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CRISPR and the Future of Fertility Innovation

*June Carbone**

In 2018, Dr. He Jiankui announced that he had used CRISPR, a gene-editing tool, to produce newborn twin girls with the gene for HIV resistance.¹ The announcement caused a global uproar. Dr. He appeared to have tried the procedure without advance testing.² He did so without assurance the procedure was safe; indeed, unintended side effects could affect not only the twins but the twins' own offspring.³ And he did it to otherwise healthy embryos.⁴ While the twins risked exposure to the HIV virus their father carried, less risky treatments exist that reduce the risk of transmission.⁵ Dr. He also tried the technique without following appropriate Chinese protocols.⁶ As a result of the outcry that followed his announcement, use of the procedure in China has been effectively shut down.⁷ This leaves open the question: if CRISPR is to be used again in the reproductive context, how and why is it to occur?

CRISPR creates new possibilities for genetic engineering, which alters a person's—or an embryo's—genetic inheritance in ways that alter the germline, in turn passing on the alterations to subsequent generations. CRISPR technology has the potential to save lives, enable prospective par-

* Robina Chair in Law, Science and Technology, University of Minnesota Law School. I would like to thank Aron Mozes for his research assistance.

1. Mara Hvistendahl, *China's Bioethics Struggles Enter the Spotlight*, SLATE (Nov. 27, 2018, 2:42 PM), <https://slate.com/technology/2018/11/he-jiankui-crispr-babies-informed-consent-china-science.html>. Dr. He has a Ph.D., but not an M.D. This article will refer to him as Dr. He in part to avoid confusion with the pronoun "he." For a discussion of his background, see generally Henry T. Greely, *CRISPR'd Babies: Human Germline Genome Editing in the 'He Jiankui Affair,'* 6 J.L. & BIOSCIENCES 111 (2019).
2. Greely, *supra* note 1, at 131. Dr. He did claim that he had tried CRISPR on three hundred embryos, but that claim has not been independently verified.
3. See Rachael Rettner, *A Scientist Edited Babies' Genes in Utero. It Could Make Them More Likely to Die*, LIVESCIENCE (June 3, 2019), <https://www.livescience.com/65620-crispr-babies-gene-mutation-early-death.html> (indicating that a study showed that the gene added to confer HIV resistance was associated with increased risk of early death from other causes, but errors in the study led it to be withdrawn).
4. *Id.*
5. Jing-ru Li et al., *Experiments that Led to the First Gene-edited Babies: The Ethical Failings and the Urgent Need for Better Governance*, 20 J. ZHEJIANG U. SCI. B. 32, 35 (2019).
6. *Id.* at 36. An investigation by the Chinese government reported that Dr. He conducted the experiments in violation of a Chinese ban on germline editing. Greely, *supra* note 1, at 142. In addition, although Dr. He claimed to have advance approval from the hospital where the procedure was performed, the validity of that approval is questionable.
7. Greely, *supra* note 1, at 140.

ents to reproduce without risk of transmitting unwanted genetic material to their offspring and, indeed, to eliminate a defective gene from a family line altogether.⁸ Yet, the technology is untried and could cause unanticipated harms.⁹ This article does not address whether such innovations should occur, but instead focuses on how they are likely to do so, and whether the development of the technology can and should be channeled in particular ways.

This inquiry starts by distinguishing between two different issues that raise concerns about future use. The first involves safety and efficacy. As with any other medical techniques, it is impossible to identify every potential side effect without testing.¹⁰ Testing protocols typically involve starting with animals.¹¹ In the case of human reproduction, the next step would be experimentation on embryos who are not allowed to develop into babies.¹² Then, if those steps look promising, the procedure should be tried on a limited number of humans, typically humans who might otherwise not exist or would be born with life threatening illnesses.¹³ Finally, after human trials that establish safety and efficacy, the technique might be approved for use in accordance with appropriate treatment protocols.¹⁴ In the context of assisted reproduction, however, the funding for these steps has typically not been available.¹⁵ Congress has banned the expenditure of federal funds on any embryo research, and private commercial donors have been reluctant to fund research that benefits only a relatively small patient population.¹⁶ As a result, most innovations in assisted reproduction have occurred when fertility professionals simply try a new technique on patients, typically without human trials and sometimes even without extensive animal experimentation.¹⁷ CRISPR, on the other hand, is currently the subject of extensive research, including animal experimentation, human trials in adults, and some testing in embryos.¹⁸ This testing should lead to refinements and increased confidence in the safety and

