

REGULATING HUMAN GERMLINE MODIFICATION IN LIGHT OF CRISPR

INTRODUCTION

Scientific advancement is notorious for pushing legal and ethical boundaries, but never more so than recently. For the first time in history, we have the potential to not only recreate genetic marvels of the past, but also reshape the genetic destiny of future generations. This is due to the development of a new, revolutionary technology in genetic engineering called CRISPR—short for clustered regularly interspaced short palindromic repeats.¹

CRISPR has the potential to eradicate genes that increase a person's risk of cancer or heart disease and correct mutations for serious genetic diseases like cystic fibrosis, sickle-cell anemia, and Huntington's disease, to name a few.² And the best part: CRISPR is easy to use, inexpensive, and extraordinarily effective.³

Often compared to the find-and-replace function in a word-processing program, CRISPR can correct genetic defects in whole organisms, as well as ensure that the changes will be passed on from one generation to the next (changing the organism's "germline").⁴ Human germline modification ("HGM"), or deliberately changing the genes in reproductive cells or embryos, is distinguishable from somatic gene editing ("gene therapy").⁵ Genetic

1. PAUL KNOEFFLER, *GMO SAPIENS: THE LIFE-CHANGING SCIENCE OF DESIGNER BABIES* 258 (2016) [hereinafter *GMO SAPIENS*].

2. See Michael Specter, *The Gene Hackers*, *THE NEW YORKER* (Nov. 16, 2015), <http://www.newyorker.com/magazine/2015/11/16/the-gene-hackers>.

3. David Baltimore et al., *A Prudent Path Forward for Genomic Engineering and Germline Gene Modification*, 348 *SCI.* 36, 36–37 (2015).

4. See, e.g., Jon Entine, *Ethical and Regulatory Reflections on CRISPR Gene Editing Revolution*, *GENETIC LITERACY PROJECT* (June 25, 2015), <https://www.geneticliteracyproject.org/2015/06/25/ethical-and-regulatory-reflections-on-crispr-gene-editing-revolution/> ("It's akin to a biological word processing system that allows scientists to cut and paste DNA almost as easily as if they were editing a journal article.")

5. See ASS'N OF REPROD. HEALTH PROF'LS, *HUMAN CLONING AND GENETIC MODIFICATION: THE BASIC SCIENCE YOU NEED TO KNOW* 5, [hereinafter *ARHP, HUMAN*

alterations in reproductive cells and embryos affect more than just an individual consenting patient—they become part of the resulting child’s genetic make-up.⁶ This creates the potential to introduce changes that will echo through future gene pools and alter the legacy of human diversity.

Between forced sterilization laws in the 1920s and Nazi eugenics experiments during World War II, the United States and other countries already have a sordid history of trying to “improve” the human race via heritable genetic modification.⁷ Thus, some are concerned history will repeat itself if current regulations do not evolve to confront this revolutionary advancement.

CRISPR advocates are enthusiastic about its promise for correcting mutations for serious genetic diseases.⁸ Some proponents go so far as to say that bioethics should simply “[g]et out of the way,” and that “slowing down research has a massive human cost.”⁹ To these optimists, society should “cure” as many people as possible, as soon as possible, and should focus on the ethical issues as they arise. However, even scientists that support the use of CRISPR as a gene-editing tool agree that its potential to alter the legacy of human diversity has progressed much faster than society’s ability to deliberate its social implications and permissible uses.¹⁰ These more moderate proponents say that pausing to apply a moral imagination to the future does not kill research or its potential applications.¹¹

While opponents of CRISPR technology advise banning it for the foreseeable future, some argue that anything short of a complete and total ban is insufficient.¹² The reason for such strong

CLONING] <http://www.arhp.org/upload Docs/cloning.pdf>.

6. *See id.*

7. *See generally* ADAM COHEN, IMBECILES: THE SUPREME COURT, AMERICAN EUGENICS, AND THE STERILIZATION OF CARRIE BUCK 251–83 (2016) (discussing the history of eugenics in the United States).

8. *See, e.g.*, Steven Pinker, Opinion, *The Moral Imperative for Bioethics*, BOS. GLOBE (Aug. 1, 2015), <https://www.bostonglobe.com/opinion/2015/07/31/the-moral-imperative-for-bioethics/JmEkoyzITAu9oQV76JrK9N/story.html> (arguing against bioethicists “bog[ging] down research” because of the positive implications of CRISPR).

9. *Id.*

10. *See* Edward Lanphier et al., *Don’t Edit the Human Germ Line*, 519 NATURE 410, 410–11 (2015).

11. *See id.*

12. *See* Sarah Karlin, *Gene Editing: The Next Frontier in America’s Abortion Wars*, POLITICO (Feb. 16, 2016, 5:21 AM), <http://www.politico.com/story/2016/02/gene-editing-abortion-wars-219230>.

opposition is twofold: some feel human beings should never be the subject of experimentation, regardless of their stage in life; others see the potential for “designer babies” and worry the technology will result in social inequality.¹³

This comment evaluates the United States’ current regulatory scheme as it applies to CRISPR and related gene-modifying technologies and discusses the ethical ramifications of regulating human germline modification versus continuing to allow self-regulation within the scientific community. Part I explains what CRISPR is, how it works, and its impact on genetic engineering technology. Although CRISPR offers “unparalleled potential for modifying [both] human and nonhuman genomes,”¹⁴ this comment focuses primarily on the use of CRISPR technology to manipulate the human germline.¹⁵ Part II discusses the social and bioethical implications of altering the human germline, including safety concerns, multigenerational consequences, equity issues, and ethical complications involved with editing human embryos. Part III examines the United States’ current regulatory scheme as it applies to gene-modifying technologies, discusses the need for reform in light of CRISPR germline-editing therapies, looks at several possible solutions to improve the existing scheme, and proposes an adapted regulatory framework.

I. WHAT IS HUMAN GERMLINE MODIFICATION?

HGM means deliberately changing the genes that are transmitted to future generations by modifying DNA in eggs, sperm, or very early embryos.¹⁶ Germline modification is distinguishable from somatic gene editing because genetic alterations in reproductive cells and embryos are heritable and affect more than just an individual consenting patient—they affect every cell in the body and become part of the resulting child’s genetic make-up.¹⁷

13. *See id.*

14. Baltimore et al., *supra* note 3, at 36.

15. Hongbao Ma & Guozhong Chen, *Gene Transfer Technique*, 3 NATURE & SCI. 25, 25 (2005). (“Gene transfer can be targeted to somatic (body) or germ (egg and sperm) cells. In somatic gene transfer the recipient’s genome is changed, but the change will not be passed on to the next generation. In germline gene transfer, the parents’ egg and sperm cells are changed with the goal of passing on the changes to their offspring.”).

16. ARHP HUMAN CLONING, *supra* note 5, at 5.

17. *Id.* (defining somatic genetic engineering as “genetic engineering that targets the genes in specific organs and tissues of the body of a single existing person without affecting genes in their eggs or sperm”).

Thus, unlike somatic genetic modification, HGM has the potential to introduce changes that will echo through future gene pools and “alter the legacy of human diversity.”¹⁸

Until recently, most research and clinical resources have been directed toward developing somatic gene therapy techniques.¹⁹ But inheritable genetic modifications are preferable to non-heritable alterations for several reasons, such as to prevent the inheritance of fatal genetic diseases or avoid having to repeat somatic therapy generation after generation.²⁰ Moreover, HGM offers the long-term benefit of decreasing the prevalence of certain inherited diseases that currently plague the human gene pool.²¹ Because somatic gene therapy treats only the affected individual, it could not produce the same long-term effect of reducing the incidence of genetic diseases.²²

Another alternative to HGM is pre-implantation genetic diagnosis (“PGD”), which can be used to detect genetic abnormalities prior to pregnancy.²³ PGD works as follows:

Couples at risk for having a child with a chromosomal or genetic disease undertake IVF to permit embryo screening before transfer, obviating the need for later prenatal diagnosis and possible abortion. A dozen or more eggs are fertilized and the embryos are grown to the four-cell or the eight-to-ten-cell stage. One or two of the embryonic cells (blastomeres) are removed for chromosomal analysis and genetic testing. Using a technique called polymerase chain reaction to amplify the tiny amount of DNA in the blastomere, researchers are able to detect the presence of genes responsible for one or more genetic disorders. Only the embryos free of the genetic or chromosomal determinants for the disorders under scrutiny are made eligible for transfer to the woman to initiate a pregnancy.²⁴

PGD was developed as a way for parents to have children free of severe or fatal genetic disorders without having an abortion.²⁵

18. Editorial, *Future-Proofing*, 528 NATURE 164, 164 (2015).

19. See MARK S. FRANKEL & AUDREY R. CHAPMAN, AM. ASS'N FOR THE ADVANCEMENT OF SCI., HUMAN INHERITABLE GENETIC MODIFICATIONS 1 (2000), <http://www.aaas.org/sites/default/files/migrate/uploads/germline.pdf>.

20. *Id.* at 3.

21. *Id.*

22. *Id.*

23. See THE PRESIDENT'S COUNCIL ON BIOETHICS, BEYOND THERAPY: BIOTECHNOLOGY AND THE PURSUIT OF HAPPINESS 38 (2003) [hereinafter BEYOND THERAPY], <http://www.vanderbilt.edu/olli/files/Beyond-Therapy-Kass.pdf>.

24. *Id.* at 38–39.

25. See Susannah Baruch, *Preimplantation Genetic Diagnosis and Parental Preferences: Beyond Deadly Disease*, 8 HOUSING J. HEALTH L. & POL'Y 245, 245–46 (2008) (indicating PDG was initially created as an “alternative to prenatal genetic diagnosis and ter-

However, there are certain situations in which genetic screening and embryo selection are not effective for this purpose.²⁶ For example, if both parents have the same genetic mutation—meaning 100% of their offspring are guaranteed to have that same disorder—then PGD would be useless because there are no mutation-free embryos from which to choose.²⁷ Another example is where only one parent carries the genetic disorder, but there are so few embryos that PGD is unable or unlikely to find one lacking a mutation.²⁸ HGM, on the other hand, offers the potential to completely eradicate the genetic mutation from this homozygous couple's germline, thereby giving them the opportunity to have a biologically related child that does not suffer from the disorder.²⁹

In the same way that HGM has the potential to produce lasting benefits, it also has the potential to produce lasting physical, social, and ethical consequences. Despite the advent of CRISPR, there are still important technical obstacles to inheritable genetic applications.³⁰ The technology in its current form is not error-free;

mination”).

26. *Id.* at 250.

27. See Eric S. Lander, *Brave New Genome*, 373 *NEW ENG. J. MED.* 5, 6 (2015) (indicating that while there are roughly 3600 rare monogenic disorders—or disorders caused by single-gene defects, which would be the easiest to correct with CRISPR technology—cases where one parent is homozygous for a dominant disorder or both parents are homozygous for a recessive disorder are very rare).

