displaced Agendas: Current Regulatory Strategies for Germline Gene Therapy*, 45 MCGILL L.J. 461, 473-74 (2000).

<sup>74</sup> See Elizabeth C. Price, *Does the FDA have authority to regulate human cloning?*, 11 HARV. J. LAW & TECH 619 (1998) (discussing the possible statutory basis for FDA authority over reproductive technologies, such as cloning).

<sup>75</sup> See 21 C.F.R. § 1271.3.

assisted reproduction technology (ART), such as cloning.<sup>76</sup> While it is interesting to consider the full scope of the FDA's authority to regulate HGM, such an analysis is beyond the scope of this paper.

As a result of the FDA's authority over HGM, premarket approval and/or licensing would be required to market any germline correction therapy.<sup>77</sup> As a necessary step in the process, an Investigational New Drug (IND) application must be filed with the FDA and the procedure must be subjected to rigorous clinical evaluation.<sup>78</sup> It has been proposed that the FDA should apply an additional level of scrutiny to HGM, ensuring safety for both the children born from the process as well as any of those children's offspring.<sup>79</sup> However, clinical investigation into the safety of HGM is currently impossible in the U.S. under the existing legal framework.<sup>80</sup>

### ***B. The 2017 Rider***

Human germline modification is currently banned in the United States, the result of a rider on the *Consolidated Appropriations Act of 2016* (2016 Act).<sup>81</sup> The rider first appeared in the House of Representatives' draft of the *Agriculture, Rural Development, FDA and Related Agencies Appropriations Act of 2016*.<sup>82</sup> This draft was later incorporated into the 2016 Act, which was signed into law on December 18, 2015.<sup>83</sup> Located in Division A, Title VII, section 749 of the 2016 Act, the rider reads as follows:

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<sup>76</sup> See Price, *supra* note 74; see also Marden, *supra* note 73 (briefly applying Price's analytical framework to FDA jurisdiction over HGM).

<sup>77</sup> See 58 Fed. Reg. 53,248.

<sup>78</sup> See 21 C.F.R. § 312.20 (requiring an IND application for both new drugs under 21 U.S.C. 355(i) and biological products under 42 U.S.C. 262(a)(3)).

<sup>79</sup> Niklaus H. Evitt, et al., *Human Germline CRIPSR-Cas Modification: Toward a Regulatory Framework*, 15 AM. J. BIOETHICS 25 (Dec. 2, 2015), available at <http://www.tandfonline.com/doi/full/10.1080/15265161.2015.1104160>.

<sup>80</sup> See I. Glenn Cohen & Eli Y. Adashi, *The FDA is prohibited from going germline*, 353 SCIENCE 545 (Aug. 5, 2016), available at <http://science.sciencemag.org/content/sci/353/6299/545.full.pdf>.

<sup>81</sup> Consolidated Appropriations Act, 2016, Pub. L. No. 114-13, 129 Stat. 2241, 2282 (2015).

<sup>82</sup> Consolidated Appropriations Act of 2016, H.R. 2029, 114th Cong. (2015), available at <https://www.congress.gov/bill/114th-congress/house-bill/2029> [hereinafter 2016 Act].

<sup>83</sup> *Id.*

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.<sup>84</sup>

The rider remained in place as part of the *Consolidated Appropriations Act of 2017*, located in Division A, Title VII, § 736 of the 2017 Act.<sup>85</sup> This same rider is currently attached to the Senate draft of the *Agriculture, Rural Development, FDA and Related Agencies Appropriations Act of 2018*, which will likely become part of the *Consolidated Appropriations Act of 2018*.<sup>86</sup> Thus, there is a considerable chance that the effects of this rider will perpetuate for at least another year.

### C. *Effect of the Rider*

The rider effectively prevents the FDA from evaluating the safety and efficacy of any clinical therapy that requires a heritable genetic modification of a human embryo.<sup>87</sup> As any treatment utilizing HGM necessarily results in a heritable genetic modification, these treatments are prohibited by the rider.<sup>88</sup> The rider also has the effect of precluding the development of MRT, which can result in an embryo with

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<sup>84</sup> Consolidated Appropriations Act, 2016, Pub. L. No. 114-13, § 749, 129 Stat. 2241, 2283 (2015).

<sup>85</sup> Consolidated Appropriations Act, 2017, Pub. L. No. 115-31, § 736, 131 Stat. 135 (2017) [hereinafter 2017 rider].

<sup>86</sup> The rider is now included as § 734 of the bill. *See* Making appropriations for Agriculture, Rural Development, Food and Drug Administration, and Related Agencies programs for the fiscal year ending September 30, 2018, and for other purposes, S. 1603, 115th Cong. § 734 (as reported by S. Comm. on Appropriations, July 20, 2017), available at <https://www.congress.gov/bill/115th-congress/senate-bill/1603/text>.

<sup>87</sup> *See* Cohen & Adashi, *supra* note 80.

<sup>88</sup> *See* Sara Reardon, *US Congress moves to block human-embryo editing*, NATURE (Jun. 25, 2015), <http://www.nature.com/news/us-congress-moves-to-block-human-embryo-editing-1.17858>.

alterations in its genome due to the incorporation of mitochondrial DNA from the donor.<sup>89</sup>

This blanket prohibition on HGM and MRT is achieved by blocking the FDA from reviewing or acknowledging the receipt of an IND Application.<sup>90</sup> An IND or application for marketing approval can be obtained either by an application 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)).<sup>91</sup> By blocking both of these paths, the rider effectively precludes the FDA review required to initiate a clinical trial.

By precluding the FDA's review of IND applications through either the "new drug" or "biological product" routes, the rider prevents scientists and clinicians from accurately assessing the safety and efficacy of HGM therapies.<sup>92</sup> Although not technically a "ban" on HGM, the rider is sufficiently restrictive to preclude the clinical-stage research that is required to obtain either a new drug approval or a biological license.<sup>93</sup> Without either of these, anyone attempting to practice HGM in the U.S. would be subject to severe civil penalties and/or criminal sanctions.<sup>94</sup> Thus, the rider is a complete and effective deterrent.

#### ***D. Additional Sources of Regulating in the United States***

Although HGM is primarily regulated by the rider, there are several additional layers of regulation that are relevant to HGM. First, the NIH has some influence over the development of HGM through its ability to appropriate funding.<sup>95</sup> As opposed to the FDA, the NIH does consider moral and ethical considerations

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<sup>89</sup> See Cohen & Adashi, *supra* note 80.

<sup>90</sup> *Id.* (citing National Academies of Sciences, Engineering, and Medicine, *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations* (National Academies, Washington, DC, 2016)).

<sup>91</sup> See 21 C.F.R. § 312.120 (2017).

<sup>92</sup> See Cohen & Adashi, *supra* note 80.

<sup>93</sup> See *id.*

<sup>94</sup> See, e.g., 42 U.S.C. § 262(f) (2017) (violations of 42 U.S.C. § 262(a)(3) (2017) are misdemeanors punishable by fines up to \$500 and/or imprisonment up to one year); 42 U.S.C. § 262(d)(2) (2017) (civil penalties of up to \$100,000 per day for biological products that are deemed by the Secretary to be a public health hazard); 21 U.S.C. § 333(a) & 333(e) (2017) (violations of 21 U.S.C. § 355(i) may be misdemeanors or felonies); 21 U.S.C. § 333(f) (2017) (civil penalties for violations pertaining to medical devices).

<sup>95</sup> Collins, *supra* note 69.

when allocating its funds.<sup>96</sup> Currently, federal funds may not be used for research on HGM.<sup>97</sup> The NIH guidelines indicate that the institute “will not at present entertain proposals for germline alteration,”<sup>98</sup> precluding any NIH funding for this work.<sup>99</sup>

Second, the Dickey-Wicker Amendment (DWA) prohibits federal funding for most embryonic research.<sup>100</sup> Specifically, the DWA prohibits the use of federal funds for: “(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death.”<sup>101</sup> As the clinical development of HGM would necessarily entail the creation of human embryos for research purposes, the DWA would prevent federal funds from being used to develop this technology.<sup>102</sup> However, these policies have no effect on the legality of privately-funded research.<sup>103</sup>

#### IV. INTERNATIONAL LAWS REGULATING HGM

The current status of international HGM regulation is a mosaic of laws, guidelines, and recommendations.<sup>104</sup> A study from 2014 found that 29 countries had a statutory ban on germline editing.<sup>105</sup> However, in some of those countries with a statutory

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<sup>96</sup> See, e.g., *Guiding Principles for Ethical Research*, NAT'L INSTITUTES OF HEALTH, GUIDING PRINCIPLES FOR ETHICAL RESEARCH, <https://www.nih.gov/health-information/nih-clinical-research-trials-you/guiding-principles-ethical-research>.