8. Kerry Lynn Macintosh, *Heritable Genome Editing and the Downsides of a Global Moratorium*, 2 CRISPR J. 272, 272 (2019).

9. See Greely, *supra* note 1, at 153 (describing potential harms).

10. *Id.*

11. *Id.* at 154.

12. For a description of this process, see *id.* at 128 (observing that the FDA would require either animal experimentation or in vitro experimentation with embryos or both before allowing human trials). “In vitro” means in the lab, as opposed to “in vivo” embryo experiments, which take place in the human body.

13. *Id.*

14. *Id.*

15. Greely, *supra* note 1, at 128.

16. *Id.* at 129.

17. *Id.*

18. *Id.* at 179.

efficacy of the technique.¹⁹ Nonetheless, the issue that cannot be determined without human trials is the safety of its use in human reproduction and the ways that it might affect future generations. To test for effects on future generations requires testing in a patient population and following that population to see what the effect of the genetic alterations are on the patients' children.²⁰ It is possible, nonetheless, that CRISPR use could produce otherwise healthy individuals who are still at risk of transmitting genetic defects to their children in ways that researchers cannot effectively anticipate or eliminate.²¹ Waiting until the safety of the technique is conclusively established would therefore mean limiting the use of an otherwise promising technique for decades.

The second issue involves the potential consequences of germline genetic alterations as a general practice. Preventing disease, in and of itself, is generally regarded as admirable and CRISPR's primary use could be to delete genes that cause disease.²² The most controversial applications are the ones that go beyond that.²³ For example, some recessive genes, such as those associated with sickle cell anemia, transmit what could be a devastating illness in a child who receives two copies of the gene, but have potential advantages in combatting malaria if the child receives only one copy of the gene.²⁴ Genetic engineering that prevented transmission of sickle cell anemia to a child might therefore be considered a good thing, while elimination of the genes associated with sickle cell disease from the family line altogether might have negative consequences. Further, CRISPR may be used not just to eliminate genes associated with disease but to introduce new genes that the child would not otherwise have.²⁵ In the case of the Chinese twins, for example, Dr. He introduced genes that confer HIV resistance.²⁶ This raises concerns about what some see as a slippery slope. Once CRISPR is used to introduce new genes associated with advantageous traits, what are the limits on such use? For example, if CRISPR is used to alter the genes associated with dwarfism, is there any reason not to introduce a gene associated with height greater than six feet? Or to offer a package of genes associated with

19. *Id.*

20. *Id.* at 114.

21. Greely, *supra* note 1, at 114.

22. Henry T. Greely, *Human Germline Genome Editing: An Assessment*, 2 *CRISPR J.* 253, 257 (2019).

23. Of course, some ethicists and theologians object to all human interventions in the human genome. These objections go beyond the scope of this article. *Id.* at 263.

24. *Id.* at 260.

25. *Id.* at 263.

26. Hvistendahl, *supra* note 1.

choices that may include enhanced memory, fast twitch muscles and greater sprinting speed, or other traits?²⁷

Looking at how other innovations in assisted reproductive technologies answered these questions—how innovations have accounted for safety and efficacy considerations and how new technologies have dealt with the slippery slope of ethically questionable applications—may be instructive in predicting CRISPR’s likely future. For instance, the development of assisted reproductive technologies (ARTs) generally, in vitro fertilization (IVF) as the most critical part of ART, and experimentation with more recent innovations (such as three parent IVF) offer examples that may be instructive. These developments suggest that the answers reflect path dependent experiences, supply and demand pressures, sources of funding, and the contexts in which the innovations occur.