For dominant Huntington's disease, for example, the total number of homozygous patients in the medical literature is measured in dozens. For most recessive disorders, cases are so infrequent (1 per 10,000 to 1 per million) that marriages between two affected persons will hardly ever occur unless the two are brought together by the disorder itself. The most common situation would probably be two parents with recessive deafness due to the same gene (among the many that can cause inherited deafness) who wish to have a hearing child.

Id.

28. See *GMO SAPIENS*, *supra* note 1, at 243 (discussing couples dealing with infertility or genetic problems including mitochondrial disorders).

29. See FRANKEL & CHAPMAN, *supra* note 19, at 3. For example, this may be necessary in a situation where both parents have sickle cell anemia because 100% of their offspring will be afflicted with the disease. Henry I. Miller, Letter to the Editor, *Germline Gene Therapy: We're Ready*, 348 *SCI.* 1325, 1325 (2015). Alternative techniques such as pre-implantation genetic diagnosis would be inadequate in this situation because the purpose of genetic screening is to select embryos that do not carry the condition. See FRANKEL & CHAPMAN, *supra* note 19, at 3. Thus, the only way for this couple to have a biological child that does not also have sickle cell anemia would be to genetically modify the child's germline prior to ex vivo.

30. FRANKEL & CHAPMAN, *supra* note 19, at 3.

and even if it were, successful germline intervention would still pose the risk of unknown multigenerational side effects.³¹

A. *Explanation of CRISPR Technology*

1. How CRISPR Works

CRISPRs are genomic elements in bacteria that provide immunity against future viral infection.³² Essentially, it is a bacterial defense mechanism that operates as a “genetic sandwich.”³³ After being infected by a virus, the bacteria “remember” it by sandwiching remnants of viral genes between odd, repeated bacteria DNA sequences—these are the “clustered regularly interspaced short palindromic repeats” from which the CRISPR name is derived.³⁴ These sequences are then stored in the bacterial genome, which enable a bacterium and its ancestors to more easily defend themselves using an enzyme, typically Cas9, if infected by the same virus in the future.³⁵

Upon discovering this immune response in bacteria, researchers began programming CRISPR for use in other organisms by simply replacing the viral DNA that is sandwiched between CRISPR sequences with the DNA of other cell types, including that of humans.³⁶ The entire process is actually very simple and is accomplished by the interaction of two elements. First, researchers program CRISPR by matching a “guide” molecule with a specific DNA sequence and aligning the molecule against a precise position on the DNA double helix where editing is required.³⁷ Once deployed, these serve as a road map for CRISPR to reach its

31. *See infra* text accompanying note 107.

32. GMO SAPIENS, *supra* note 1, at 12.

33. *See* Carl Zimmer, *Breakthrough DNA Editor Born of Bacteria*, QUANTA MAG. (Feb. 6, 2015), <https://www.quantamagazine.org/20150206-crispr-dna-editor-bacterial/>.

34. John Travis, *Making the Cut*, 350 SCI. 1456, 1457 (2015); *see also* Zimmer, *supra* note 33 (indicating bacteria use Cas9 enzymes to grab fragments of viral DNA then chop it in two, preventing the virus from replicating).

35. GMO SAPIENS, *supra* note 1, at 12 (“Much the same way as the police have a database of the ‘fingerprints’ of criminals, CRISPR elements act as a store of viral fingerprints that generations of bacteria keep and use to mount rapid immune responses to viral infections.”).

36. *Id.* at 12–13; *see also* Zimmer, *supra* note 33 (indicating scientists successfully cut out a particular piece of DNA in human cells and replaced it with another one in January 2013).

37. *See* Amy Maxmen, *The Genesis Engine*, WIRED (Aug. 2015), <http://www.wired.com/2015/07/crispr-dna-editing-2/>.

intended target.³⁸ Once there, CRISPR cuts and splices both strands of the DNA double helix with an enzyme, typically Cas9, in order to remove the sequence from the genome.³⁹

2. Current and Future Uses for CRISPR Technology

Researchers have already used CRISPR in a variety of settings, most of which have nothing to do with germline modification. Some examples include: making blight-resistant wheat crops;⁴⁰ prolonging the life of tomatoes by turning off genes that control how quickly they ripen;⁴¹ altering the genes in pigs so they could, in theory, “grow human organs for transplant;”⁴² repairing defective DNA in mice and curing them of genetic disorders;⁴³ knocking out every gene in a cancer-cell line to identify every one of the cell’s “Achilles’ heels,” which should make it “possible to build a comprehensive road map for [every type of specific] cancer”;⁴⁴ and permanently inactivating HIV in patient’s blood cells, which could potentially cure AIDS.⁴⁵

In the germline modification setting, CRISPR has already been used successfully to modify germ cells, non-reproductive cells, and both human and primate embryos.⁴⁶ While CRISPR’s use in modifying human embryos was limited to those that were non-viable,

38. *See id.*

39. *See id.*

40. *See* Kristen V. Brown, *Inside the Garage Labs of DIY Gene Hackers, Whose Hobby May Terrify You*, FUSION (Mar. 29, 2016, 7:00 AM), <http://fusion.net/story/285454/diy-cris-pr-biohackers-garage-labs/>.

41. *See* Specter, *supra* note 2 (explaining this approach is distinguishable from using genetically modified organisms—or “GMOs”—to enhance food crops because GMOs require the *introduction* of foreign DNA *into* foods, whereas CRISPR may be achieved by the *deletion* of certain genes *out of* foods).

42. Brown, *supra* note 40.

43. Zimmer, *supra* note 33.

44. Specter, *supra* note 2 (indicating “every cancer is a specific, personal disease” and that, until CRISPR, the wide genetic variations in cancer cells made it difficult to effectively develop treatments).

45. *See* Rafal Kaminski et al., *Elimination of HIV-1 Genomes from Human T-Lymphoid Cells by CRISPR/Cas9 Gene Editing*, 6 SCI. REP. 1, 1–2 (Mar. 4, 2016), <http://www.nature.com/articles/srep22555>.

46. Jennifer Doudna, *Perspective: Embryo Editing Needs Scrutiny*, 528 NATURE S6 (2015); *see* Yuyu Niu et al., *Generation of Gene-Modified Cynomolgus Monkey via Cas9/RNA-Mediated Gene Targeting in One-Cell Embryos*, 156 CELL 836, 839 (2014) (using cynomolgus monkey embryos); *see also* Puping Liang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Triprenuclear Zygotes*, 6 PROTEIN & CELL 363, 363–64 (2015) (modifying nonviable human embryos).

the fact that the technology *could* be used to genetically modify human embryos prompted an international summit comprised of leading doctors and biomedical researchers in December 2015.⁴⁷ The purpose of the summit was to discuss the safety and ethical implications of human gene editing and to confront a newly plausible prospect: altering the human germline to correct genetic diseases, versus altering it to offer “enhancements.”⁴⁸

Some of CRISPR’s futuristic uses include creating glowing plants and reviving the woolly mammoth: the former has already been accomplished;⁴⁹ the latter is still a work-in-progress.⁵⁰ Other more chilling possibilities include the use of CRISPR to create bioweapons,⁵¹ conjure “invasive mutant[]” species,⁵² “catalyze specific genetic changes in an entire population or environmental system,”⁵³ or develop “designer babies” for enhancement purposes, rather than to correct genetic abnormalities.⁵⁴

II. CRISPR’S IMPACT ON GENETIC ENGINEERING TECHNOLOGY

The importance of CRISPR technology in the realm of biomedical technology “cannot be overstated.”⁵⁵ “CRISPR has already revolutionized basic research by allowing scientists to readily modify the genome of cells and model organisms, enabling the development of an expanding set of tools to understand fundamental biological questions.”⁵⁶

This section proceeds in three parts. First, in order to fully appreciate CRISPR’s impact on genetic engineering technology, it

47. John Travis, *Making the Cut*, 350 SCI. 1456, 1456 (2015).

48. *Id.*

49. See Brown, *supra* note 40.

50. See Zimmer, *supra* note 33 (indicating scientists are trying to “rewrite the genomes of elephants, with the ultimate goal of re-creating a woolly mammoth”). *But see* GMO SAPIENS, *supra* note 1, at 69 (admitting de-extinction is a “fun idea,” but warning of the potential risks, including the subtle increase in public acceptance of cloning, specifically, human cloning).

51. GMO SAPIENS, *supra* note 1, at 196.

52. Maxmen, *supra* note 37.

53. GMO SAPIENS, *supra* note 1, at 191 (referring to this hypothetical large-scale genetic process as “gene drive”).

54. See *generally id.* (discussing the effects of the CRISPR-Cas9 technology on the possibility of “designer babies”).

55. Ante S. Lundberg & Rodger Novak, *CRISPR-Cas Gene Editing to Cure Serious Diseases: Treat the Patient, Not the Germ Line*, 15 AM. J. BIOETHICS 38, 38 (2015).

56. *Id.*

sets the stage by reciting the accolades received and critical acclaim prompted by CRISPR's discovery. It next explains the distinguishing features that make CRISPR worthy of such honor and reception. Finally, it describes the ways in which the very features that make CRISPR so revolutionary are also cause for serious concern.

A. *Accolades*

Although it is not the first of its kind, given its revolutionary nature and international recognition, it is no surprise that CRISPR and the researchers responsible for its development have already received numerous accolades. CRISPR was named *Science* magazine's 2015 Breakthrough of the Year,⁵⁷ has been described by *MIT Technology Review* as “the [b]iggest [b]iotech [d]iscovery of the [c]entury,”⁵⁸ and is expected to “change medicine forever.”⁵⁹ In addition, CRISPR's cofounders, Jennifer Doudna and Emmanuelle Charpentier, have received several prominent honors and awards for their collaborative discovery⁶⁰—including the 2016 L'Oréal-UNESCO for Women in Science award,⁶¹ the Princess of Asturias Award for Technical and Scientific Research,⁶² and *Time* magazine's list of 100 Most Influential People

57. Travis, *supra* note 47, at 1456–57 (proclaiming CRISPR promises to do everything from wiping out diseases to creating super crops and that “it's only slightly hyperbolic to say that if scientists can dream of a genetic manipulation, CRISPR can now make it happen”).

58. Antonio Regalado, *Who Owns the Biggest Biotech Discovery of the Century?*, MIT TECH. REV. (Dec. 4, 2014), <https://www.technologyreview.com/s/532796/who-owns-the-biggest-biotech-discovery-of-the-century/>.

59. Zimmer, *supra* note 33, reprinted in *The Biggest Biotech Discovery of the Century is About to Change Medicine Forever*, BUS. INSIDER (Feb. 18, 2015, 4:44 PM), <http://www.businessinsider.com/the-biggest-biotech-discovery-of-the-century-is-about-to-change-medicine-forever-2015-2>; see also Press Release, Gairdner Found., 2016 Canada Gairdner Awards Honour CRISPR-Cas Researchers and HIV/AIDS Leaders (Mar. 23, 2016) [hereinafter 2016 Gairdner Awards] (announcing that the winners of all five 2016 Canada Gairdner International Awards were scientists who played a significant role in the discovery and development of CRISPR technology).