<sup>97</sup> Collins, *supra* note 69.

<sup>98</sup> *Id.* at 51.

<sup>99</sup> The Collins statement does not discuss the modification of human gametes for research purposes. It is possible that such research may still be eligible for NIH funding.

<sup>100</sup> See Erik Parens & Lori P. Knowles, *Reprogenetics and Public Policy: Reflections and Recommendations*, HASTINGS CTR. REP. S11, S13 (2003), available at [http://www.thehastingscenter.org/wp-content/uploads/reprogenetics\\_and\\_public\\_policy.pdf](http://www.thehastingscenter.org/wp-content/uploads/reprogenetics_and_public_policy.pdf).

<sup>101</sup> Consolidated Appropriations Act, 2017, Pub. L. No. 115-31, § 508, 131 Stat. 135 (2017).

<sup>102</sup> Collins, *supra* note 69.

<sup>103</sup> See Parens & Knowles, *supra* note 100.

<sup>104</sup> See Heidi Ledford, *Where in the World Could the First CRISPR Baby be Born?*, 526 NATURE 310, 311 (Oct. 15, 2015), available at <http://www.nature.com/news/where-in-the-world-could-the-first-crispr-baby-be-born-1.18542>; see also Sara Reardon, *Global summit reveals divergent views on human gene editing*, 528 NATURE 173 (Dec. 8, 2015), available at <http://www.nature.com/news/global-summit-reveals-divergent-views-on-human-gene-editing-1.18971>.

<sup>105</sup> Motoko Araki & Tetsuya Ishii, *International regulatory landscape and integration of corrective genome editing into in vitro fertilization*, 12 REPROD.

ban, such as in Belgium, Bulgaria, Canada, and Sweden, there may be ambiguity as to what is proscribed by these laws.<sup>106</sup> For example, it is ambiguous whether a germline correction that resulted in a wild-type gene would actually be banned under the laws of these countries.<sup>107</sup> Moreover, the guidelines that ban HGM in China, India, Ireland, and Japan may not be strictly enforced.<sup>108</sup> Of the legality of the procedure in ten other countries, nine were also ambiguous.<sup>109</sup> In the absence of a clear worldwide consensus, this fluid patchwork of international regulation will probably leave sufficient room for HGM research to continue somewhere in the world.<sup>110</sup> Two of the countries that may be most likely to influence HGM regulation in the US are the United Kingdom and China.

### A. *The United Kingdom*

The U.K. has one of the most comprehensive regulatory systems in the world for assessing the scientific and medical merits of new fertilization technology. In the United Kingdom, IVF and other more advanced ART procedures are under the regulation of the Human Fertilization and Embryology Authority (HFEA).<sup>111</sup> The HFEA is an independent regulatory body that oversees research and fertility treatments that utilize gametes and embryos.<sup>112</sup> The HFEA was created in 1990 with the passage of the Human Fertilisation and Embryology (HFE) Act of 1990, which was recently amended in 2008.<sup>113</sup>

The U.K. is the most progressive country in the world with respect to the use of MRT; in fact, clinics in the U.K. may begin performing MRT as early as this year. The HFEA recently announced that authorized clinics may apply to the HFEA for

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BIOL. ENDOCRINOL. 108, (Nov. 24, 2014), available at <https://rbej.biomedcentral.com/articles/10.1186/1477-7827-12-108>.

<sup>106</sup> See Ishii, *supra* note 36.

<sup>107</sup> *Id.*

<sup>108</sup> *Id.*

<sup>109</sup> *Id.*

<sup>110</sup> Lauren F. Friedman, *These are the countries where it's 'legal' to edit human embryos (hint: the US is one)*, BUSINESS INSIDER (Apr. 23, 2015, 2:15 PM), <http://www.businessinsider.com/china-edited-human-genome-laws-2015-4>.

<sup>111</sup> See HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY; <http://www.hfea.gov.uk> (last visited Dec. 21, 2017).

<sup>112</sup> See *id.*

<sup>113</sup> See *IVF the Law*, HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY (July 25, 2013), <http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/134.html>.

license to treat patients using MRT.<sup>114</sup> Parliament passed regulations permitting the use of MRT in February 2015 and the regulatory framework was put into place in October of 2016.<sup>115</sup> However, the HFEA delayed their announcement until after they received the official recommendations of the appointed expert panel. The scientific panel recommended the use of MRT “as a risk reduction treatment for carefully selected patients.”<sup>116</sup> The panel also recommended that the procedures be coupled with prenatal testing and restricted to patients that do not have viable alternatives, such as PGD.<sup>117</sup>

Obtaining authorization to treat a patient with MRT requires a two-step process. First, a clinic must be reviewed by the HFEA’s License Committee, who assess the clinic’s skill, experience, and facilities.<sup>118</sup> Next, the clinics must apply to the Statutory Approvals Committee (SAC) for authorization to treat any individual patient.<sup>119</sup> After approval by both the HFEA and the SAC, the clinics may perform MRT on the authorized patient using either Maternal Spindle Transfer or Protonuclear Transfer techniques.<sup>120</sup>

The regulation of HGM with CRISPR/Cas9 is far more stringent than those governing MRT. As of early 2016, only one molecular biologist, Kathy Niakan, has been granted permission to perform gene editing in human embryos.<sup>121</sup> However, the embryo must be destroyed within 14 days and no embryo may be implanted into a woman.<sup>122</sup> Moreover, no research can be undertaken without explicit approval from the HFEA ethics

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<sup>114</sup> See *HFEA permits cautious use of mitochondrial donation in treatment, following advice from scientific experts*, HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY (Dec. 15, 2016), <http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/10563.html>.

<sup>115</sup> *Id.*

<sup>116</sup> See *UK’s independent expert panel recommends “cautious adoption” of mitochondrial donation in treatment*, HUMAN FERTILISATION & EMBRYOLOGY AUTHORITY (Dec. 15, 2016), <http://hfeaarchive.uksouth.cloudapp.azure.com/www.hfea.gov.uk/10559.html>.

<sup>117</sup> *Id.*

<sup>118</sup> *Id.*

<sup>119</sup> *Id.*

<sup>120</sup> *Id.*

<sup>121</sup> See *HFEA approval for new “gene editing” techniques*, FRANCIS CRICK INSTITUTE (Feb. 1, 2016), <https://www.crick.ac.uk/news/science-news/2016/02/01/hfea-decision/>.

<sup>122</sup> See Fiona MacDonald, *10 things you need to know about the UK allowing genetic modification of human embryos*, SCIENCE ALERT (Feb. 2, 2016), <http://www.sciencealert.com/10-things-you-need-to-know-about-the-uk-s-decision-to-allow-genetic-modification-of-human-embryos>.

committee.<sup>123</sup> Although the use of HGM for reproduction is prohibited in the U.K., their recent approval of MRT indicates that the U.K. may be among the first nations to approve of therapeutic applications of HGM.

## **B. China**

China was the first country to report the editing of the human germline.<sup>124</sup> Accordingly, the regulation of HGM in China has become a hot topic of debate in the past two years.<sup>125</sup> Many in the West have accused the Chinese of being lackadaisical with enforcement of regulations against HGM.<sup>126</sup> However, others argue that China's ethical stance on the issue is not substantially different than the United States or Europe.<sup>127</sup> For example, Chinese guidelines on HGM stipulate that "gene manipulation on human gamete, zygote and embryo for the purpose of reproduction is banned."<sup>128</sup>

In China, HGM is regulated by a detailed regulatory framework.<sup>129</sup> Regulations promulgated by China's Ministry of Health<sup>130</sup> include the *Ethical Principles for ART and the Human Sperm Bank* of 2003, the *Ethical Principles on ART* of 2001, and *The Interim procedures for Human Genetic Resources Management* of 1998.<sup>131</sup> The State Council has published a preliminary draft of *The Regulation of the Human Genetic Resources*, which will eventually replace the 1998 interim

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<sup>123</sup> *Id.*

<sup>124</sup> See Liang, et al., *supra* note 62.

<sup>125</sup> See, e.g., Sarah Knapton, *China shocks world by genetically engineering human embryos*, THE TELEGRAPH (Apr. 23, 2015, 2:36 PM), <http://www.telegraph.co.uk/news/science/11558305/China-shocks-world-by-genetically-engineering-human-embryos.html>; G. Owen Schaefer, *China may be the future of genetic enhancement*, BBC FUTURE (Aug. 8, 2016), <http://www.bbc.com/future/story/20160804-china-may-be-the-future-of-genetic-enhancement>.