Applying this framework to the use of CRISPR in assisted reproduction provides a framework for assessing the likely developments on the horizon. This analysis suggests that the demand for CRISPR, at least initially, is likely to be limited and where the demand is small, doctors may be tempted to simply do it, either in isolated trials or in underground networks. This analysis also suggests that the potentially greater demand requires that CRISPR use interact with two developing sources of innovation: (1) innovation involving egg freezing and treatment of patients with a limited number of gametes; and (2) innovation addressing the needs of families at risk of passing on identified genetic defects. These two groups are different from each other and suggest development of CRISPR along different trajectories.²⁸

This article attempts to consider supply and demand for CRISPR in accordance with these two different patient populations and to chart the likely trajectory of the technology in accordance with each, suggesting very different outcomes. In accordance with this analysis, this article will, first, consider the history of innovation in ART.

Second, it will identify the forces remaking reproductive medicine, arguing the industry is experiencing greater consolidation, with pressures for growth and increased geographic reach. These developments create larger platforms capable of exploiting jurisdictional differences in price and regulation.²⁹ In addition, the future of fertility treatments is likely to focus much more intently on the supply of gametes as women seek to reproduce at later ages.³⁰ These developments may, at least in the short run, focus more attention on egg freezing, preimplantation genetic diagnoses, and the management

27. For a discussion of ethics of human enhancement, see generally KERRY LYNN MACINTOSH, *ENHANCED BEINGS: HUMAN GERMLINE MODIFICATION AND THE LAW* 11–29 (2018) (discussing prospects to use CRISPR to enhance human performance).

28. Macintosh, *supra* note 8, at 274.

29. Greely, *supra* note 1, at 130.

30. Macintosh, *supra* note 8, at 274.

of reproduction in the context of other medical treatments, including genomic medicine.³¹

Third, the article explores how human genome editing may occur in the context of these developments. The article will maintain that the patient population seeking to use genome editing to prevent the transmission of disease is likely to remain fairly small, but that the demand in the context of other fertility services may be significantly larger.

The article concludes that thinking about CRISPR use for germline genome editing requires consideration of the broader forces remaking reproductive medicine.

I. INNOVATION IN ART: JUST DO IT?

The use of CRISPR in China is not the first controversial use of ART, nor the first time such technologies have been used to alter the genetic inheritance a new baby may have or may pass onto its offspring.³² Arguably, the first instance of genetic alteration, that could be passed on to offspring, occurred in New Jersey in the 1990s.³³ There, doctors inserted cytoplasm from donor eggs into the intended mother's eggs creating embryos that could end up with DNA from three sources: the intended mother and father whose gametes created the embryo and small amounts of mitochondrial DNA from the donor.³⁴ Over thirty children were born using the technique, with tests showing that at least two of the children had mitochondrial DNA from the donor.³⁵ The Food and Drug Administration (FDA) asserted jurisdiction over the procedure, effectively shutting down use of the procedure in the United States.³⁶

31. *Id.* at 274–75.

32. Jason A. Barritt et al., *Epigenetic and Experimental Modifications in Early Mammalian Development: Part II, Cytoplasmic Transfer in Assisted Reproduction*, 7 HUMAN REPRODUCTION UPDATE 428, 428 (2001).

33. *Id.* at 428–29.

34. *See id.* at 429 (describing process which involved injection of father's sperm and a small amount of cytoplasm from a donor egg into the intended mother's egg).

35. Kim Tingley, *The Brave New World of Three Parent I.V.F.*, N.Y. TIMES (June 27, 2014), <https://www.nytimes.com/2014/06/29/magazine/the-brave-new-world-of-three-parent-ivf.html>. A subsequent study surveying the parents of thirteen of the seventeen children reported that the children seemed to be developing normally.