60. For a complete list of honors and awards, see Jennifer A. Doudna, *Curriculum Vitae* [hereinafter Doudna, CV], https://biosciences.lbl.gov/wp-content/uploads/2015/10/Doudna_cv_082815-CURRENT.pdf (last visited Dec. 16, 2016) and Emmanuelle Charpentier, *Curriculum Vitae*, http://www.leopoldina.org/fileadmin/redaktion/Mitglieder/CV_Charpentier_Emmanuelle_EN.pdf (last visited Dec. 16, 2016).

61. *Honoring Women Scientists Who Are Changing the World*, UNESCO, [hereinafter *Honoring Women Scientists*] <http://en.unesco.org/news/honoring-women-scientists-who-are-changing-world> (last visited Dec. 16, 2016).

62. Doudna, CV, *supra* note 60; see also Lourdes Riquelme, *CRISPR Technology Receives the Spanish 'Nobel Prize'*, LABIOTECH.EU (June 1, 2015), <http://labiotech.eu/crispr->

in the world, to name a few.⁶³ There have also been “whispers” of a possible Nobel prize in CRISPR’s future.⁶⁴

B. *Distinguishing Features*

So what makes CRISPR worthy of being called this century’s biggest discovery in biotechnology? One reason is that nature, not science, is at the heart of this gene-editing tool.⁶⁵ But aside from being a product of Mother Nature, CRISPR has three features that distinguish it from other methods of gene editing and make it the most revolutionary technique on the market today: (1) simplicity, (2) accuracy, and (3) affordability.

1. Simplicity

First, CRISPR makes the complex work of editing the human genome relatively easy. Previous technologies using molecules known as zinc finger nucleases (“ZFNs”) and transcriptional activator-like effector nucleases (“TALENs”) also precisely alter chosen DNA sequences,⁶⁶ and are currently used in clinical trials.⁶⁷

technology-receives-the-spanish-nobel-prize/ (calling the Princess of Asturias Award the “Spanish equivalent to the Nobel prize”).

63. Mary-Claire King, *Emmanuelle Charpentier & Jennifer Doudna*, TIME (Apr. 16, 2015) <http://time.com/3822554/emmanuelle-charpentier-jennifer-doudna-2015-time-100/>; see also 2016 Gairdner Awards, *supra* note 59 (naming Doudna and Charpentier as two of the five scientists chosen to receive Canada Gairdner International Awards).

64. See, e.g., John Travis, *Inside the Summit on Human Gene Editing: A Reporter’s Notebook*, SCI. MAG. (Dec. 4, 2015, 3:45 PM), <http://www.sciencemag.org/news/2015/12/inside-summit-human-gene-editing-reporter-s-notebook> (saying a Nobel prize is “widely expected” for the scientists that discovered this new DNA-changing technology); Philip Hemme, *CRISPR Patent War to End After the Discovery of a New Editing Protein Other Than Cas9?*, LABIOTECH.EU (Sept. 30, 2015), <http://labiotech.eu/crispr-patent-war-end-discovery-new-editing-protein-cas9/> (predicting in 2015 that Doudna and Charpentier were “short-listed to receive the next [N]obel prize”); Joe Palca, *In Hopes of Fixing Faulty Genes, One Scientist Starts with the Basics*, NPR (Oct. 13, 2014, 3:20 AM), <http://npr.org/sections/health-shots/2014/10/13/354934248/in-hopes-of-fixing-faulty-genes-one-scientist-starts-with-the-basics>. But see Dani Bancroft, *Sorry CRISPR, You’ll Have to Wait Another Year to Win a Nobel Prize!*, LABIOTECH.EU (July 10, 2015), <http://labiotech.eu/sorry-crispr-youll-have-to-wait-another-year-to-win-a-nobel-prize/> (stating even though CRISPR is “[b]iotech history in the making” and “one of the most talked about gene-editing tools” in the industry, Doudna and Charpentier surprisingly did not win the 2015 Nobel Prize in Chemistry); Sarah Buhr, *CRISPR Loses Nobel to Tiny Machines*, TECHCRUNCH (Oct. 5, 2016), <https://techcrunch.com/2016/10/05/crispr-loses-nobel-to-tiny-machines/> (calling it “quite a shock” that CRISPR did not receive a Nobel prize, yet again, in 2016).

65. See Zimmer, *supra* note 33.

66. Travis, *supra* note 47, at 1456.

67. STEVEN OLSON, INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: A GLOBAL DISCUSSION 3 (2015) [hereinafter OLSON, INTERNATIONAL SUMMIT].

However, these gene targeting technologies are much more cumbersome and difficult to use than their CRISPR counterpart.⁶⁸

A side-by-side comparison reveals that, while all three are highly specific and efficient, CRISPR is the only technique that is easily constructed and able to edit multiple sites simultaneously.⁶⁹ First, CRISPR offers a one-component target design system, which is easy for researchers to construct.⁷⁰ This enables researchers to easily target a gene by replacing its complementary nucleotide sequence, which will modify the new target gene.⁷¹ This feature “not only simplifies the experimental design, it also yields equal or greater guiding efficiency.”⁷² Second, CRISPR is capable of introducing multiple gene disruptions simultaneously.⁷³ This feature allows researchers to edit multiple genes in a single organism with only one transformation, avoiding the need to complete several time-consuming screening procedures.⁷⁴ Given these deficiencies, CRISPR appears to be the superior gene-editing technology, as well as the most user friendly.⁷⁵

The simplicity with which CRISPR allows researchers and students to change genomes has furthered countless experiments that were “previously difficult or impossible to conduct.”⁷⁶ Beyond being difficult to perform, prior methods of gene editing were very long and drawn-out in two respects. First, depending on the organism, the process of editing a gene, much less a genome, often took scientists several months to perform.⁷⁷ Second, even after

68. *Id.* ZFNs are accurate and effective, but expensive and difficult to engineer. See Heidi Ledford, *CRISPR, The Disruptor*, 522 NATURE 20, 21 (2015); see also *infra* text accompanying note 90 (comparing the cost of ZFNs to that of CRISPR). Thus, ZFN technology was never widely adopted. Ledford, *supra* at 21. TALENs are more similar to CRISPR technology; however, like ZFNs, they are also fairly complicated and expensive. See Maxmen, *supra* note 37.

69. Jin-Song Xiong et. al, *Genome-Editing Technologies and their Potential Application in Horticultural Crop Breeding*, 2 HORTICULTURE RES. 2, 7 tbl.2 (2015).

70. See Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCI. 816, 820 (2012).

71. Xiong et al., *supra* note 69, at 5.

72. *CRISPR Cas9-gRNA Design*, APPLIED BIOLOGICAL MATERIALS, https://www.abmgood.com/marketing/knowledge_base/CRISPR_Cas9_gRNA_Design.php (last visited Dec. 16, 2016).

73. Xiong et al., *supra* note 69, at 5.

74. *Id.*

75. See GMO SAPIENS, *supra* note 1, at 12; see also Ledford, *supra* note 68, at 21 (“CRISPR methodology is quickly eclipsing zinc finger nucleases and other editing tools.”).

76. Doudna, *supra* note 46, at S6.

77. See Alex Buckley, *CRISPR-Cas9: Harbinger of Human Gene Editing and Its Ethical Turmoil*, FRONTIERS MAG. (Nov. 5, 2015), <http://frontiersmag.wustl.edu/2015/11/05/crispr-cas9>

scientists completed the editing process, it would often take another few months for the experiment to reach maturity.⁷⁸

To put this into perspective, in the past, a researcher studying the effects of a specific gene in mice models would have to introduce, or “knock out,”⁷⁹ a specific gene into a blastocyst,⁸⁰ insert the blastocyst into a female uterus, wait several months for the female to produce offspring, wait for the resulting offspring to sufficiently age and, only then, could the researcher study the gene’s effect.⁸¹ In contrast, with CRISPR technology, a researcher performing the same experiment no longer has to wait six months for the mice to breed in order to study the gene. Instead, scientists can use CRISPR to directly edit a mouse’s genome and study the side effects in a matter of weeks.⁸²

Scientists and researchers are not alone in reaping the benefits of this easy-to-use gene-editing technology. CRISPR has also catalyzed a movement of “DIY scientists” hoping to try their hand at modifying genes in plants, animals, and perhaps even one day, humans.⁸³ While it may be too soon to predict garage labs of DIY babies, CRISPR starter kits have already hit the market and now offer a wide range of potential products and uses.⁸⁴

spr-cas9-harbinger-of-human-gene-editing-and-its-ethical-turmoil/ (indicating that, with CRISPR, “researchers no longer have to wait six months for their mice to breed,” but can “directly edit the animals’ genomes in mere weeks”).

78. *See id.*

79. Kyle Davis, *CRISPR Probes the Inner Workings of the Genome in Real Time*, NAT’L HUM. GENOME RES. INST. (May 8, 2015), <https://www.genome.gov/27560763> (indicating that, unlike early techniques, CRISPR enables a gene to be “knocked out” while the mouse is alive, which decreases the longevity of experiments).

80. *See* FRANKEL & CHAPMAN, *supra* note 19, at 59 (defining a blastocyst as “[a] pre-implantation embryo consisting of 30–150 cells”).

81. *See* Buckley, *supra* note 77.

82. *See id.*

83. *See, e.g.*, Brown, *supra* note 40 (explaining how “a 30-year-old Mississippi resident who never attended college, first started doing at-home experiments after seeing [CRISPR] kits to make glowing plants . . . online.”).

84. *See, e.g.*, DIY Yeast CRISPR Kit, ODIN, <http://www.the-odin.com/diy-bacterial-gene-engineering-crispr-kit/> (last visited Dec. 16, 2016) (offering a CRISPR starter kit for \$160 that edits the ADE2 gene to give it a red pigment); GLOWING PLANT, <http://www.glowing-plant.com/maker> (last visited Dec. 16, 2016) (selling glowing plants for \$100, glowing plant seeds for \$40, and a DIY glowing plant maker kit for \$300); *see also* Loz Blain, *Do-It-Yourself CRISPR Genome Editing Kits Bring Genetic Engineering to Your Kitchen Bench*, NEW ATLAS (Nov. 11, 2015), <http://www.newatlas.com/home-crispr-gene-editing-kit/40362/> (indicating it costs only \$130 to “have a crack at re-engineering bacteria so that it can survive on a food it normally wouldn’t be able to handle,” and \$160 to “get your eukaryote on and edit the ADE2 gene of yeast to give it a red pigment”).