<sup>126</sup> See, e.g., Rebecca Taylor, *Mad Scientists in China Attempt to Create Genetically-Modified Babies, It Didn't Go Well*, LIFENEWS.COM (Apr. 24, 2015), <http://www.lifenews.com/2015/04/24/mad-scientists-in-china-attempt-to-create-genetically-modified-babies-it-didnt-go-well/>.

<sup>127</sup> See Xiaomei Zhai, et al., *No ethical divide between china and the West in human embryo research*, 16 DEVELOPING WORLD BIOETHICS 116 (Jan. 21, 2016), available at <http://onlinelibrary.wiley.com/doi/10.1111/dewb.12108/full>.

<sup>128</sup> *Id.* at 118.

<sup>129</sup> See *id.*

<sup>130</sup> The MoH is now known as the National Health and Family Planning Commission. *Id.*

<sup>131</sup> See Zhai, *supra* note 126, at 118 (and references therein).

procedures.<sup>132</sup> The net effect of these regulations is a system very similar to those of many western countries, requiring informed consent by participants and providing an absolute ban on the use of HGM in reproduction.<sup>133</sup> Nevertheless, the current law in China amounts to non-binding guidelines and as a result, development of HGM might continue in the future.<sup>134</sup>

## V. *Statement of the Issue*

The United States should amend the rider on the Consolidated Appropriations Act of 2019 (2019 Act) to create an exception to its current prohibition of HGM that would allow the FDA to receive and review applications pertaining to the use of HGM for the treatment of heritable monogenic diseases where the edit would result in a wild-type gene. Such an exception would provide a number of benefits, while minimizing the current safety and ethical concerns surrounding HGM. Moreover, this would set a precedent that would have a positive impact on the international regulation of HGM, leading other countries to seriously consider legalization and regulation. Although a similar exception should also be made to facilitate the practice of MRT, a full discussion of the policy implications leading to this suggestion are beyond the scope of this paper.

## VI. ANALYSIS

Unless and until the United States is prepared to adopt a formal legislative scheme to regulate HGM, there are three main legislative options available: (1) completely remove the rider from the 2019 Act; (2) leave the intact rider in place for the foreseeable future; or (3) keep the rider in place and adopt a specific exception or exceptions, such as those that would allow the FDA to receive and review IND applications for the use of HGM to treat specific monogenic diseases. The Author encourages the pursuit of the third option for reasons that are discussed in the balance of this article.

### A. *Rationale Behind the Rider*

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<sup>132</sup> *Id.*

<sup>133</sup> *Id.*

<sup>134</sup> *See* Ishii, *supra* note 36.

The House of Representatives Committee Report, which accompanied the 2016 Act, outlined the Congressional concerns that led to the rider's adoption:

The Committee understands the potential benefits to society in the genetic modification of living organisms. However, researchers do not yet fully understand all the possible side effects of editing the genes of a human embryo. Editing of the human germ line may involve serious and unquantifiable safety and ethical issues. Federal and non-Federal organizations such as the National Academy of Sciences and National Academy of Medicine will soon engage in more extensive scientific analysis of the potential risks of genome editing and a broader public discussion of the societal and ethical implications of this technique. In accordance with the current policy at the National Institutes of Health, the Committee includes bill language that places a prohibition on the FDA's use of funds involving the genetic modification of a human embryo. The Committee continues to support a wide range of innovations in biomedical research, but will do so in a fashion that reflects well-established scientific and ethical principles.<sup>135</sup>

From the text above, it is evident that the two predominant Congressional concerns that led to the rider were those of safety and ethics. Moreover, this passage indicates that future policies on the subject must reflect "well-established scientific and ethical principles."<sup>136</sup>

Statements made during the hearing on "The Science and Ethics of Genetically Engineered Human DNA" may shed some light on these Congressional concerns.<sup>137</sup> In the Statement of Lamar Smith (R-TX), several points were raised.<sup>138</sup> First, there is

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<sup>135</sup> See *Report of the House Committee on Appropriations, Together with minority views* (to accompany H.R. 3049) (2015), <https://www.congress.gov/114/crpt/hrpt205/CRPT-114hrpt205.pdf>.

<sup>136</sup> *Id.*

<sup>137</sup> *The Science and Ethics of Genetically Engineered Human DNA: Hearing Before the H. Comm. on Science, Space, and Technology*, 114 Cong. 8-9 (2015) (statement of Lamar Smith, Chairman of the Subcomm. on Research and Technology), available at <http://bit.ly/HouseSciCtte> [hereinafter Lamar Smith].

<sup>138</sup> *Id.*

a need “to prevent dangerous abuses and unintended consequences” that might result from the inappropriate use of this technology.<sup>139</sup> Second, the U.S. should take the lead in the scientific development and ethical application of genetic engineering.<sup>140</sup> Finally, our current technological understanding of the CRISPR/Cas9 system needs to be refined so that patients can be assured safe and ethical treatment.<sup>141</sup>

Some commenters contend that the major—if not only—Congressional concern is that of ethics, not safety.<sup>142</sup> For one, the FDA already thoroughly investigates the safety of any procedure during the IND application and subsequent clinical trials.<sup>143</sup> Before any clinical trial commences, an applicant must prove that the proposed drug is likely to be safe and effective by providing data from extensive preclinical testing.<sup>144</sup> During clinical evaluation, the FDA requires standardized protocols,<sup>145</sup> detailed records,<sup>146</sup> safety reports,<sup>147</sup> and oversight by the Institutional Review Board.<sup>148</sup> Furthermore, if at any point during clinical evaluation, the process does not appear safe, they may stop the trial by placing it on “clinical hold.”<sup>149</sup> Although inheritable germline alterations may be unique insofar as they effect the offspring of those who have undergone the therapy,<sup>150</sup> the FDA may already be well-suited to evaluate applications for

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<sup>139</sup> *Id.* at 8.

<sup>140</sup> *Id.* (noting that “the United States can and should provide scientific and moral leadership” in the field of HGM and “must take the lead in reviewing new and innovative areas of science, such as genetically engineered DNA.”)

<sup>141</sup> *Id.* (emphasizing the “need to better understand the technology and procedures being used so that we can ensure patients are treated in the safest and most ethical manner possible”).

<sup>142</sup> *See, e.g.,* Regalado, *supra* note 57 (quoting Professor Hank Greely as saying, “I would not want to use safety as an excuse for a non-safety-based ban,” when referring to the rider).

<sup>143</sup> *See generally* U.S. DEPT. OF HEALTH & HUMAN SERV., SAFETY REPORTING REQUIREMENTS FOR INDs AND BA/BE STUDIES: GUIDANCE FOR INDUSTRY AND INVESTIGATORS (2012), *available at* <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf>.

<sup>144</sup> Food & Drugs Act, 21 U.S.C. § 355(i)(1)(A) (2015) (requiring “the submission to the Secretary before any clinical testing of a new drug is undertaken, of reports . . . preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing”).

<sup>145</sup> 21 C.F.R. § 312.23(a)(6) (2017).

<sup>146</sup> 21 C.F.R. §§ 312.57, 312.62, 312.64.

<sup>147</sup> 21 C.F.R. § 312.32.

<sup>148</sup> 21 C.F.R. § 312.66.

<sup>149</sup> 21 U.S.C. § 355(i)(3)(B)(i).

<sup>150</sup> Edward Lanphier, et al., *Don’t edit the human germ line*, 519 NATURE 410, 410-11 (Mar. 26, 2015), *available at* <http://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111>.

therapeutic HGM by applying enhanced scrutiny to its existing IND procedure.<sup>151</sup>

While evaluation of safety is squarely within the FDA's jurisdiction, ethical or moral review is not.<sup>152</sup> Congress has never before used the FDA to enforce a prohibition on germline modification.<sup>153</sup> By precluding FDA review concerning the safety and efficacy of any potential HGM applications, lawmakers have demonstrated that they consider the ethical implications of HGM to be the overriding concern. Interestingly, the rider was passed only a few weeks after a summit, where the committee highlighted the need to further evaluate the safety and ethics of germline modification, discussed in greater detail below.<sup>154</sup> It is possible that the intention of the rider is to ensure a sound ethical evaluation of HGM before proceeding to the assessment of its safety.

These considerations of safety and ethics, as they apply to each potential option, are considered below, with an emphasis on relevant ethical issues. The potential effect of each policy on the leadership of the U.S. in the field of HGM is also discussed.

## ***B. Evaluation of Potential Policy Options***

### ***1. Refusal to Renew the Rider***

Congress could refuse to renew the rider for the 2019 Act. This would lift the ban on FDA receipt and review of any IND applications for the use of HGM. Importantly, this would potentially allow the clinical evaluation of HGM for both therapeutic uses and non-therapeutic enhancement procedures. Given the infancy of the technology, as well as the current widespread disapproval of non-therapeutic applications of HGM, failure to renew the rider is highly unlikely. Moreover, it may be an ethically undesirable outcome that could lead to severe unintended consequences for the industry.