36. *See* June Carbone & Jody Lyneé Madeira, *Buyers in the Baby Market: Toward a Transparent Consumerism*, 91 WASH. L. REV. 71, 93 (2016) (describing FDA assertion over jurisdiction); Judith Daar, *Multi-Party Parenting in Genetics and Law: A View from Succession*, 49 FAM. L.Q. 71, 74 (2015) (observing that after the FDA said in 2001 that any further use of cytoplasmic injection would require an Investigational New Drug application, the practice ceased throughout the United States); *see also* Myrisha S. Lewis, *How Subterranean Regulation*

In a limited follow-up study that surveyed twelve parents, the children appeared to be developing normally.³⁷ However, given the lack of a control group and the lack of follow-up testing, it is unclear whether the technique made the pregnancies possible and how much, if any, of the donor DNA influenced the children's development.

The second innovation that can be passed onto offspring involves mitochondrial replacement therapy (MRT).³⁸ Mitochondrial DNA mutations can cause a variety of diseases in children, including devastating neurological disorders and early death.³⁹ Existing genetic tests cannot screen eggs for mitochondrial disorders because the diseases depend on the distribution and location of the mutations, which cannot be determined from the single cell testing used in preimplantation genetic diagnoses (PGD).⁴⁰ The only way to

Hinders Innovation in Assisted Reproductive Technology, 39 CARDOZO L. REV. 1239, 1256 (2018) (questioning the basis for the FDA's assertion of jurisdiction and arguing that the FDA actions have a chilling effect on research). In addition, in December, 2015, Congress added a rider to the FDA appropriations bill that prevents the FDA from using federal funds "to notify a sponsor or otherwise acknowledge receipt of a submission for an exemption for investigational use of a drug or biological product under Section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) or Section 351(a)(3) of the Public Health Service Act (42 U.S.C. 262(a)(3)) in research in which a human embryo is intentionally created or modified to include a heritable genetic modification. Any such submission shall be deemed to have not been received by the Secretary, and the exemption may not go into effect." The Consolidated Appropriations Act of 2016, H.R. 2029, Pub. L. No. 114-113, § 749. See Greely, *supra* note 1, at 129 (noting that the rider has been renewed in every appropriations bill since).

37. See Serena H. Chen et al., *A Limited Survey-based Uncontrolled Follow-up Study of Children Born After Ooplasmic Transplantation in a Single Centre*, 33 REPROD. BIOMEDICINE ONLINE 737, 740-42 (2016). Two of the embryos conceived using the technique developed Turner syndrome, a rare chromosomal abnormality. One of women miscarried and the other aborted the fetus. Tingley, *supra* note 35. For a discussion of the safety issues, see Kerry L. Macintosh, *Brave New Eugenics: Regulating Assisted Reproductive Technologies in the Name of Better Babies*, 2010 U. ILL. J.L. TECH. POL'Y 257, 272 (2010).
38. See Daniel Green, *Assessing Parental Rights for Children with Genetic Material from Three Parents*, 19 MINN. J.L. SCI. & TECH. 251, 255 (2018) (describing MRT as the transfer of nuclear DNA from intended parents to an egg or fertilized embryo from a donor, eliminating transmission of the intended mother's mitochondrial DNA to the child).
39. Andrew M. Schaefer et al., *The Epidemiology of Mitochondrial Disorders—Past, Present and Future*, 1659 BIOCHIMICA ET BIOPHYSICA ACTA 115, 118 (2004).
40. See Amy B. Leiser, *Parentage Disputes in the Age of Mitochondrial Replacement Therapy*, 104 GEO. L.J. 413, 419 (2016); see also NUFFIELD COUNCIL ON BIOETHICS, NOVEL TECHNIQUES FOR THE PREVENTION OF MITOCHONDRIAL