2. Accuracy

Second, in addition to being a user-friendly tool, CRISPR is able to modify DNA sequences in living organisms with unprecedented precision.⁸⁵

CRISPR-Cas9 can pinpoint important but tiny gene sequences in our vast genomes, the genetic equivalent of finding a needle in a haystack. Once there, it can erase and/or change A's, C's, G's, or T's, or even larger genomic regions, in surprisingly precise ways. CRISPR can literally re-write the genomic book inside of us.⁸⁶

Traditional gene-editing techniques worked more like a “hatchet than [a] scalpel” and were rarely precise.⁸⁷ Though the development of ZFNs and TALENs did provide a more enhanced form of genome editing than traditional methods, CRISPR will make this process even faster, easier, and more accurate than ever before.⁸⁸

3. Affordability

Third, CRISPR has made the gene editing process not only simple and reliable, but also much more affordable.⁸⁹ “Customized Zinc finger and TALENs systems can cost anywhere around ~\$5000 or ~\$500 respectively, while a CRISPR/Cas9 system can cost as little as \$30.”⁹⁰ These price differences can be attributed to a variety of factors. One reason is that ZFNs are very difficult to construct in ordinary research labs, so they are typically designed by commercial sources and, thus, expensive.⁹¹ Although TALENs cost less than ZFNs, they are more difficult to deliver efficiently due to their large size.⁹² Another reason the TALEN system is

85. OLSON, INTERNATIONAL SUMMIT, *supra* note 67, at 1.

86. GMO SAPIENS, *supra* note 1, at 11–12.

87. See Specter, *supra* note 2 (attributing the imprecision of earlier gene-editing technologies to the fact that “they could recognize only short stretches within the vast universe of the human genome”).

88. *Id.*

89. *See id.*

90. Nathan Guo, *CRISPR—The Future of Synthetic Biology*, LUX CAP. (July 7, 2015) <http://www.luxcapital.com/news/crispr/>; see also Ledford, *supra* note 68, at 21 (“Researchers often need to order only the RNA fragment; the other components can be bought off the shelf. Total cost: as little as \$30.”).

91. CTR. FOR MOUSE GENOMICS, GENOME ENGINEERING WITH ZFNs, TALENS AND CRISPR/CAS9, <http://www.ucalgary.ca/mousegenomics/files/mousegenomics/introduction-to-engineered-nucleases.pdf> (last visited Dec. 16, 2016); Ledford, *supra* note 68, at 21 (stating ZFNs typically start at \$5000 or more to order.)

92. See Jeffrey M. Perkel, *Genome Editing with CRISPRs, TALENs and ZFNs*,

more expensive than CRISPR is because TALENs are more time consuming to construct, which requires additional labor costs.⁹³

C. Concerns

The development of CRISPR technology represents an unprecedented advancement in germline engineering and holds great promise for next generation therapeutics; however, it has sparked an ethical firestorm. Now that CRISPR has been used to modify nonviable human embryos⁹⁴ and to create a generation of gene-modified primates that are physiologically similar to humans,⁹⁵ it is only a matter of time before HGM clinical trials will be pursued. This raises numerous challenges across the spectrum, from research to implementation.

Several scientists have expressed both safety and ethical concerns associated with CRISPR technology—specifically, the potential for exploiting non-therapeutic modification, off-target genome modifications, and the existence of viable alternatives, such as in vitro genetic profiling and screening.⁹⁶ Other major concerns include unequal access to CRISPR germline technology (if and when it reaches the distribution phase), the potential for eugenics, whether the costs outweigh the expected benefits, and “moral grayness inherent to genetic modification of human life.”⁹⁷

This comment addresses many of these concerns. Part III proposes a regulatory framework with specific policies that conscientiously phase the use of CRISPR technology in HGM at a pace responsive to ethical examination.

BIOCOMPARE (Aug. 27, 2013), <http://www.biocompare.com/Editorial-Articles/144186-Genome-Editing-with-CRISPRs-TALENs-and-ZFNs/> (“Labs can build custom TALENs for a fraction of what ZFNs cost. Addgene sells individual TALEN plasmids for \$65 apiece, and complete kits for a few hundred dollars. Dan Voytas’ popular Golden Gate TALEN 2.0 kit costs \$425.”).

93. See A. A. Nemudryi et al., *TALEN and CRISPR/Cas Genome Editing Systems: Tools of Discovery*, 6 ACTA NATURAE 19, 36 (2014).

94. See generally Liang et al., *supra* note 46 (discussing CRISPR gene editing in nonviable human embryos).

95. See Yuyu Niu et al., *supra* note 46, at 836–37 (indicating researchers selected cynomolgus monkey as the model because of their similarities to humans).

96. See, e.g., Baltimore et al., *supra* note 3, at 37; Edward F. Lanphier et al., *supra* note 10, at 410–11; see also GMO SAPIENS, *supra* note 1, at 260 (defining off-target effect as an errant edit by CRISPR).

97. Niklaus H. Evitt et al., *Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework*, 15 AM. J. BIOETHICS 25, 25 (2015).

While advocates and skeptics of CRISPR technology put forth a wide range of social and ethical arguments, many of these issues are beyond the scope of this comment, including parental autonomy, constitutional reproductive issues, cloning, gender selection, and abortion. Instead, three social and bioethical issues are discussed. The first addresses concerns about CRISPR's ease of use and wide spread availability. This concern sparked the recent debate concerning CRISPR technology, and it is the primary reason many scientists and bioethicists are calling for regulation of HGM. The second focuses on the technical issues associated with using CRISPR technology to perform HGM. The third addresses ethical concerns of HGM.

1. Ease of Use and Widespread Accessibility

Last year, *Nature Biotechnology* asked a group of scientists whether they thought HGM was inevitable; many of them responded yes.⁹⁸ Why? Because CRISPR technology is widely used, easy to repeat, and makes the possibility of germline editing “more accessible to a wider range of individuals.”⁹⁹ While there are still challenges on both the technical and biological fronts, “the rapid development and widespread adoption of [this] simple, inexpensive, and remarkably effective genome engineering method” is catalyzing the conversation about how HGM should be managed and regulated.¹⁰⁰

2. Underdeveloped Safety Mechanisms

CRISPR is still far from ready to modify the human germline,¹⁰¹ but that may not stop over-ambitious scientists who are anxious to get in on the CRISPR revolution. In its current form, CRISPR poses several safety concerns, namely off-target effects, unex-

98. See Katrine S. Bosley et al., Supplementary Comments, *CRISPR Germline Engineering—The Community Speaks*, 33 NATURE BIOTECH. 478–86 (2015), <http://www.nature.com/nbt/journal/v33/n5/extref/nbt.3227-S1.pdf> (providing the unedited responses of Bosley and colleagues and showing that far more scientists think germline modification is inevitable than represented in the edited published version) [hereinafter Supplementary Comments].

99. *Id.*

100. Baltimore et al., *supra* note 3, at 36–37.

101. Lander, *supra* note 3, at 6; see also Maxmen, *supra* note 37 (“Engineered humans are a ways off—but nobody thinks they’re science fiction anymore.”).

pected multigenerational side effects, and a lack of a validated reversal mechanism.¹⁰²

Researchers in China recently applied the technique to a non-viable human embryo in an attempt to correct a disorder that interferes with the ability to make healthy red blood cells.¹⁰³ However, their efforts were largely unsuccessful.¹⁰⁴ The study demonstrated that CRISPR was much less accurate in targeting genes in embryos than it is in isolated cells and highlighted that “much remains to be learned regarding the efficiency and specificity of CRISPR/Cas9-mediated gene editing in human cells, especially in embryos.”¹⁰⁵ However, this “failure” is unlikely to discourage others from trying CRISPR again in the HGM setting. After all, that is the purpose of experimentation—the failure of one is simply a learning experience for another.

Even with enhanced accuracy, the practice will not likely be risk-free.¹⁰⁶ The CRISPR technique could be completely perfected and still lead to unexpected multigenerational side effects that go unnoticed for several years.¹⁰⁷ For example, a genetic variant that decreases the risk of one disease could increase the risk of another.¹⁰⁸ Unless these effects are studied closely over time and against a diverse backdrop, the full medical implications of many genetic variants will not be fully understood until they present themselves in fully developed human subjects.¹⁰⁹ In the end, even in a hypothetical future scenario with an essentially perfectly accurate gene-editing technology, “opting for PGD is going to be the wiser choice for parents and doctors almost every time.”¹¹⁰ “The reality of PGD as a competing and generally superior technology to human genetic modification needs further discussion.”¹¹¹

102. See Evitt et al., *supra* note 97, at 28.

103. See Liang et al., *supra* note 46, at 363–64; Maxmen, *supra* note 37.

104. See Maxmen, *supra* note 37.

105. Liang et al., *supra* note 46, at 364; see also Maxmen, *supra* note 37.

106. Lander, *supra* note 27, at 6.

107. See Evitt et al., *supra* note 97, at 28.

108. See Lander, *supra* note 27, at 6 (“[T]he *CCR5* mutations that protect against HIV also elevate the risk for West Nile virus, and multiple genes have variants with opposing effects on risk for type 1 diabetes and Crohn’s disease.”).

109. See *id.* at 6–7.

110. GMO SAPIENS, *supra* note 1, at 123; see also BEYOND THERAPY, *supra* note 23, at 41 (discussing various uses for pre-implantation genetic diagnosis).

111. GMO SAPIENS, *supra* note 1, at 123.

In addition to posing unknown multigenerational risks, the CRISPR method also currently lacks a validated reversal method.¹¹² Meaning, if the process *is* used and *does* result in unintended side effects, there would be no way to undo the modifications. This issue further complicates an already controversial matter because, even if the resulting side effects are not necessarily dangerous (or even negative), there is something intrinsically wrong with modifying the genetic disposition of a person's lineage and not providing a companion reversal mechanism for future generations to utilize if they so choose.¹¹³

3. Ethical Dilemmas

CRISPR's potential to alter the genetic destiny of generations to come is both exciting and dangerous. Thus, the arguments on both sides of the controversial public debate surrounding the use of CRISPR to modify the human germline are as fervent as to be expected. On the one hand, if we *can* eradicate devastating diseases such as sickle cell anemia, should we not? If the basic technology is already in place, there may come a time when it is morally justifiable, even obligatory, to use CRISPR to modify a defective germline that poses an imminent threat to afflicted individuals.¹¹⁴ On the other hand, just because we *can* fix so-called "defective" genes, does that necessarily mean that we should? Having the basic technology already in place may not actually be a good thing if it can be easily manipulated for unethical purposes or pose danger to the resulting child. This concerns human beings, after all—real-life, walking, talking, breathing people who will forever feel the repercussions of the decisions we make today concerning their biological fate.