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<sup>151</sup> Evitt, *supra* note 79.

<sup>152</sup> See 21 U.S.C. § 301 et seq.; Fed. Reg. 53.248, *supra* note 73; PRESIDENT'S COUNCIL ON BIOETHICS (U.S.), REPRODUCTION & RESPONSIBILITY: REPORT ON THE REGULATION OF NEW BIOTECHNOLOGIES xii (2004), available at <https://repository.library.georgetown.edu/handle/10822/559381>.

<sup>153</sup> Cohen & Adashi, *supra* note 80.

<sup>154</sup> Steve Olson, et al., *International Summit on Human Gene Editing: A Global Discussion*, NAT'L ACAD. PRESS (Dec. 3, 2015), available at <http://nationalacademies.org/gene-editing/Gene-Edit-Summit/>.

a. *Plausibility*

Complete removal of the rider may not be popular given the current status of public opinion concerning the propriety of HGM.<sup>155</sup> A recent Pew Research Center poll indicated that a significantly portion of the U.S. public is worried about the prospect of HGM (68%), and a much smaller population is enthusiastic about the subject (49%).<sup>156</sup> As the public is significantly more adverse to the idea of genetic enhancements than it is germline therapy, any policy that fails to draw a distinction between therapeutic and non-therapeutic enhancement is not likely to be received with public approval.<sup>157</sup> Lack of public support among Congressional constituencies may translate to less Congressional votes against renewing the rider.

Any attempt to repeal the rider in its entirety is particularly unlikely to succeed because it would theoretically enable FDA review of HGM for non-therapeutic enhancements. The most zealous critiques of HGM pertain to its use in non-therapeutic enhancement and the possibility of eugenic applications.<sup>158</sup> Even among commenters who acknowledge the potential utility of corrective germline therapy, many caution against therapeutic use because of fears that it may lead to a slippery slope resulting in non-therapeutic or eugenic applications.<sup>159</sup> Any action that opens up the possibility for genetic enhancement is not likely to be well received.

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<sup>155</sup> Reardon, *supra* note 104.

<sup>156</sup> Cary Funk, et al., *U.S. Public Wary of Biomedical Technologies to 'Enhance' Human Abilities – 2. U.S. public opinion on the future use of gene editing*, PEW RES. CTR. REP. (Jul. 26, 2016), available at <http://www.pewinternet.org/2016/07/26/u-s-public-opinion-on-the-future-use-of-gene-editing/>.

<sup>157</sup> See *id.* (demonstrating that only 15% of adults believed enhancing intelligence was an appropriate use for HGM, compared to 46% for reducing the risk of serious diseases).

<sup>158</sup> See, e.g., Robert Pollack, *Eugenics lurk in the shadow of CRISPR*, 348 SCIENCE 871 (May 22, 2015), available at <http://science.sciencemag.org/content/348/6237/871.1>.

<sup>159</sup> See, e.g., Nathaniel Comfort, *Can We Cure Genetic Diseases Without Slipping into Eugenics?*, NATION (Jul. 16, 2015), available at <https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/>; John Harris & Marcy Darnovsky, *Pro and Con: Should Gene Editing Be Performed on Human Embryos?*, NAT'L GEOGRAPHIC (Aug. 2016), <http://www.nationalgeographic.com/magazine/2016/08/human-gene-editing-pro-con-opinions/>.

b. *Safety and Ethical Implications*

Nor is it necessarily desirable to permit the application of HGM to non-therapeutic enhancement, as such application raises significant ethical concerns. While supporters of HGM for enhancement offer a variety of arguments in favor of the practice,<sup>160</sup> such practices raise deep-rooted concerns about the close relationship between genetic enhancement and eugenics.<sup>161</sup> The eugenics movement has been roundly criticized for promoting a bigoted concept of genetic superiority based on race, class, religious, and sexual prejudices.<sup>162</sup> The American eugenic movement led to the forced sterilization of over 64,000 people<sup>163</sup> and may have contributed to the use of African-American men for the Tuskegee study of untreated syphilis.<sup>164</sup> Moreover, the eugenic practices of Nazi Germany were modeled at least in part by eugenics laws in U.S. states, particularly those in California.<sup>165</sup> Given the potential social harm that could result from the eugenic applications of HGM, use of this technology requires exceptionally strong validation, which is lacking in the case of non-therapeutic uses.

Some commentators have argued that the “new eugenics” of the 20th Century is different than the “old eugenics” of historic infamy and they highlight several distinctions between the

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<sup>160</sup> See, e.g., NICHOLAS AGAR, *LIBERAL EUGENICS: IN DEFENSE OF HUMAN ENHANCEMENT* (2008) (arguing that that it is immoral to deprive parents of the choice to enhance their children); Carl Shulman & Nick Bostrom, *Embryo Selection for Cognitive Enhancement: Curiosity or Game-changer?*, 5 *GLOBAL POLICY* 1, 85-92 (2014), available at <http://www.nickbostrom.com/papers/embryo.pdf> (noting that that society could be benefitted by enhanced individuals through innovation); John Harris, *Why human gene editing must not be stopped*, *GUARDIAN* (Dec. 2, 2015), <https://www.theguardian.com/science/2015/dec/02/why-human-gene-editing-must-not-be-stopped>.

<sup>161</sup> See, e.g., Pollack, *supra* note 158; Anna Zaret, *Editing Embryos: Considering Restrictions on Genetically Engineering Humans*, 67 *HASTINGS L.J.* 1805 (July 2016).

<sup>162</sup> See Martin S. Pernick, *Eugenics and Public Health in American History*, 87 *AMER. J. PUB. HEALTH* 1767, 1770 (Nov. 1997), available at <http://ajph.aphapublications.org/doi/pdf/10.2105/AJPH.87.11.1767>.

<sup>163</sup> See Teryn Bouche & Laura Rivard, *America’s Hidden History: The Eugenics Movement*, *NATURE EDUC.* (Sept. 18, 2014), <http://www.nature.com/scitable/forums/genetics-generation/america-s-hidden-history-the-eugenics-movement-123919444>.

<sup>164</sup> See Allan Brandt, *Racism and Research: The Case of the Tuskegee Syphilis Study*, in *SICKNESS AND HEALTH IN AMERICA*, 331, 331-43 (Judith Leavitt & Ronald Numbers eds., 2nd ed. 1985).

<sup>165</sup> See EDWIN BLACK, *WAR AGAINST THE WEAK: EUGENICS AND AMERICA’S CAMPAIGN TO CREATE A MASTER RACE* (2003).

two.<sup>166</sup> First, many of the tragedies of the old eugenic movement, such as forced sterilizations of convicted criminals and people with mental disabilities, were the result of government control.<sup>167</sup> Enhancement applications of HGM would be guided by the choices of individual parents, not government mandate, thereby reducing the risk that such events would be repeated.<sup>168</sup> Second, society now has a more advanced understanding of the basic biology of heredity than it did in the early 19th century.<sup>169</sup>

Opponents of this viewpoint argue this “new eugenics” of genetic choice would lead to the same results as the “old eugenics.”<sup>170</sup> To begin with, there are several forces that may undermine a parent’s autonomy in deciding to enhance their children.<sup>171</sup> In some situations, there may be community pressure on a parent to obtain a specific enhancement for their child.<sup>172</sup> Thus, the individual autonomy used to validate the “new eugenics” may not be as clear of a distinction as its proponents suggest.

There are also significant safety concerns that weigh against the use of HGM for enhancement. Most importantly, the traits that are most desirable to enhance are too complex to achieve safe editing in human embryos, even if the technology evolves to the point that prevention of monogenic diseases becomes facile and safe. Traits such as height or intelligence are controlled by potentially hundreds of genes.<sup>173</sup> With every additional edit, the chances of an off-target mutation grow exponentially, increasing the probability of a serious adverse

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<sup>166</sup> See, e.g., A. Buchanan, *Choosing Who Will Be Disabled: Genetic Intervention and the Morality of Inclusion*, 13 SOCIAL PHIL. & POLICY 18, 18-19 (1996); J. HARRIS, ENHANCING EVOLUTION: THE ETHICAL CASE FOR MAKING BETTER PEOPLE (2007).

<sup>167</sup> See Eesha Pandit, *America’s secret history of forced sterilization: Remembering a disturbing and not-so-distant past*, SALON (Jan. 29, 2106), [http://www.salon.com/2016/01/29/americas\\_secret\\_history\\_of\\_forced\\_sterilization\\_remembering\\_a\\_disturbing\\_and\\_not\\_so\\_distant\\_past/](http://www.salon.com/2016/01/29/americas_secret_history_of_forced_sterilization_remembering_a_disturbing_and_not_so_distant_past/).