eliminate the transmission of the mother's potentially defective mitochondrial DNA to a fetus therefore, is through MRT.⁴¹ MRT involves taking a donor egg or embryo, removing the nucleus, and inserting nuclear DNA from the intended parents.⁴² The resulting embryo would then contain the nuclear DNA from the intended parents and the mitochondrial DNA from the donors.⁴³ Since mitochondrial DNA is passed to offspring only through the mother's egg cells, women, but not men, would then pass on the donor mitochondrial DNA to their offspring.⁴⁴ Some commentators accordingly regard MRT as involving a modification of the "human germline."⁴⁵

The United Kingdom became the first country to approve the technique in 2016.⁴⁶ The first known case of MRT, however, took place in Mexico.⁴⁷ Dr. John Zhang, a New York doctor, assisted an American patient in using MRT after the patient had already lost two children to early deaths from

DNA DISORDERS: AN ETHICAL REVIEW 27–28 (2012), https://nuffieldbioethics.org/wp-content/uploads/2014/06/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf.

41. See, e.g., PARLIAMENTARY OFFICE OF SCIENCE AND TECHNOLOGY, PREVENTING MITOCHONDRIAL DISEASE, 2013, HOUSES OF PARLIAMENT 431, at 2 (UK) (providing an overview of mitochondrial disease and potential treatments as part of the United Kingdom preparation to consider approving MRT).
42. *Id.*
43. *Id.*
44. See Mark S. Frankel & Brent T. Hagen, *Germline Therapies*, 11 NUFFIELD COUNCIL ON BIOETHICS (May 2011), http://nuffieldbioethics.org/wp-content/uploads/Germline_therapies_background_paper.pdf (observing that while boys and girls can both develop mitochondrial diseases, only girls pass on mitochondrial DNA to their offspring).
45. Lewis, *supra* note 36, at 1249–50 (describing controversy but concluding that the concept of a "human germline" has not been definitely defined and questioning whether it should include mutations causing birth defects); Frankel & Hagen, *supra* note 44, at 1, 5–6 (observing that some, but not all, researchers and clinicians restrict the definition of germline modification solely to the modification of nuclear DNA).
46. Michael Le Page, *UK Becomes First Country to Give Go Ahead to Three-Parent Babies*, NEW SCIENTIST (Dec. 15, 2016), <https://www.newscientist.com/article/2116407-uk-becomes-first-country-to-give-go-ahead-to-three-parentbabies/> ("[The United Kingdom's] Human Fertilisation and Embryo Authority has given a cautious go-ahead to the use of mitochondrial replacement therapy to prevent mitochondrial disorders, which can be fatal.").
47. See Jessica Hamzelou, *Exclusive: World's First Baby Born with New "3 Parent" Technique*, NEW SCIENTIST (Sept. 27, 2016), <https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parenttechnique/>.

mitochondrial disease and had miscarriages caused by the mutation.⁴⁸ Initial research had focused on the use of donor embryos,⁴⁹ but the patient, who was Muslim, preferred to use a donor egg. So, Dr. Zhang transferred nuclear DNA from the intended parents to an unfertilized embryo, resulting in the birth of a healthy child with mitochondrial DNA only from the donor.⁵⁰ When Dr. Zhang took steps to form a company that offers the procedure, the FDA threatened to take action against him if he did so.⁵¹ A subsequent child, however, has been born using MRT in the Ukraine.⁵²

A third example involves the use of egg specific stem cells to boost fertility. While these techniques use the intended parents' own cells, and thus do not introduce donor DNA, they may alter the DNA that the resulting children transmit to their offspring from that which would occur through in vivo reproduction.⁵³ These techniques involve the use of gamete specific stem cells to create new eggs and sperm, or to boost the efficacy of existing ones.⁵⁴

At one time, scientists believed that a woman had all the eggs she would ever have inside her body at birth.⁵⁵ In the last few years, however, researchers have discovered that women have egg specific stem cells in their ovaries, which the researchers believe can be coaxed in to developing new, mature