This part addresses four ethical dilemmas related to CRISPR germline modification. The first issue concerns the stigmas and inequalities that the use of CRISPR technology in the HGM setting could create or exacerbate. The second dilemma confronts the potential economic pressures to undergo HGM procedures, as well as issues related to consumer demand for HGM products and services. The third concerns how all of these factors—social stigma, inequality, economic pressure, and consumer demand—could re-

112. See Evitt et al., *supra* note 97, at 26.

113. See *id.*

114. See GMO SAPIENS, *supra* note 1, at 99.

sult in what is known as “positive” eugenics. The fourth issue relates to embryonic research and development.

a. Reinforcing Stigmas and Exacerbating Inequalities

Social justice considerations demand that discrimination and oppression be addressed when it comes to preventing disease and promoting health. “[T]he line between diversity and disability is fuzzy.”¹¹⁵ By treating certain conditions as disabilities that need to be “fixed” via biomedical interventions like HGMs, biomedical researchers may overlook, and unintentionally reinforce, stigmas and social disparities.¹¹⁶ In addition, “[t]he association of racial, ethnic, and other groups with particular diseases could lead to new forms of stigmatization.”¹¹⁷ The use of gene-editing techniques is sown with economic and social values and interests that could easily reproduce existing hierarchies without careful scrutiny.¹¹⁸

Science that is intended to benefit society can “unintentionally reproduce social injustices—for example, in the way that genomics has inadvertently reinforced certain racial categories.”¹¹⁹ For this reason, it is vitally important to include diverse perspectives of actors outside the medical field (such as policy makers and historians) in order to ensure that “assessments of risks and benefits are not limited to medical risks alone.”¹²⁰ As HGM technology “becomes more widespread, it will serve to further stigmatize the disabled and promote the notion that some lives are not worth living or are better off prevented in the first place.”¹²¹ Un-

115. OLSON, INTERNATIONAL SUMMIT, *supra* note 67, at 4.

116. *Id.*

117. *Id.*

118. *Id.*

119. *Id.*

120. *Id.*

121. PRESIDENT’S COUNCIL ON BIOETHICS, REPRODUCTION AND RESPONSIBILITY: THE REGULATION OF NEW BIOTECHNOLOGIES 97 (2004) [hereinafter REPRODUCTION AND RESPONSIBILITY], https://repository.library.georgetown.edu/bitstream/handle/10822/55938/1/_pcbe_final_reproduction_and_responsibility.pdf?sequence=1&isAllowed=y. Frankel and Chapman argue HGM may lead to increased prejudice against persons with disabilities “as long as Americans still discriminate unfairly on the basis of physical appearance, ancestry, or abilities.” FRANKEL & CHAPMAN, *supra* note 19, at 38. They argue that in a country like the United States,

which has a long and disturbing history of drawing sharp distinctions among citizens on the basis of race and ethnicity and where many persons harbor beliefs in biological determinism. It is important to remember [that] past attempts to use reproductive interventions to improve the genetic prospects of

less covered by insurance or subsidized by taxpayers, widespread use of HGM could also expand the gap between the “haves” and the “have-nots” in society.¹²²

b. Economic Pressures and Consumer Demand

“[T]he private sector has strong commercial motivations to develop both treatments for disease and procedures to enhance human traits.”¹²³ This is, in part, due to the 1980 Supreme Court decision *Diamond v. Chakrabarty*, which allowed genetically modified organisms (“GMOs”) to be characterized as intellectual property and, therefore, be owned.¹²⁴ This decision “opened the door to the patenting of almost any GMO,” thereby setting the stage for private companies to pursue gene-editing technology as a strong source of potential new income.¹²⁵

“This momentum for GMOs was further bolstered by the U.S. FDA’s approval two years later in 1982 of the first human GMO product: insulin made from GM bacteria that had been designed in a laboratory to produce large amounts of the drug.”¹²⁶

While genetically modified humans would not be patentable, GM techniques for making modified people likely would be.¹²⁷ These methods—more specifically, those focused on curing or treating human disease—are where the long-term financial gain of CRISPR will ultimately lie.¹²⁸ If achieved, economic forces to reduce health care costs could put pressure on people to change the genetic sequences associated with disease. “The association of

future generations [ultimately] reinforced and exacerbated social injustices against the poorer, less powerful, and more stigmatized [members of society].

Id.

122. FRANKEL & CHAPMAN, *supra* note 19, at 37.

123. OLSON, INTERNATIONAL SUMMIT, *supra* note 67, at 3.

124. See 447 U.S. 303, 310 (1980) (finding that a genetically modified bacterial strain is patentable); see also GMO SAPIENS, *supra* note 1, at 33, 35.

125. GMO SAPIENS, *supra* note 1, at 35.

126. *Id.*

127. See *id.* (indicating patents for technologies that could, in the future, be used in the process of making GM humans are pending and that some have already been awarded, including Professor Feng Zhang’s CRISPR-Cas9 patent, which is currently disputed by CRISPR co-founder Jennifer Doudna). But see Stephanie M. Lee, *Jennifer Doudna Has Won a CRISPR Gene-Editing Patent*, BUZZFEED (Feb. 16, 2016, 5:15 PM), https://www.buzzfeed.com/stephaniemlee/new-crispr-patent?utm_term=.faAJ9wAg2v#.jkmR4rBnay (stating that Doudna was recently awarded a patent encompassing a much wider range of CRISPR uses, but that the patent dispute with Zhang is still ongoing).

128. See Maxmen, *supra* note 37.

racial, ethnic, and other groups with particular diseases could lead to new forms of stigmatization,” while “[t]he belief that genes influence particular behaviors or other complex traits could lead to pressures to change those genes in future generations.”¹²⁹

Similarly, patients with genetic diseases have a strong drive to find cures for those diseases, and their ardor should not be underestimated. Many of these patients would be interested in HGM if it were to become clinically available.¹³⁰ Perhaps, more concerning than the desperate patient is the concerned parent. While they may have good intentions, one cannot reasonably expect future parents to resist the slew of pharmaceutical marketing campaigns promoting the use of HGM for improvement purposes, rather than for medical necessity, that would occur if CRISPR technology became widely available to consumers at an affordable price. By nature, parents are fundamentally predisposed to want the very best for their children.¹³¹ As a result, many parents might not be able to distinguish between appropriate intervention and unnecessary enhancement:

[M]ost of us parents want our children to be healthy and happy. One could view basic parenting efforts as a form of “enhancement” over the grim alternative of putting your child at risk of malnutrition and such. However, common sense dictates that doing things such as feeding our child a healthy diet and taking care of one’s own health as a mother during pregnancy are entirely different than genetically enhancing your child by heritably altering her or his DNA in every cell of their body.¹³²

Thus, parents’ desire to nurture, protect, and see their offspring thrive could translate into consumer demand for particular attributes and could lead people to pursue options for human gene editing in the private sector.¹³³ And while doing so would be within their rights as parents, the fact that it would be difficult to regulate under the current regulatory scheme could pose serious concerns as to the safety and validity of such procedures.¹³⁴

129. OLSON, INTERNATIONAL SUMMIT, *supra* note 67, at 4.

130. *Id.* at 3.

131. See FRANKEL & CHAPMAN, *supra* note 19, at 40.

132. GMO SAPIENS, *supra* note 1, at 171–72.

133. See OLSON, INTERNATIONAL SUMMIT, *supra* note 67, at 4.

134. *See id.*

c. “Positive” Eugenics

Working in combination with one another, the above factors could lead to what is known as “positive” eugenics. If certain genetic characteristics are perceived to be of a lesser quality than others, that stigma, combined with economic pressures from interested third parties—such as insurance companies or drug manufacturers—could lead to greater support for genetic human enhancement for the purpose of making people “better,” even where there is no medical necessity.¹³⁵ While it is a far cry from the forced sterilization or controlled breeding America experienced in the 1960s, this type of thinking could cause people to associate human “quality” with genetics and make potential parents feel morally obligated to utilize HGM technology—as if doing otherwise would be a disservice to their unborn child and generations to come.¹³⁶

While the selection of gametes through sperm banks and oocyte donation with the intention of making better babies—an already widespread practice that is largely accepted by society—is arguably a form of eugenics, it is notably different than using technology to proactively alter the human germline. On the most extreme end of the spectrum, the technology has the potential to alter the genetic destiny of the human race in a single generation.¹³⁷ On the more realistic end of the spectrum, HGM could “lead to decreased diversity in our species and to more discrimination against certain classes of people.”¹³⁸

135. See GMO SAPIENS, *supra* note 1, at 173, 176.

136. See *id.* at 172–73 (quoting fertility innovator and eugenicist Robert Edwards who stated, “[s]oon it will be a sin of parents to have a child that carries the heavy burden of genetic disease. We are entering a world where we have to consider the quality of our children.”).

137. Paul Knoepfler touches on this by comparing it to dog breeding. *Id.* at 178. Eugenicist Julian Savulescu says, “what works for dog breeding should work for humans as well, except hugely accelerated by genetic technology. . . . What took us ten thousand years in the case of dogs could take us a single generation through genetic selection of embryos.” *Id.* at 178. Similarly, Professor Gregory Pence argues that “[m]any people love their retrievers and their sunny dispositions around children and adults. . . . Would it be so terrible to allow parents to at least aim for a certain type, in the same way that great breeders . . . try to match a breed of dog to the needs of a family?” *Id.* Knoepfler calls these dog-human trait modification analogies “disturbing” and Professor Pence’s idea of creating “sunny” children via genetics particularly “creepy.” *Id.*

138. *Id.* at 180 (suggesting parents have an obligation to avoid letting racism, sexism, and other forms of discrimination influence reproductive choices).

Further, even if HGM does not result in a superior class of human beings, there is still likely to be an equity problem in terms of access to HGM technologies on both a national and international scale.¹³⁹ On a national scale, for example, if and when CRISPR technology becomes operable in human beings, treating or curing sickle-cell anemia would indeed be one of its most compelling uses.¹⁴⁰ But because sickle-cell anemia affects primarily black communities,¹⁴¹ and because only about one in four blacks have health insurance,¹⁴² the very class of people that would benefit from the technology would be unlikely to create a huge demand absent state intervention and assistance. Similarly, on the international front, “Nigeria is very interested in human gene editing, given that it has the highest number of sickle cell cases in the world.”¹⁴³ However, the country would not likely be able to take advantage of the technology unless it improved its clinical and research capacity.¹⁴⁴ If not properly controlled, CRISPR and other cutting-edge gene-editing technologies have the potential to empower this new, more powerful form of “positive” eugenics, and pose major social risks, such as deepening the socioeconomic divide and creating new genetic divisions amongst classes and countries.¹⁴⁵

d. Human Embryo Experimentation

Research involving HGM in human embryos has the potential to provide invaluable information about gene editing and lead to major discoveries concerning fertility and early human development.¹⁴⁶ Therefore, rather than be prohibited, such research

139. See OLSON, INTERNATIONAL SUMMIT, *supra* note 67, at 5.

140. See Miller, *supra* note 29, at 1325 (recalling a “20-year-old patient with sickle cell anemia who had suffered three strokes, been crippled by hemorrhages into his major joints, and was in unrelenting pain from the arthritis that resulted” and thus arguing that we “need to push the frontiers of medicine to rid families of [such] monstrous genetic diseases.”).

141. *Who Is at Risk for Sickle Cell Disease?*, NAT’L HEART, LUNG & BLOOD INST., (Aug. 2, 2016), <https://www.nhlbi.nih.gov/health/health-topics/topics/sca/atrisk>.

142. CTRS. FOR DISEASE CONTROL & PREVENTION, SUMMARY HEALTH STATISTICS: NATIONAL HEALTH INTERVIEW SURVEY (2014), http://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2014_SHS_Table_P-11.pdf.