<sup>168</sup> See Agar, *supra* note 160.

<sup>169</sup> See Felipe E. Vizcarrondo, *Human enhancement: The new eugenics*, 81 LINACRE Q. 239, 240 (Aug. 2014), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4135459/>.

<sup>170</sup> See Robert Sparrow, *A Not-So-New Eugenics: Harris and Savulescu on Human Enhancement*, 41 HASTINGS CTR. REP. 32 (Jan. 2011), available at <http://onlinelibrary.wiley.com/doi/10.1002/j.1552-146X.2011.tb00098.x/abstract?wollURL=/doi/10.1002/j.1552-146X.2011.tb00098.x/abstract&regionCode=US-CA&identityKey=7dcdcb83-d981-423c-8aa4-fd9936536702>.

<sup>171</sup> *Id.* at 37-38.

<sup>172</sup> *Id.* at 38-39.

<sup>173</sup> See Frazer, *supra* note 20.

event. With the technology still in its infancy, attempting such experiments would constitute an unacceptable safety risk with a high probability of treatment leading to an adverse event.

## 2. *Leaving the Rider Intact for Future Years*

The second option is to leave the language of the current rider intact for the 2019 Act. Absent significant lobbying effort on behalf of the biotech industry, this may be the most likely outcome for the foreseeable future. Similar riders have carried substantial legislative inertia in the past, eventually becoming the “new normal.” However, significant harm may result from such a course because it may prevent the development of life-saving therapies.

### a. *Plausibility*

Riders pertaining to reproductive choice have exhibited striking longevity.<sup>174</sup> For example, the DWA has been in effect for twenty years.<sup>175</sup> The DWA was originally attached to an appropriations bill for the Department of Labor, Health and Human Services and later became part of the Continuing Resolution for Fiscal Year 1996.<sup>176</sup> In addition, the Hyde Amendment, which restricts the use of federal funds to pay for abortion services, has been law for over four decades.<sup>177</sup> The Hyde Amendment was originally attached to the annual appropriations bill in 1976.<sup>178</sup> Both of these examples illustrate the fact that riders governing reproductive health have considerable long-term staying power. If a concerted effort is not made to change the

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<sup>174</sup> See Cohen & Adashi, *supra* note 80.

<sup>175</sup> See Eli Y. Adashi & I. Glenn Cohen, *Selective Regrets: The “Dickey Amendments” 20 Years Later*, JAMA F. (Nov. 5, 2015), <https://newsatjama.jama.com/2015/11/05/jama-forum-selective-regrets-the-dickey-amendments-20-years-later/>.

<sup>176</sup> *Id.*

<sup>177</sup> See *Access Denied: Origins of the Hyde Amendment and other restrictions on public funding for abortion*, ACLU (last visited Dec. 21, 2017), <https://www.aclu.org/other/access-denied-origins-hyde-amendment-and-other-restrictions-public-funding-abortion>; see also Destiny Lopez, *The Hyde Amendment Has Been Hurting Women for 40 Years, But It’s Days Are Numbered*, COSMOPOLITAN (Sept. 23, 2016), <http://www.cosmopolitan.com/politics/a3621396/hyde-amendment>.

<sup>178</sup> See Marlene Gerber Fried, *The Hyde Amendment: 30 Years of Violating Women’s Rights*, CENTER FOR AMERICAN PROGRESS (Oct. 6, 2006, 9:00 AM), <https://www.americanprogress.org/issues/women/news/2006/10/06/2243/the-hyde-amendment-30-years-of-violating-womens-rights/>.

current rider, the blanket prohibition on HGM could continue for decades to come.

*b. Safety and Ethical Implications*

This path of least resistance is not without its own risks. The longer the rider remains in place, the more difficult it may be to repeal, as it becomes the “new normal.”<sup>179</sup> If this broad prohibition remains in place for too long, it may have the unintended effects of (1) chilling important therapeutic research; (2) causing the U.S. to forfeit its place as the world leader in the scientific and ethical debate; and (3) preventing potential parents from obtaining access to HGM for the treatment of debilitating genetic diseases.

First, the rider may have the effect of chilling necessary research and development on therapeutic gene editing in the U.S. Long-term riders have already produced unfortunate consequences for the scientific community.<sup>180</sup> For example, the DWA was present on the appropriations bill in 2009, which President Obama signed just two days after lifting President Bush’s executive order banning federal funding for stem cell research.<sup>181</sup> In 2010, the DWA was used to obtain a federal injunction against federally-funded stem cell research that had been approved by President Obama’s executive order.<sup>182</sup> The injunction was overturned the next year by the Court of Appeals for the District of Columbia.<sup>183</sup> Nevertheless, the uncertainty caused by the temporary injunction disrupted the field of stem

<sup>179</sup> See Cohen & Adashi, *supra* note 80; see also Eli Y. Adashi & I. Glenn Cohen, *Reproductive Freedom and the 2012 Presidential Election*, JAMA F (Oct. 11, 2012), <https://newsatjama.jama.com/2012/10/11/jama-forum-reproductive-freedom-and-the-2012-presidential-election/>.

<sup>180</sup> Aaron D. Levine, *Policy Uncertainty and the Conduct of Stem Cell Research*, 8 CELL STEM CELL 132, 132 (Feb. 2011), available at <http://www.sciencedirect.com/science/article/pii/S1934590911000038>; see also Sarah Rodriguez, et al., *An Obscure Rider Obstructing Science: The Conflation of Parthenotes with Embryos in the Dickey-Wicker Amendment*, 11 AMER. J. BIOETHICS 20, 20-21 (Mar. 10, 2011), available at <http://www.tandfonline.com/doi/abs/10.1080/15265161.2010.546472>.

<sup>181</sup> *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells*, Executive Order 13505, 74 Fed. Reg. 10667 (Mar. 9, 2009), available at <http://edocket.access.gpo.gov/2009/pdf/E9-5441.pdf>; see also Terrence P. Jeffery, *Obama Signs Law Banning Federal Embryo Research Two Days After Signing Executive Order to OK It*, CNSNEWS.COM (Mar. 12, 2009, 5:04 PM), <http://www.cnsnews.com/news/article/obama-signs-law-banning-federal-embryo-research-two-days-after-signing-executive-order>.

<sup>182</sup> *Sherley v. Sebelius*, 704 F. Supp. 2d 63 (D.D.C. 2010).

<sup>183</sup> *Sherley v. Sebelius*, 644 F.3d 388 (D.C. Cir. 2011).

cell research, leading to a chilling effect on research and the loss of valuable resources.<sup>184</sup> To avoid similar uncertainty in the policy around HGM, it would be prudent to amend the current rider before it leads to a similar result.

Second, the rider's continued presence may prevent the U.S. from "provid[ing] scientific and moral leadership" in the field, thereby impeding another Congressional objective.<sup>185</sup> Some have already argued that the current regulatory framework puts the U.S. at risk of falling behind in the development of gene therapy.<sup>186</sup> As of April 2016, experiments utilizing CRISPR/Cas9 on human embryos had either been approved or already performed in China, Sweden, and the United Kingdom.<sup>187</sup> More experiments are likely to be approved in the near future, causing the U.S. to lag behind in the research and development of HGM. Falling behind on the scientific development of HGM in the long term may negatively affect our legitimacy in the international community, undermining our leadership role in important ethical and scientific discussions.

Third and most importantly, failure to amend the rider may prevent parents from having access to potentially life-saving treatment, creating unnecessary suffering and increasing the financial burden on the healthcare system. The WHO indicates that "[t]he global prevalence of all single gene diseases at birth is approximately 10/1,000."<sup>188</sup> It is estimated that monogenic diseases affect up to 13 million people in the U.S., causing nearly one-fifth of infant mortality.<sup>189</sup> Many of the thousands of monogenic diseases lead to severe physiological impairment or early death.<sup>190</sup> Prevention of these diseases using HGM could prevent suffering for those afflicted as well as their family members.

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<sup>184</sup> See Alla Katsnelson, *US court suspends research on human embryonic stem cells*, NATURE (Aug. 25, 2010), <http://www.nature.com/news/2010/100824/full/news.2010.428.html>.

<sup>185</sup> *Id.*

<sup>186</sup> Alex Pearlman, *Scientists Argue the US Ban on Human Gene Editing Will Leave It Behind*, MOTHERBOARD (August 4, 2016, 11:02 AM), <http://motherboard.vice.com/read/scientists-argue-the-us-ban-on-human-gene-editing-will-leave-it-behind>.

<sup>187</sup> Ewen Callaway, *Gene-editing research in human embryos gains momentum*, 532 NATURE 289, 289-90 (Apr. 19, 2016), available at <http://www.nature.com/news/gene-editing-research-in-human-embryos-gains-momentum-1.19767>.