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48. *Id.*; see also Michelle Roberts, *First 'Three Person Baby' Born Using New Method*, BBC NEWS (Sept. 27, 2016), <http://www.bbc.com/news/health-37485263>.
 49. For description of the differences, see Glenn Cohen, *Circumvention Medical Tourism and Cutting Edge Medicine: The Case of Mitochondrial Replacement Therapy*, 25 IND. J. GLOBAL LEGAL STUD. 439, 441 n.6 (2018).
 50. Hamzelou, *supra* note 47.
 51. See Ariana Eunjung Cha, *FDA Cracks Down on Company Marketing 'Three-Parent' Babies*, WASH. POST (Aug. 8, 2017, 7:04 AM), https://www.washingtonpost.com/news/to-your-health/wp/2017/08/07/fda-cracks-down-on-company-marketing-three-parent-babies/?utm_term=.0562ad833f54.
 52. See Akshat Rathi, *The World's Second Three-Parent Baby Has Been Conceived Using a Controversial Technique*, QUARTZ (Jan. 18, 2017), <https://qz.com/887916/the-worlds-second-three-parent-baby-has-been-conceived-using-a-controversial-pronuclear-transfer-ivftechnique> (reporting that Ukrainian doctors use the technique to assist a Ukrainian woman whose previous pregnancies had failed to progress).
 53. Zubin Master, *Embryonic Stem-Cell Gametes: The New Frontier in Human Reproduction*, 21 HUM. REPROD. 857, 857 (2006).
 54. *Id.*
 55. See, e.g., Dori C. Woods et al., *Oocyte Family Trees: Old Branches or New Stems?*, 8 PLOS GENETICS 1, 1 (2012), <https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1002848> (considering whether women's ovaries can produce new eggs in adulthood).

eggs.⁵⁶ A team including researchers from Israel and Cambridge University has announced that they have been able to produce new eggs from the stem cells in the lab.⁵⁷ The French declared in 2015, that they had created new sperm in the lab, using sperm specific stem cells in a similar fashion.⁵⁸ These developments are a potential game changer for ART because doctors could then produce an unlimited number of new gametes for older patients or patients unable to reproduce because of the destruction of their existing sperm and eggs.⁵⁹ The ability to produce an unlimited gamete supply would also make it easier to select for disease free embryos—or to select for embryos with desired traits.⁶⁰ Without further manipulation, however, this technology would not be able to introduce new traits outside of those within the intended parents' existing genome.⁶¹

While these technologies are not yet ready for human use, a Boston company, OvaScience, created a procedure called “AUGMENT.”⁶² This procedure was designed to extract a woman’s egg specific stem cells from her ovaries, and inject them into her mature eggs with the hope of boosting the woman’s ability to produce a successful pregnancy.⁶³ OvaScience research-