143. OLSON, INTERNATIONAL SUMMIT, *supra* note 67, at 5.

144. *Id.*

145. See GMO SAPIENS, *supra* note 1, at 173–74, 176, 180.

146. See *id.* at 239.

“should only be conducted under certain very limited and strictly controlled conditions.”¹⁴⁷

“To optimize gene-editing tools for clinical use in human embryos intended to produce babies, you are likely to need to ‘practice’ on thousands of embryos to perfect the methodology.”¹⁴⁸ This prompts serious moral and ethical considerations.¹⁴⁹ “[E]mbryos bear an intermediate moral status between nonhuman life and a fetus.”¹⁵⁰ Thus, both “researchers and future parents have an obligation to respect the moral[] . . . status of the human embryo.”¹⁵¹ There is a strong argument, however, that HGM fails to meet this obligation because it “either renders the embryo morally neutral or diminishes it to the status of property or goods.”¹⁵²

III. RECOMMENDATIONS

The development of CRISPR technology represents a revolutionary advancement in genetic engineering: it is simple to use, inexpensive, highly accessible, and has proven to be remarkably effective in a variety of genomic settings.¹⁵³ However, this comment suggests that these features—the very characteristics that make CRISPR such a revolution in biotechnology—also pose numerous safety and ethical concerns to modern society.¹⁵⁴ And while the technology has not yet reached a point at which it can be safely used to modify the human genome, in light of the rapid advancements to date, it would be wise to begin implementing a mechanism of oversight.¹⁵⁵

147. *Id.* at 239–40 (stating editing work involving human embryos should be only done in a laboratory setting).

148. *Id.* at 160 (indicating these tests may be done with no intention to use the embryos to produce babies).

149. *See, e.g., id.* at 160 (“Is that ethical? And where do you get all those human eggs and embryos?”).

150. Evitt et al., *supra* note 97, at 26; *see also* REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 111 (indicating embryos are not considered “human subject[s],” and thus fall outside FDA oversight and protection until and unless they are implanted in vivo).

151. OLSON, INTERNATIONAL SUMMIT, *supra* note 67, at 4.

152. *Id.*

153. *See* Baltimore et al., *supra* note 3, at 36.

154. *See supra* Part II.C (identifying the negative implications related to CRISPR’s ease of use and widespread accessibility, explaining the risks of using CRISPR technology in its current form, and discussing four major ethical dilemmas posed by the use of CRISPR in HGM).

155. Baltimore et al., *supra* note 3, at 37.

This part proceeds in two sections. First, it discusses deficiencies with current regulation.¹⁵⁶ It then proposes an expanded regulatory framework that addresses the social and bioethical concerns discussed throughout this comment.

A. *Lack of Existing Regulation*

At present, there are no federal laws or regulations governing human germline modification.¹⁵⁷ However, the Dickey-Wicker Amendment (D-W) prevents federal funding of research involving the destruction of human embryos¹⁵⁸ and there is extensive federal regulation of research involving somatic gene therapy.¹⁵⁹ This aperture in applicable regulation is likely attributable to the fact that, until recently, HGM has been merely speculative.¹⁶⁰ While the idea of altering the genetic makeup of a human being has been *theoretically* possible for some time, it has also been highly impractical given the technical barriers, monetary cost, and its controversial nature.¹⁶¹ CRISPR has changed all of that. HGM is not only on the table, it is now considered inevitable by many scientists due to the advent of CRISPR technology.¹⁶² Those who believe HGM is evitable base their rationale on human decision-making: “When it comes to germ-line engineering, we are masters of our own destiny. The sun rising and setting every day is inevitable. Germ-line engineering is a choice we have the opportunity to make.”¹⁶³

The scientific community has done well to confront the implications of CRISPR early and head-on. Researchers from around the world have met to discuss the potential and formidable uses of CRISPR, held workshops to produce a consensus report on the

156. These ideas were adapted from Girard Kelly, Comment, *Choosing the Genetics of Our Children: Options for Framing Public Policy*, 30 SANTA CLARA TECH. L.J. 303 (2014).

157. See REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 110. *But see* GMO SAPIENS, *supra* note 1, at 96 (indicating some states—including Michigan, Minnesota, and Pennsylvania—prohibit research on embryos if it leads to their destruction).

158. The Balanced Budget Downpayment Act, Pub. L. No. 104-99, § 128, 110 Stat. 34 (1996); *see* GMO SAPIENS, *supra* note 1, at 96.

159. See REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 110.

160. See *id.* at 168.

161. See Bosley et al., *supra* note 98. Qi Zhou and Jinsong Li discuss the technical and ethical barriers surrounding HGM. *Id.*

162. See *id.* Researchers, ethicists, and business leaders tend to agree on its inevitability. *Id.*

163. *Id.*

ethical and policy issues of gene transfer, and collaborated with major scientific journals to publish articles that encourage researchers to “slow down, ask difficult questions beyond the science, and make[] conscious and well-considered decision[s].”¹⁶⁴ However, the current laissez-faire approach to regulation is based largely on the notion that health professionals are better suited to make crucial judgment calls on a case-by-case basis, as they have specialized expertise and are more “familiar with the details and circumstances involved.”¹⁶⁵ But because CRISPR has the potential to be used outside just the medical profession, encouragement will likely not go far before enforcement will need to step in.

At present, the National Institute of Health (“NIH”) and the Food and Drug Administration (“FDA”) are two main federal bodies overseeing gene-transfer research. The NIH oversees the federal funding of gene-transfer research through its Recombinant DNA Advisory Committee (“RAC”), while the FDA regulates gene-transfer clinical trials and products.¹⁶⁶ In their current form, these authorities would fail to adequately regulate the use of CRISPR for HGM purposes due to the following limitations: First, FDA oversight is limited to gene-therapy products and research protocols involving “human subject[s].” Therefore, experimentation on human embryos and gametes fall outside the FDA’s purview.¹⁶⁷ Second, oversight by RAC is limited to projects and institutions that receive NIH funding.¹⁶⁸ Thus, privately funded experiments fall outside the RAC’s purview. The following sections separately address these limitations.

1. Food and Drug Administration (FDA)

The FDA is responsible for ensuring the safety and effectiveness of all gene-transfer therapy products and research protocols.¹⁶⁹ Gene-therapy products mean biologically based articles—which are those removed from a human subject, modified outside the body, and then reintroduced back into the same human subject—as well as new articles, either natural or synthetic, that are

164. *Id.*

165. REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 8–9 (implying that the practice of medicine occupies a special place in the American legislative and legal system).

166. *Id.* at 110–11.

167. *See id.* at 111.

168. *Id.*

169. *Id.* at 110–11.

transferred to the human subject for the purpose of genetically altering the subject's cells.¹⁷⁰ Research protocols that fall within the purview of the FDA include any transfers in which new genetic material is introduced into a human subject to replace missing or flawed DNA, for the purpose of treating or curing a disease.¹⁷¹ This type of gene-transfer is considered a "clinical trial" and requires prior approval from the FDA.¹⁷²

While the FDA has broad authority to regulate all research and products related to somatic gene editing, the legal situation regarding the use of CRISPR technology to modify the human genome is less clear.¹⁷³ Technically, the FDA has no general authority to regulate research and products related to HGM because gametes and embryos are not "human subjects."¹⁷⁴ This effectively allows for experimentation on any human embryos as long as they are not thereafter placed in utero or "aimed at the development of a 'product' subject to its approval."¹⁷⁵

If and when technology becomes safe enough to use in utero at the clinical development phase, the FDA would have the authority to regulate claims of safety and effectiveness of germline therapy products—but probably not the products themselves.¹⁷⁶ Because human subject protections only reach embryos once they are implanted through in vitro fertilization ("IVF"), FDA regulations may not legally apply to early embryos or gametes that are not considered legal subjects.¹⁷⁷ However, if the regulations did apply, the FDA would not likely approve HGM technologies at this time, as CRISPR has not been proven entirely safe or effective in editing the human genome.

170. *Id.* at 111.

171. *Id.*

172. *Id.* (indicating an investigational new drug (IND) application must be submitted to the FDA prior to any gene-transfer clinical trial).

173. *See* GMO SAPIENS, *supra* note 1, at 95.

174. REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 111 (indicating embryos are not considered "human subjects," and thus do not receive all the attendant protections of the Common Rule and FDA safeguards until they are implanted in vivo).

175. *Id.* at 131.

176. *See id.* at 54–55.

177. *See supra* note 174 and accompanying text; *see also* REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 113 (explaining that the FDA has no "clear legal authority to consider the safety of future generations"). The Office of Human Research Protections (OHRP) and the FDA under the Common Rule protect embryos outside a woman's uterus as human subjects for the purpose of research on pregnant women and fetuses. *See id.* at 131–32, 135.

2. National Institute of Health (NIH)

The NIH provides oversight of gene-transfer technologies and funding.¹⁷⁸ Compared to the FDA, the NIH “provides more limited oversight through its Recombinant DNA Advisory Committee.”¹⁷⁹ The RAC considers the “ethical implications of—and offers advice to the NIH director about—novel gene-transfer research protocols” that involve introducing genes into human subjects and are connected to NIH funding.¹⁸⁰ While the NIH is responsible for overseeing some gene-transfer research studies, its oversight and review is limited to the projects and institutions it funds.¹⁸¹

Currently, the RAC’s decision not to consider HGM studies that aim to produce modified children effectively prevents funding for any such work.¹⁸² However, this moratorium on federally funded gene editing is simply a policy not to “entertain proposals for germ line alterations,” not a proscription.¹⁸³ Moreover, because the NIH’s policy is limited to the federal funding of research involving embryos, it does not stop or attempt to regulate research and development by private parties.¹⁸⁴

Despite its limited authority, the NIH’s policy against funding HGM has likely served as a deterrent based on the costs and complexities associated with traditional HGM techniques, the associated risks, and poor public perception.¹⁸⁵ However, all of this has changed in light of the development of CRISPR technology. Given that CRISPR is easy to use and highly affordable, “it would not take an outrageous amount of money to try to do it privately.”¹⁸⁶ Thus, the NIH’s moratorium is “unlikely to be much of a deterrent,” since its policy is limited to research funded by the federal government and D-W only prevents federal funding of research that destroys an embryo.¹⁸⁷

178. See REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 114 (calling the NIH a “major funder of human gene-transfer research and the basic science that underpins it”).

179. *Id.* at 111.

180. *Id.*

181. See *id.* at 114 (noting that the NIH may also accept and review “protocols from researchers who voluntarily submit them, regardless of the funding source”).

182. See *id.* at 198.

183. FRANKEL & CHAPMAN, *supra* note 19, at 45–46.

184. See John A. Robertson, *Procreative Liberty in the Era of Genomics*, 29 AM. J.L. & MED. 439, 483 (2003) (stating the Congressional ban on funding for embryo research left “the matter in the hands of the private sector”).