<sup>188</sup> *Genomic resource centre: Genes and human disease*, WORLD HEALTH ORG., <http://www.who.int/genomics/public/geneticdiseases/en/index2.html>

<sup>189</sup> *Id.*

<sup>190</sup> See *id.*

Some proponents of the ban contend that the development HGM is not necessary because alternative means would be effective in a majority of cases.<sup>191</sup> For example Eric Lander notes that “it would be easier and safer simply to use PGD . . . in the typical cases of a parent heterozygous for a dominant disease or two parents who are carriers for a recessive disease.”<sup>192</sup> Lander concludes that situations that would necessitate HGM are “vanishingly rare for most monogenic diseases.”<sup>193</sup>

Nevertheless, there are clearly situations in which HGM might be required and in those cases, the real benefit to the parents and children outweighs the speculative harm that drives much of the opposition to HGM. For example, PGD would not be sufficient when one parent is homozygous for an autosomal dominant disease or both parents have a homozygous autosomal-recessive disease.<sup>194</sup> Incidences of homozygosity have already been documented in several deadly monogenic diseases, including cystic fibrosis<sup>195</sup> and Huntington’s disease.<sup>196</sup> For these people, the choices are clear: obtaining treatment using HGM, rearing a sick child, or abstaining from procreation. Although these situations may be rare, those inflicted are still human. Preventing these people from receiving treatment should not be morally justified by references to the speculative harm that may be brought about by potential cosmetic applications of HGM.

### 3. *Amend the Rider to Include a Specific Exception*

The third option available to Congress is to amend the rider, providing for specific exceptions for particular applications

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<sup>191</sup> Heidi Mertes & Guido Pennings, *Modification of the Embryo’s Genome: More Useful in Research Than in the Clinic*, 15 AM. J. BIOETHICS 52, 53 (Dec. 2015), available at

<http://www.tandfonline.com/doi/abs/10.1080/15265161.2015.1103813>.

<sup>192</sup> Eric S. Lander, *Brave New Genome*, 373 N. ENG. J. MED. 5, 7 (Jul. 2, 2015), available at <http://www.nejm.org/doi/full/10.1056/NEJMp1506446#t=article>.

<sup>193</sup> *Id.*

<sup>194</sup> See Donald B. Kohn, et al., *Ethical and regulatory aspects of genome editing*, 126 BLOOD 2553, 2554 (Apr. 6, 2016), available at <http://www.bloodjournal.org/content/127/21/2553.abstract?sso-checked=true>.

<sup>195</sup> Vassos Neocleous, et al., *Apparent homozygosity of p.Phe508del in CFTR due to a large gene deletion of exons 4-11*, 2014 CASE REP. GENET. 1, 2 (Feb. 6, 2014), available at <https://www.hindawi.com/journals/crig/2014/613863/>.

<sup>196</sup> Ferdinando Squitieri, et al., *Homozygosity for CAG mutation in Huntington disease is associated with a more severe clinical course*, 126 BRAIN 946, 946-47 (Apr. 1, 2003), available at <http://brain.oxfordjournals.org/content/brain/126/4/946.full.pdf>.

of HGM. For example, it would be sensible to allow the use of HGM in the treatment of selected, well-studied monogenic diseases. A specific exception for the use of HGM in monogenic diseases would provide for the most ethically sound use of the technology. Such an exception could help save human lives, reduce the costs associated with genetic diseases, and protect the reproductive freedom of individuals. Furthermore, these exceptions would allow the scientific freedom that is necessary for the U.S. to remain at the technical and ethical forefront of this emerging technology. The author proposes one such exception.

The proposed amended rider reads as follows, where the bold text indicates the amendment:

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 . . . in which a human embryo is intentionally created or modified to include a heritable genetic modification, **with the exception of a submission pertaining to the treatment of embryos where there is a substantial risk that the child will be born with a severe or life-threatening genetic disease, where the disease has a well-established and specific genetic cause, where the modification results in wild-type gene, and where the patients could not obtain equally effective treatment using other means.** Any such submission shall be deemed to have not been received by the Secretary, and the exemption may not go into effect.<sup>197</sup>

*a. Plausibility*

Amending the rider would not be unprecedented; riders have been known to evolve over time. For example, the Hyde Amendment initially provided a full ban on the use of federal funds for abortion services.<sup>198</sup> Since then, the Hyde Amendment

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<sup>197</sup> 2017 rider, *supra* note 85 (text from the original rider has been preserved, with the proposed amendment in bold for emphasis).

<sup>198</sup> See ACLU, *supra* note 176.

has been changed several times.<sup>199</sup> In 1981, the amendment was altered to include an exception “where the life of the mother would be endangered if the fetus was carried to term.”<sup>200</sup> It was changed again in 1993, expanding federal funding to abortions related to incidents of rape and incest.<sup>201</sup> The first explicit call to repeal the amendment was not until 2016.<sup>202</sup>

The proposed exception would reflect the differences in public opinion between the use of HGM for therapy and its use for enhancement. Polls indicate that people in the United States are significantly less concerned about the use of genetic engineering to treat disease than they are about its use for enhancement or trait selection.<sup>203</sup> In fact, 59% of parents with a child under the age of 18 said that they would want gene editing to reduce their baby’s risk of disease, while only 39% of these parents indicated that they would not.<sup>204</sup> As people learn more about the subject, it is likely that their attitudes will shift in favor of therapeutic HGM.<sup>205</sup>

*b. The Proposed Exception is in Line with Expert Consensus*

The proposed exception is generally in line with the recommendations from the National Academy of Sciences and the National Academy of Medicine, which were released earlier this year in the Human Genome Editing Report (the Report).<sup>206</sup> The Report was authored following the conclusion of the 2015

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<sup>199</sup> Julie Rovner, *Abortion Funding Ban Has Evolved Over The Years*, NAT’L PUBLIC RADIO (Dec. 19, 2009, 6:00 AM), <http://www.npr.org/templates/story/story.php?storyId=121402281>.

<sup>200</sup> *Id.*

<sup>201</sup> Health and Human Services, and Related Agencies Appropriation Act, 1994, Pub. L. No. 103-112, 107 Stat. 1082, 1113 (1993).

<sup>202</sup> *DNC Platform Includes Historic Call to Repeal Anti-Choice Hyde Amendment*, DEMOCRACY NOW! (June 27, 2016), [https://www.democracynow.org/2016/6/27/headlines/dnc\\_platform\\_includes\\_historic\\_call\\_to\\_repeal\\_anti\\_choice\\_hyde\\_amendment](https://www.democracynow.org/2016/6/27/headlines/dnc_platform_includes_historic_call_to_repeal_anti_choice_hyde_amendment).

<sup>203</sup> Funk, *supra* note 155.

<sup>204</sup> *Id.*

<sup>205</sup> *See id.* (demonstrating that 57% of Americans who are familiar with gene editing would use it on their own children to reduce the risk of serious disease, while only 37% of people who know nothing about the subject would opt for the procedure).

<sup>206</sup> NAT’L ACAD. OF SCI. & NAT’L ACAD. OF MED., *Human Genome Editing: Science, Ethics, and Governance – Report Highlights* (Feb. 2017), available at [http://nationalacademies.org/cs/groups/genesite/documents/webpage/gene\\_177260.pdf](http://nationalacademies.org/cs/groups/genesite/documents/webpage/gene_177260.pdf) [hereinafter NAT’L ACADEMIES].

International Summit on Human Gene Editing.<sup>207</sup> Its authors include experts in science, medicine, and public policy from around the world.<sup>208</sup> The Report was compiled after an extensive review of the literature, as well as discussions with clinicians, researchers, policymakers, and patient advocates, among others.<sup>209</sup> Thus, the Report represents over a year of concerted effort by a collection of some of the most qualified experts in the world and their recommendations should be afforded due consideration.

The two major recommendations with respect to HGM were (1) to “[p]ermit clinical research trials only for compelling purposes of treating or preventing serious disease or disabilities, and only if there is a stringent oversight system able to limit uses to specified criteria”; and (2) that “[o]ngoing reassessment and public participation should precede any heritable germline editing.”<sup>210</sup> The committee defined a set of criteria for the clinical use of HGM in treating disease that closely mirrors the proposed amendment.<sup>211</sup> With respect to genetic enhancement, the Academies suggested “not [to] proceed at this time with human genome editing for purposes other than treatment or prevention of disease and disability.”<sup>212</sup> Adoption of the proposed amendment — or something of similar scope — would ensure that the committee’s recommendations are respected, and HGM would not be applied recklessly.