185. See *supra* Part II.

186. GMO SAPIENS, *supra* note 1, at 96.

187. *Id.*

B. *Recommended Regulatory Framework*

While the current regulatory scheme does not attempt to strike a balance between the safety concerns and moral imperatives of HGM, preexisting laws governing other types of genetic modifications indicate Congress acknowledges that both safety and ethics are important considerations in this area. For example, the existence of regulation in somatic gene therapy suggests a general intention by Congress to oversee and ensure the safety of research involving genetic engineering in human beings. Similarly, the federal prohibition on funding research that destroys human embryos likely indicates a Congressional intention to impose moral restrictions on scientific experiments. Given that Congress has already adopted laws to address these issues separately, it would not be a huge leap to pass a law that allows for the consideration of both safety and morality when it comes to the development and use of HGM technologies.

Congress could pass legislation either expanding the scope of FDA authority to encompass HGM technologies or create a new regulatory agency. Given the American legal landscape and the fact that CRISPR is still so new, it is unlikely that Congress would be able to get past the politicization that goes along with embryonic research and development to create a new agency. Thus, it would be more realistic to expand the scope of FDA authority. Doing so would provide a mechanism for oversight without having to create a new regulatory agency. The FDA already has vast experience in regulating the safety and efficacy of clinical research and development; thus, its skills would arguably transfer well to the area of HGM.

One concern with expanding the FDA's jurisdiction to include CRISPR germline-editing technologies is that "it might be necessary for the FDA to construe an embryo that might be transferred into a uterus as a 'drug,' 'biological product,' or 'device.'"¹⁸⁸ However, this will not likely be the case. According to the FDA, gene transfer technology is "any exposure to gene therapy products . . . by any route of administration" and gene therapy products are "[a]ll products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids,

188. REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 61.

viruses, or genetically engineered microorganisms.”¹⁸⁹ “CRISPR-Cas systems certainly fall under this broad purview, as they are virally delivered, genomically stored, and mediate their effects via transcriptional machinery.”¹⁹⁰

The current regulatory system has several advantages—it offers scientists the freedom to develop new and improved biotechnologies, promotes the safety and efficacy of products, and “provides an extensive system of protections for human subjects participating in clinical trials.”¹⁹¹ However, there is no positive authority that empowers the federal government to consider the safety of yet-to-be-conceived future generations who may be inadvertently affected by HGM.¹⁹² Nor does the current system provide a means for addressing problems related to immature safety mechanisms, unintended multigenerational side effects, the ethics of embryonic experimentation, and equal access to CRISPR germline-editing technologies.¹⁹³

Thus, a model regulatory framework is one that combats the four primary issues articulated by this comment—(1) the reinforcement of social stigmas and exacerbation of inequalities, (2) economic pressures and consumer demands, (3) positive eugenics, and (4) human embryonic experimentation—and permits the use of CRISPR technology in HGM only where such use either avoids or outweighs these social and ethical concerns.

This section argues that the United States should adopt the framework laid out by Niklaus H. Evitt, Shamik Mascharak, and Russ B. Altman because their proposed regulatory framework meets the above-stated ethical criteria. Evitt, Mascharak, and Altman propose a model regulatory framework for research, clinical development, and distribution of CRISPR germline-editing technology that utilizes existing regulatory bodies, but calls for heightened scrutiny at each phase.¹⁹⁴ This section expounds on their proposed regulatory framework, but draws from other sources as well.

189. U.S. FOOD & DRUG ASS'N, GUIDANCE FOR INDUSTRY: GENE THERAPY CLINICAL TRIALS—OBSERVING SUBJECTS FOR DELAYED ADVERSE EVENTS 2, 4 (2006).

190. Evitt et al., *supra* note 97, at 27.

191. REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 170.

192. *Id.* at 169.

193. See Evitt et al., *supra* note 97, at 28.

194. See *id.* at 28–29.

1. Research Phase

Although CRISPR must overcome several technical and ethical obstacles before it can be used safely for HGM purposes, the technology is developing at an unprecedented rate, and is poised to shock an unsuspecting society if not carefully considered and properly regulated.¹⁹⁵ In the interest of preparing the public for such developments, a system of oversight should be put in place at the national level and should regulate HGM in both the public and private sector.¹⁹⁶

Regulating HGM should occur in two ways. First, there should be an ethical threshold test that all proposed studies must pass in order to be approved for research. Second, specialized oversight committees (“SOCs”) that are composed of well-trained, disinterested members should be responsible for rendering such approval. Researchers also must meet certain ethical training requirements for approval of their respective study.

a. Ethical Threshold Test

Given the ethical and safety concerns posed by CRISPR technology in HGM, research and clinical development should not proceed unless (1) germline intervention is the only way to produce healthy offspring or (2) the benefits of the proposed therapy significantly outweigh the embryo loss and other associated risks.¹⁹⁷ In either situation, any HGM study that lacks a validated reversal mechanism should be prohibited.¹⁹⁸

There are two basic scenarios in which the use of CRISPR in HGM should be permissible. First is where germline intervention is the only way to produce healthy offspring. This situation would

195. *Id.* at 25 (indicating “an urgent need for practical paths for the evaluation of these capabilities”).

196. FRANKEL & CHAPMAN, *supra* note 19, at 51.

197. Evitt et al., *supra* note 97, at 26.

198. *Id.* There is currently no way to reverse the effects of harmful germline modifications. *Id.* at 26. Thus, a proven reversal strategy must be developed for any HGM study to move forward. Prospects such as the gene drive strategy, a chemically induced secondary gene program, are still theoretical. Kevin M. Esvelt et al., *Concerning RNA-Guided Gene Drives for the Alternation of Wild Populations*, *ELIFE* 1, 10 (2014). In theory, the gene drive overwrite strategy can “precisely reverse the original therapeutic edit.” Evitt et al., *supra* note 97, at 26 (suggesting “chemical induction of reversal mechanisms must be orthogonal to natural biochemistry so that removal of original gene edits is not accidentally triggered”).

apply where one parent is homozygous for a dominant disorder or where both parents are homozygous for a recessive disorder.¹⁹⁹ In these situations, all embryos would be affected by the disorder and would not benefit from screening and selection procedures.²⁰⁰ Thus, HGM would be morally justifiable because there are few alternatives for the parents to avoid passing on defective genes to their biological offspring.²⁰¹

Second, the use of CRISPR technology in HGM should be permissible only where the benefits of the proposed therapy significantly outweigh the embryo loss and other associated risks. This situation involves performing a cost-benefit analysis of the proposed therapy with the primary goal of minimizing embryonic destruction throughout the research process.²⁰² This would provide an ethical use of germline editing for diseases with a large potential patient population because, in the end, fewer embryos would be destroyed—thus addressing the fourth concern of CRISPR germline-editing technology: the destruction of human embryos in embryonic experimentation.²⁰³ Even if parents could avoid passing on defective genes to their child via screening and selection procedures, embryos carrying genetic disorders are ultimately destroyed every time parents conduct prenatal genetic diagnosis during an *in vitro* fertilization cycle.²⁰⁴ In other words, where there is a large patient population, *in vitro* genetic profiling and screening is sure to result in significant embryo loss. If the population-wide embryo loss in prenatal genetic diagnosis is likely to surpass the embryo loss during CRISPR research, then developing a CRISPR germline-editing therapy is morally justified because doing so would minimize the net embryo loss.²⁰⁵ In either situation, “there must be a compelling reason for doing the gene editing in human embryos” rather than using the less ethically

199. Lander, *supra* note 27, at 6; *see also* FRANKEL & CHAPMAN, *supra* note 19, at 62 (defining homozygosity as the “state in which the two alleles of a gene at a specific locus are identical”).

200. *See* Lander, *supra* note 27, at 6.

201. *See* FRANKEL & CHAPMAN, *supra* note 19, at 13.

202. *See* Evitt et al., *supra* note 97, at 26 (maintaining that “embryos bear an intermediate moral status between nonhuman life and a fetus”).

203. *Id.* While the destruction of *no* human embryos would be an ideal result, one must take into account that embryonic destruction already occurs in genetic screening and embryo selection procedures. Therefore, it is important to keep in mind that this conclusion is based upon a comparative analysis to not only the current regulatory scheme, but also to current medical practices and procedures.

204. *Id.*

205. *Id.*

challenging method involving human cells cultured in a dish and limited to the laboratory setting.²⁰⁶

b. SOC Approval

If and when a proposed therapy passes either threshold test by showing necessity or benefit, researchers should be required to obtain approval from local SOCs for any studies involving genetic modification in human stem cells and embryos. These committees will supervise the proposed study if it passes the other regulatory guidelines.²⁰⁷

In the United Kingdom, the Human Fertilization and Embryology Authority (“HFEA”) regulates all experiments involving human embryos by requiring researchers to obtain a license in order to perform any such experiment.²⁰⁸ Researchers are not even permitted to apply for a license, unless and until they have sought and been granted “research ethics approval by a properly constituted ethics committee.”²⁰⁹ In the United States, institutional review boards (IRBs) serve a similar function; however, their regulatory focus is on biomedical research involving early-stage human embryos.²¹⁰ Because embryos are not considered “human subjects” and, consequently, not afforded the same protections under the Common Rule (e.g., informed consent), research involving CRISPR germline-editing technologies may fall outside of IRB authority.²¹¹ In addition, IRBs are not required to consider long-term social ramifications when deciding to approve research.²¹²

Given these inadequacies in existing regulatory oversight, SOCs should be created to oversee the ethical development of

206. GMO SAPIENS, *supra* note 1, at 239.

207. See Evitt et al., *supra* note 97, at 26–27; see also GMO SAPIENS, *supra* note 1, at 240 (indicating that “[m]ost U.S. universities already have committees that oversee stem cell and embryo research (often called “SCRO” for stem cell research and oversight) . . . [and] these same committees could review applications from researchers wanting to make” genetically modified human embryos).

208. *Legislative Guide to Licensing*, HUMAN FERTILIZATION & EMBRYOLOGY AUTH. 1, http://www.hfea.gov.uk/docs/Legislative_Guide_to_Licensing.PDF (last visited Dec. 16, 2016).

209. *Id.* at 10.

210. See REPRODUCTION AND RESPONSIBILITY, *supra* note 121, at 201.

211. See *id.* at 134.

212. See *id.* at 201 (indicating IRBs generally do not apply special rules for research involving early-stage human embryos or consider the “moral questions relating explicitly to the destruction of developing human life”).

HGM technologies and should have responsibilities that extend beyond the Common Rule's "human subject" protection.²¹³

SOCs should be composed of disinterested, specialized, and diverse stakeholders.²¹⁴ To reduce the risk that these committees will simply "rubber stamp" research proposals,²¹⁵ there should be national membership guidelines that require the committees to meet specific composition requirements.²¹⁶ Similarly, researchers proposing to conduct research on the genetic modification of human germ cells or embryos should also be required to have a certain level of specialized training, particularly in the area of bioethics, to submit a research proposal.²¹⁷ HGM raises complicated bioethical issues, and requiring bioethical training "would serve to provide a strong educational component."²¹⁸ For example, CRISPR human genetic modification research could substantially increase the research demand for human eggs.²¹⁹ Scientists should be equipped to handle the ethical considerations related to sourcing human oocytes and prepared to recognize with certainty "what might be ethical or unethical in this area of research."²²⁰

SOC power and authority should be standardized by federal mandate in order to grant the appropriate level of oversight and ensure consistent policy at a national level.²²¹ Granting such authority to specialized committees will not only reduce the risk of unethical research and development, but will also put the power of scientific research and development back in the hands of scientists, who are best suited to make such decisions—rather than giving unspecialized regulatory agencies and knee-jerk politicians the authority to make unfounded assessments.