*c. The IOM Report Further Bolsters the Case for an HGM Exception*

Congress may already have to amend the FDA rider to accommodate recommendations by the Institute of Medicine (IOM), which suggested that the U.S. move forward with limited clinical trials for MRT. As the rider has been interpreted to

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<sup>207</sup> See Sara Reardon, *US science advisers outline path to genetically modified babies*, NATURE (Feb. 14, 2017), available at <http://www.nature.com/news/us-science-advisers-outline-path-to-genetically-modified-babies-1.21474>.

<sup>208</sup> See NAT’L ACADEMIES, *supra* note 206, at 4.

<sup>209</sup> *Id.* at 1.

<sup>210</sup> *Id.* at 3.

<sup>211</sup> The criteria includes, among other things “[1] absence of reasonable alternatives; [2] restriction to preventing a serious disease or condition; [and] [3] restriction to editing genes that have been convincingly demonstrated to cause or strongly predispose to that disease or condition[.]” *Id.* at 3. Many of the additional criteria could be achieved by allowing the FDA to put into place a specialized clinical evaluation process for HGM. *See id.* at 4.

<sup>212</sup> *Id.*

preclude any clinical evaluation of MRT, Congress may have to amend the rider if they are to heed the recommendations of the IOM report.<sup>213</sup>

In 2016, the IOM provided a report at the request of the FDA and the National Academies proposing a path forward for the clinical application of MRT.<sup>214</sup> Acknowledging that the FDA's purview extends only to safety and efficacy, the IOM committee specifically reviewed the "social, ethical and policy" considerations of MRT.<sup>215</sup> They concluded that most of the concerns about germline modification (1) could be "avoided through limitations on the use of MRT" or (2) "are blunted by meaningful differences between the heritable genetic modification of nDNA and that introduced by MRT."<sup>216</sup>

First, the report suggested that only limited applications of MRT should be evaluated, especially at the early stages of development.<sup>217</sup> In addition to other restrictions,<sup>218</sup> the IOM recommended that the clinical evaluation of MRT should proceed for clinical trials that involved "transferring only male embryos for gestation to avoid introducing heritable genetic modification[.]"<sup>219</sup> This is because the mtDNA from the father is not passed on during procreation,<sup>220</sup> which may be caused by degradation of the mtDNA during fertilization of an oocyte.<sup>221</sup> Only the mother's mtDNA are passed down to the children.<sup>222</sup> Because the male children could not pass on the donor's mtDNA,

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<sup>213</sup> See Cohen & Adashi, *supra* note 80.

<sup>214</sup> Claiborne, *supra* note 28.

<sup>215</sup> See *id.*

<sup>216</sup> *Id.*

<sup>217</sup> *Id.* at 10.

<sup>218</sup> *Id.* (The IOM also recommended that only pursuing studies (1) that "focus on minimizing the future child's exposure to risk while ascertaining the safety and efficacy of the techniques;" and (2) were limited to "women who are otherwise at risk of transmitting a serious mtDNA disease, where the mutation's pathogenicity is undisputed, and the clinical presentation of the disease is predicted to be severe.").

<sup>219</sup> *Id.*

<sup>220</sup> See Tanya Lewis, *Why Paternal Mitochondria Aren't Passed On to Offspring*, SCIENTIST (Jun. 24, 2016), <http://www.the-scientist.com/?articles.view/articleNo/46414/title/Why-Paternal-Mitochondria-Aren-t-Passed-On-to-Offspring/>.

<sup>221</sup> See Qinghua Zhou, et al., *Mitochondrial endonuclease G mediates breakdown of paternal mitochondria upon fertilization*, SCIENCE (Jun. 23, 2016), available at <http://science.sciencemag.org/content/early/2016/06/22/science.aaf4777.full.pdf+html>.

<sup>222</sup> See *id.*

the use of MRT to treat male children would not result in a “heritable genetic mutation.”<sup>223</sup>

Second, the committee noted that there were “significant and important distinctions between [the] modification of mtDNA and nDNA[,]” which affect the ethical, social, and policy considerations for MRT.<sup>224</sup> For example, although “mtDNA plays a central role in genetic ancestry,” the traits encoded in nDNA “are those that in the public understanding” are more important for genetic relatedness . . . and disease.<sup>225</sup> Moreover, while mtDNA may be used for “energetic enhancement” purposes, “they appear to be far fewer and more speculative relative to [those enhancements that] might be possible in modifications of nDNA.”<sup>226</sup> Based on these considerations, the committee “conclude[d] that it is ethically permissible to conduct clinical investigations of MRT, subject to certain conditions and principles[.]”<sup>227</sup>

Yet, clinical development of MRT may be precluded by the 2017 rider.<sup>228</sup> The 2017 rider precludes any “a human embryo is intentionally created or modified to include a heritable genetic modification.”<sup>229</sup> In theory, heritable genetic modifications could be avoided by only transferring the nuclei from male zygotes.<sup>230</sup> Such an approach would be in line with the recommendations of the IOM report.<sup>231</sup> However, a statement from Paul Richards, the spokesman for the FDA’s Center for Biologics Evaluation and Research, indicated that the agency deems the current rider to preclude any “human subject research utilizing genetic modification of embryos for the prevention of transmission of mitochondrial disease[.]”<sup>232</sup> Thus, it appears that the rider must be amended before the FDA is willing to act on the IOM Report.<sup>233</sup>

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<sup>223</sup> Claiborne, *supra* note 28.

<sup>224</sup> *Id.* at 8.

<sup>225</sup> *See id.* at 8.

<sup>226</sup> *Id.*

<sup>227</sup> *Id.*

<sup>228</sup> *See* Cohen & Adashi, *supra* note 80.

<sup>229</sup> 2017 rider, *supra* note 55.

<sup>230</sup> *See* Anne Claiborne, *supra* note 28.

<sup>231</sup> *Id.*

<sup>232</sup> *See* Zachary Brennan, *Expert Committee: FDA Should Allow Mitochondrial Replacement Trials Under Certain Conditions*, REG. AFFAIRS PRO. SOC. (Feb. 3, 2016), <http://raps.org/Regulatory-Focus/News/2016/02/03/24245/Expert-Committee-FDA-Should-Allow-Mitochondrial-Replacement-Trials-Under-Certain-Conditions/>.

<sup>233</sup> It may be possible that the FDA decides to move forward with the use of MRT in male children without an amendment to the rider. However, MRT will be eventually be required to treat female children, at which time an amendment will be necessary.

Without an exception to the 2017 rider, there is no path to clinical evaluation of MRT in the U.S. As a result, desperate parents may be forced to undergo the treatment off-shore, incurring added expense and potential danger. In fact, at least one such incident has already been reported: on April 6, 2016, the first baby was born using MRT in Mexico.<sup>234</sup> The mother carried the gene signature for Leigh syndrome, a fatal disorder caused by mutations in the mitochondrial DNA.<sup>235</sup> As MRT is not approved in the U.S. and might never be under the current language of the rider, the team of doctors decided to conduct the procedure in Mexico, where “there are no rules” against the procedure.<sup>236</sup> The baby boy, now over one year old, was last known to be in good condition and will be monitored for any safety issues.<sup>237</sup> If changes are not made to the law that accommodate treatment for select genetic diseases, these incidents are likely to continue in the future.

The IOM recommendations that allow selected applications of MRT significantly bolster the argument in favor of a limited exception that would allow FDA review of selected therapeutic uses of HGM. First, there is a similar rationale for the limited use of HGM as there is for the limited use of MRT. The IOM recommended the use of MRT for women who are otherwise at risk of transmitting a serious mtDNA disease, where the mutation’s pathogenicity is undisputed, and the clinical presentation of the disease is predicted to be severe.<sup>238</sup> Similarly, the proposed exception would allow the use of HGM to treat “severe or life-threatening genetic diseases with a well-established and specific genetic cause, when the end product is a wild-type gene and its use is restricted to patients who could not obtain equally effective treatment using other means.”<sup>239</sup> The IOM noted the compelling purpose of MRT: to “satisfy the desire of a women seeking to have a genetically related child without the risk of passing on mtDNA disease[s.]”<sup>240</sup> The purpose of therapeutic HGM is nearly identical: it would allow both men and

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<sup>234</sup> Jessica Hamzelou, *Exclusive: World’s first baby born with new “3 parent” technique*, NEW SCIENTIST (Sept. 27, 2016), <https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/>.

<sup>235</sup> *Id.*

<sup>236</sup> *Id.*

<sup>237</sup> *Id.*

<sup>238</sup> Claiborne, *supra* note 28.

<sup>239</sup> See proposed amendment, above.

<sup>240</sup> *Id.* at 1.

women who are afflicted with a genetic disease to have genetically related children without the risk of passing on nDNA diseases.