Before granting approval, SOC should evaluate whether researchers have demonstrated proof of concept by looking at whether the proposed study has been used in applying gene edits

213. See Evitt et al., *supra* note 97, at 27.

214. See *id.* ("Local oversight committees should be composed of researchers, physicians, ethicists, and community members with nonconflicting interests, much like stem cell research oversight (SCRO) committees.")

215. See GMO SAPIENS, *supra* note 1, at 240 (suggesting this is a realistic concern for some university committees).

216. Evitt et al., *supra* note 97, at 27.

217. GMO SAPIENS, *supra* note 1, at 240.

218. *Id.*

219. *Id.*

220. *Id.*

221. Evitt et al., *supra* note 97, at 27.

to appropriate “somatic cells and multigenerational animal models.”²²² Committees should also question the ethical nature of the proposed studies and the necessity of using human embryos to perform the associated experiments.²²³ If studies pose significant ethical burdens, have the potential for abuse, or can be conducted without the use of human embryos,²²⁴ then the committees should deny them.

SOC approval should be a prerequisite to FDA approval, which must be obtained for any research study to advance to the clinical development phase.

2. Clinical Development

Upon receiving approval from appropriate SOCs, research proposals should be subject to FDA review and approval before clinical use.²²⁵ As explained previously, “[p]rior FDA policies concerning gene transfer therapies readily port over to [CRISPR germline-editing therapies].”²²⁶

Clinical trials test potential treatments in human subjects to determine whether they are appropriate for widespread use in the general population.²²⁷ Potential treatments include drugs, medical devices, and biologics such as gene therapy.²²⁸ There are four phases of clinical trials, each of which is designed to answer a different research question.²²⁹

Phase I: Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Phase II: The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

Phase III: The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to

222. *Id.* at 26.

223. GMO SAPIENS, *supra* note 1, at 240.

224. For example, if the experiment can be performed just as well with cultured human cells in a petri dish, it should be rejected.

225. Evitt et al., *supra* note 97, at 27.

226. *Id.*; see also *supra* note 190 and accompanying text.

227. *Conducting Clinical Trials*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ConductingClinicalTrials/default.htm> (last visited Dec. 16, 2016).

228. *Id.*

229. See *FAQ ClinicalTrials.gov—Clinical Trial Phases*, U.S. NAT'L LIBRARY OF MED., <https://www.nlm.nih.gov/services/ctphases.html> (last visited Dec. 16, 2016).

commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

Phase IV: Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.²³⁰

Prior to Phase I clinical trials, “care should be taken to receive parental informed consent.”²³¹ Although HGM arguably leads to “generations of nonconsent,” parents regularly make medical decisions on behalf of children.²³² This notion, combined with the fact that subsequent nonexistent beings (i.e., generations that have yet to be conceived) arguably have no recognizable consent rights, may make consent a non-issue all together.²³³ Consent may also be a non-issue in this arena because it does not function to “permit what would otherwise be a violation of autonomy.”²³⁴

Even if it made sense to talk about the subsequent consent of future persons, lack of consent would not provide a justification for a blanket prohibition on germ-line genetic engineering. In fact, it provides little useful guidance. We are typically in no position to make reasonable predictions about what people in future generations will approve of and hence what they will consent to. The problem is that the cultural context may change over a number of generations. In addition, we are not able to predict what technologies will be available in the future and how they will shape values. Finally, we do not know how the moral and political debates that influence policy will turn out.²³⁵

It is a “conceptual confusion” to discuss the consent of future persons to present practices.²³⁶ Thus, well-informed parental consent should suffice for HGM clinical trials.

There should, however, be a greater standard of informed consent for all future parents participating in HGM clinical trials that emphasizes the possibility of unanticipated latent side ef-

230. *Id.*

231. Evitt et al., *supra* note 97, at 27.

232. *Id.*

233. *Id.*; see also Ronald Munson & Lawrence H. Davis, *Germ-line Gene Therapy and the Medical Imperative*, 2 KENNEDY INST. ETHICS J. 137, 143, 151–52 (1992) (arguing there is no moral objection to germline therapy too great to overcome and also suggesting the survival of the human race may depend on germline genetic manipulations one day).

234. Martin Gunderson, *Genetic Engineering and the Consent of Future Persons*, 18 J. EVOLUTION & TECH. 86, 91 (2008) (agreeing that consent is a non-issue, but “not because it is impossible to thwart the autonomy of non-existing persons”).

235. *Id.* at 88.

236. *Id.* at 86.

fects.²³⁷ While it may be impossible to inform a patient about unanticipated side effects (because, at that point, would they not be anticipated?), researchers should do their best to stress the uncertainty that goes with HGM and ensure patients understand that the realm of possible outcomes is vast and similarly uncertain. Instead of a one-size-fits-all warning label telling patients nothing more than “expect the unexpected,” scientists should instruct patients to consider the myriad of personal attributes influenced by genetics—including physical features, medical health, mental health and stability, moral character and decision making, etc. In the end, patients should not only understand the *anticipated* consequences of their specific procedure, but they should also have a general understanding of human genetics and the accompanying risks and uncertainties to be considered “informed” enough to give consent.

During Phase I–III clinical trials, CRISPR germline-editing technologies should be made readily available to patients from all socio-economic backgrounds as soon as possible, while also conclusively demonstrating safety and efficacy.²³⁸ While multigenerational trials would be the best way to conclusively demonstrate safe outcomes and obtain reproducible data over generations, “multigenerational Phase I–III trials may be impractical.”²³⁹ Instead, positive long-term outcomes could be confirmed during mandatory multigenerational Phase IV trials while also mitigating unnecessary time burdens during the development phase.²⁴⁰

3. Distribution

Following FDA approval and commercialization, CRISPR germline-editing technology should be made available to persons of all socioeconomic backgrounds at IVF clinics across the country. This would not only eliminate inequality concerns, it would

237. Evitt et al., *supra* note 97, at 27.

238. *Id.*

239. *Id.* There are several reasons multigenerational HGM trials might be impractical. One reason could be how the sheer time and money it would take to sponsor a trial spanning the course of several generations of human beings would not likely be productive nor forthcoming. Or, multigenerational trials might be impractical because there is no cognizable point at which scientists could say with certainty that the product or procedure was either a failure or success due to the possibility of latency, the influence of environmental factors, and the infinite number of possible outcomes that would vary based on the genetic makeup of the mother and father.

240. *Id.*

also combat issues related to increased social stigma and economic pressure. In order to achieve this goal, there should be legislative mechanisms in place to ensure best practices are adopted by healthcare professionals and to safeguard “those who cannot or choose not to use this technology.”²⁴¹

“For example, insurance companies should not be permitted to raise deductibles of deaf parents who choose to conceive a deaf child; regardless of the morality of this decision, it is still legally viewed as a matter of parental autonomy.”²⁴² If not properly regulated, private insurance companies might try to “punish” parents who forego HGM and, as a result, are likely to have a child that will require a more expensive procedure, such as cochlear implant surgery, which can cost between \$50,000 and \$100,000 with the required follow up.²⁴³

Further, access to useful germline-editing technologies should also be made reasonably available to parents of lower socioeconomic status.²⁴⁴ To do otherwise would “add inherited advantages to all the benefits of nurture and education already enjoyed by the affluent,” and create yet another barrier between the “haves” and “have-nots” of society.²⁴⁵ However, regulators should be careful not to do so in a manner that inappropriately encourages the use of HGM technology.

Children with physical and mental disabilities require more care and attention in the classroom than the average student. For example, “it costs at least ten times as much, on an annual basis, to educate a deaf child in a residential school for the deaf, than it does to educate that same student in a mainstream classroom.”²⁴⁶ Similarly, educating children with other impairments and disabilities—such as intellectual disabilities and visual, speech, or lan-

241. *Id.* at 27–28.

242. *Id.* at 28; *see also* FRANKEL & CHAPMAN, *supra* note 19, at 37 (“At a minimum, most private insurers are likely to delay agreeing to reimburse policy holders for these genetic services until their efficacy and safety are clearly demonstrated.”).

243. Adam B. Zimmerman, *Do You Hear the People Sing? Balancing Parental Authority and a Child’s Right to Thrive: The Cochlear Implant Debate*, 5 J. HEALTH & BIOMED. L. 309, 318 (2009).

244. *See* FRANKEL & CHAPMAN, *supra* note 19, at 36 (suggesting that major changes in the U.S. health care system are required in order to prevent a lack of equity in access to HGM products and services).

245. *Id.* at 37.

246. Zimmerman, *supra* note 243, at 319.

guage impairments—also costs considerably more in terms of the services special education children need and receive.²⁴⁷ While the Individuals with Disabilities Education Act (“IDEA”) covers only a small share of the total expenditures on special education, federal funding on special education through IDEA was around \$12 billion in 2010.²⁴⁸

If CRISPR technology reaches a point at which “correcting” such disabilities would be cheaper for the federal government than funding special education programs, it may become tempting for legislators to inappropriately incentivize HGM procedures. However, this must be fervently avoided. Under no circumstance should the government attempt to further its own fiscal agenda by incentivizing HGM procedures, by taxing the lack thereof, or by any other means.

To be sure, legislators and regulators will need to strike a delicate balance between making HGM widely available and protecting parental autonomy. But given CRISPR’s simplicity, affordability, and widespread use, providing access to those in need of CRISPR human germline modification technology, but perhaps cannot afford to finance the procedure on their own, should be a feasible policy option.

CONCLUSION

The development of CRISPR technology has prompted much debate about the ethical dilemmas presented by its use in the HGM setting, but little attention has been given to the issue of how germline therapies would be developed in a responsible and practicable manner. As discussed throughout, CRISPR technology is both revolutionary and perilous. However, the very characteristics that make CRISPR such a groundbreaking advancement are also the features that warrant careful consideration moving forward. The proposed regulatory framework would meet the ethical and technical demands posed by using CRISPR technology for HGM purposes.

247. See Laudan Aron & Pamela Loprest, *Disability and the Education System*, 22 FUTURE CHILD. 97, 99, 109 (2012).

248. *Id.* at 109.

Taken as a whole, this comment addresses concerns about multi-generational risks, underdeveloped safety mechanisms, bioethical dilemmas, and social consequences such as eugenics, inequality, economic pressures, and the like. In doing so, it seeks to promote the ongoing conversation and open the door to further legal analysis and debate, which must occur before society is ready to face the potentially powerful repercussions of modifying the human germline.

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