Second, the committee's findings that "distinctions between modification of mtDNA and nDNA" warrant treatment of mtDNA diseases but not nDNA diseases are not persuasive. The report asserts that "the replacement of whole, intact, and naturally occurring mitochondrial genomes" is significantly different from approaches using "targeted genomic editing[.]"<sup>241</sup> However, some heterogeneity of mtDNA is observed during MRT,<sup>242</sup> and targeted editing that resulted in a wild-type gene would also result in "naturally occurring" genes.<sup>243</sup> In addition, targeted editing approaches may eventually lead to less genetic disruption than MRT because they only change parts selected genes, instead of entire blocs of mtDNA.

The report contends that unlike mtDNA, "traits that are carried in nDNA are those that in the public understanding constitute the core of genetic relatedness."<sup>244</sup> However, therapeutic HGM would only be approved by the FDA if there was little to no change of off-target editing.<sup>245</sup> Thus, any clinically-acceptable use of HGM should only result in *de minimis* alteration of the genome. Those genes on the nDNA that are associated with the core of genetic relatedness would be left unaltered by HGM, and the ancestral link between parent and child would be left intact.

The report also notes that mtDNA is limited in its effect on the organism and that any opportunities for enhancement using mtDNA "appear to be far fewer and more speculative relative to what might be possible in modifications of nDNA."<sup>246</sup> This distinction is predicated on an assumption that therapeutic HGM will necessarily lead to enhancement. Yet, the report itself unambiguously proposes that the MRT ought to be—and can be—limited to therapeutic purposes.<sup>247</sup> The same limitations can and should be imposed on the use of HGM.

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<sup>241</sup> *Id.* at 8.

<sup>242</sup> Thomas Klopstock, et al., *Mitochondrial replacement approaches: challenges for clinical implementation*, 8 *GENOME MED.* 1 (Nov. 25, 2016), available at <https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0380-2>.

<sup>243</sup> By definition, a wild-type gene is a naturally occurring gene.

<sup>244</sup> *Id.*

<sup>245</sup> See generally *Cellular & Gene Therapy Guidance*, FED. DRUG ADMIN. DEPT. OF HEALTH & HUMAN SAFETY (last updated Sept. 6, 2017), <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/>.

<sup>246</sup> Claiborne, *supra* note 28, at 8.

<sup>247</sup> See *id.* at 2.

Finally, although therapeutic HGM would necessarily result in “heritable genetic mutations,” this alone is not enough to override the benefits that safe and effective HGM could offer. The IOM report indicated that the possibility of such heritable modifications should not necessarily preclude the use of MRT that resulted in inheritable mutations.<sup>248</sup> The committee proposed that the FDA could consider extending the use of MRT to female embryos as long as safety and efficacy were established and the decision was consistent with public and scientific deliberations on acceptable limits of applicability.<sup>249</sup> If such an approach is acceptable for the use of MRT, there is no reason why it should not also be adopted for the therapeutic application of HGM.

*d. Safety and Ethical Considerations*

For some afflicted with a severe genetic disease, HGM may represent the only viable option for having healthy, genetically-related children. Although these people may be relatively few in numbers, the harm that they suffer is real and their burden is immense. The current rider prevents them from accessing the one therapy that could help. It unnecessarily forces them to choose between rearing a child who will suffer a debilitating disease, or to forego parenthood in its entirety. Some may choose the latter option and for those people, the rider is a direct affront to their reproductive liberty.<sup>250</sup> Others may be forced to engage in reproductive tourism, incurring great cost and health risk for themselves and their children.

Commentators have claimed that SCE can and will provide alternative treatments, obviating the need for HGM; however, SCE is not without its drawbacks. First, SCE can be extremely expensive: the cost of Glybera, the world’s first gene therapy, is about one million dollars.<sup>251</sup> The treatment is so expensive that it

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<sup>248</sup> *Id.* at 13.

<sup>249</sup> *See id.* (noting that the FDA “could consider extending . . . MRT to . . . female embryos if clear evidence of safety and efficacy from male cohorts . . . were available, . . . preclinical research in animals has shown evidence of intergenerational safety and efficacy; and FDA’s decisions were consistent with the outcomes of public and scientific deliberations to establish . . . the acceptability of and moral limits on heritable genetic modification.”).

<sup>250</sup> A constitutional analysis of the impact of the 2017 rider on reproductive liberty is beyond the scope of this paper. For a general review of this topic, *see, e.g.*, Carl H. Coleman, *Assisted Reproductive Technologies and the Constitution*, 30 *FORDHAM URBAN L.J.* 57 (2002), <http://ir.lawnet.fordham.edu/cgi/viewcontent.cgi?article=1847&context=ulj>.

<sup>251</sup> Regalado, *supra* note 34.

has only been used commercially for one patient.<sup>252</sup> For many indications, HGM may prove to be a far cheaper and more effective option. Second, SCE is complicated and can be fraught with risk. It is well known that the retroviral vectors used to deliver the gene editing tools for SCE can lead to insertional mutagenesis, causing unintended genetic mutations in off-target and on-target cells.<sup>253</sup> Side effects of SCE include acute inflammatory reactions,<sup>254</sup> development of cancer,<sup>255</sup> and death.<sup>256</sup> While SCE requires genetic manipulation of millions of cells targeted to a specific organ, HGM requires successful gene editing only in single-celled zygotes.<sup>257</sup> Although SCE is a promising technology for the treatment of many indications, it may not be an adequate substitute for HGM in all cases.

The proposed amendment would allow the development of complementary treatments that could have the potential to save lives and reduce the debilitating costs of healthcare. Moreover, if either PGD or SCE were found to be equally efficacious alternatives, the proposed amendment would preclude the FDA development of HGM in this field, because the exception is limited to situations “where the patients could not obtain equally effective treatment using other means.”<sup>258</sup>

As previously discussed, the most widely disseminated ethical opposition to the use of therapeutic HGM is that its use will start down a slippery slope towards enhancement. Such uses can continue to be prevented in exactly the same manner as they currently are: by the precluding FDA review of any application of HGM for enhancement. The proposed amendment does just that

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<sup>252</sup> *Id.*

<sup>253</sup> See Samantha L. Ginn, et al., *Gene therapy clinical trials worldwide to 2012 – and update*, 15 J. GENE MED. 65, 68 (2013), <http://onlinelibrary.wiley.com/doi/10.1002/jgm.2698/full>; see also Christopher Baum, *Insertional mutagenesis in gene therapy and stem cell biology*, 14 CURR. OPIN. HEMATOL. 337 (Jul. 2007), <http://journals.lww.com/co-hematology/pages/articleviewer.aspx?year=2007&issue=07000&article=00006&type=abstract>.

<sup>254</sup> See M.J. Kennedy, *Current status of gene therapy for cystic fibrosis pulmonary disease*, 1 AM. J. RESPIR. MED. 349 (2002), <https://www.ncbi.nlm.nih.gov/pubmed/14720037>.

<sup>255</sup> See M.E. Gore, *Adverse effects of gene therapy: Gene therapy can cause leukemia: no shock, mild horror but a probe*, 10 GENE THERAPY 4, (2003), available at <http://www.nature.com/gt/journal/v10/n1/full/3301946a.html>.

<sup>256</sup> See Cormac Sheridan, *Gene therapy finds its niche*, 29 NATURE BIOTECH. 121, 123 (Feb. 7, 2011), <http://www.nature.com/nbt/journal/v29/n2/full/nbt.1769.html>.

<sup>257</sup> See, e.g., Liang, *supra* note 62.

<sup>258</sup> See proposed amendment, above.

by limiting the use of HGM to the “treatment of embryos where there is a substantial risk that the child will be born with a severe or life-threatening genetic disease, where the disease has a well-established and specific genetic cause.”<sup>259</sup> Limitations on the applications of therapies are ubiquitous in healthcare, including, for example, the IOM’s proposed limitation on the clinical development of MRT.<sup>260</sup>

## VII. CONCLUSION

Unless and until the U.S. adopts a comprehensive legislative scheme that regulates reproductive HGM, the current rider should be amended to permit the clinical development of HGM for a narrow subset of severe monogenic diseases. The amendment proposed in this paper represents a balanced approach to HGM policy, reflecting the nuanced safety and ethical issues that were invoked by the legislature when crafting the rider in the first place. First, the proposed amendment limits the application of HGM only to those uses with the most compelling moral imperative: the treatment of severe genetic diseases. Second, the proposed amendment maintains the current ban on the use of HGM for enhancement, which has the highest danger for misuse. Third, the amendment would only allow the gene editing that results in wild-type genes, alleviating any concern about introducing augmented genes into the gene pool. Finally, careful FDA scrutiny of any HGM protocol should be maintained throughout the entire process of clinical development, ensuring that HGM is only used if it is safe and efficacious.

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<sup>259</sup> See proposed amendment, above.

<sup>260</sup> See Claiborne, *supra* note 28.