56. *Id.*; see also HENRY T. GREELY, *THE END OF SEX AND THE FUTURE OF HUMAN REPRODUCTION* 91–93 (2016) (describing the prospect of creating new gametes from stem cells).
57. Eli Y. Adashi et al., *Stem Cell-Derived Human Gametes: The Public Engagement Imperative*, 25 *CELL PRESS REVIEWS* 165, 165 (2019); David Shamah, *Cell Breakthrough a Step Toward Curing Infertility*, *TIMES OF ISR.* (Dec. 24, 2014, 7:14 PM), <https://www.timesofisrael.com/cell-breakthrough-may-let-postmenopausal-women-give-birth/>.
58. *French Lab Claims Breakthrough with World’s First Lab Grown Sperm*, *STRAITS TIMES* (May 8, 2015, 10:02 PM), <https://www.straitstimes.com/world/europe/french-lab-claims-breakthrough-with-worlds-first-lab-grown-sperm>.
59. See, e.g., Kelly Servick, *These Lab-Grown Human Eggs Could Combat Infertility—If They Prove Healthy*, *SCI. MAG.* (Feb. 8, 2018, 7:01 PM), <https://www.sciencemag.org/news/2018/02/these-lab-grown-human-eggs-could-combat-infertility-if-they-prove-healthy>.
60. Rob Stein, *Scientists Create Immature Human Eggs From Stem Cells*, *NAT’L PUB. RADIO* (Sept. 20, 2018, 2:00 PM), <https://www.npr.org/sections/healthshots/2018/09/20/649552734/scientists-create-immature-human-eggs-from-stem-cells>.
61. See Inmaculada Moreno et al., *Artificial Gametes from Stem Cells*, 42 *CLINICAL & EXPERIMENTAL REPROD. MED.* 33, 40 (2015); see Adam Watkins, *First Working Eggs Made From Stem Cells Points to Fertility Breakthrough*, *CONVERSATION* (Oct. 17, 2016, 11:00 AM), <http://theconversation.com/first-working-eggs-made-from-stem-cells-points-to-fertility-breakthrough-67192>.
62. Karen Weintraub, *Rejuvenating the Chance of Motherhood?*, *MIT TECH. REV.* (Dec. 9, 2016), <https://www.technologyreview.com/s/603065/rejuvenating-the-chance-of-motherhood/>.
63. *Id.*; Lewis, *supra* note 36, at 1280.

ers theorized that some women, especially older women, have difficulty reproducing because of the poor quality of their eggs.⁶⁴ Adding stem cells might then serve the same purpose as Saint Barnabas's addition of donor cytoplasm; it might improve the quality of the eggs' mitochondria and overall health.⁶⁵

Before OvaScience could try the technique, however, the FDA sent the company a letter indicating the technique required preclearance review before it could be used in the United States.⁶⁶ OvaScience decided that it could not raise the funding necessary to comply with the FDA requirements, and instead introduced the technique abroad.⁶⁷ It announced the birth of the first baby born using the technique in Toronto in 2015, and after that attempted to market AUGMENT internationally with some success.⁶⁸ Over time, however, doubts arose as to whether AUGMENT in fact enhanced the likelihood of pregnancy,⁶⁹ and OvaScience was hit with a securities suit that ultimately caused the sale of the company.⁷⁰ By then, however, a number of babies had been born abroad through pregnancies produced with the use of the technique.⁷¹ There is no analysis of what impact, if any, AUGMENT has

64. Leiser, *supra* note 40, at 418; Weintraub, *supra* note 62.

65. Leiser, *supra* note 40, at 420.

66. Lewis, *supra* note 36, at 1280. The letter stated that:

Our understanding is that your autologous mitochondrial transfer product, AUGMENT, consists of cells isolated from a biopsy of ovarian tissue, which are processed to extract mitochondria that are then introduced into other reproductive tissues during the IVF process. The removal of mitochondria and introduction into other reproductive tissue appears to be more than minimal manipulation. This is based on the limited information available; please note that the addition of mitochondrial DNA to other reproductive tissue may raise additional regulatory concerns.

67. Don Seiffert, *OvaScience to Focus on Baby-Making Efforts Overseas*, Bos. Bus. J. (Jan. 15, 2014, 2:06 PM), <https://www.bizjournals.com/boston/blog/bio-flash/2014/01/ovascience-to-focus-baby-making.html>.

68. See Carbone & Madeira, *supra* note 36, at 97.

69. See *Dahhan v. OvaScience, Inc.*, 321 F. Supp. 3d 247, 250 (D. Mass. 2018) (asserting that the “real pregnancy success rate was approximately 27% of the Canadian patients, and 23.5% for all 34 patients (including the non-Canadian patients)” while “the success rate of IVF without AUGMENT for a similar patient population is 33%.”).

70. See *id.* at 247 (rejecting OvaScience's motion to dismiss); see *Millendo Therapeutics Announces Successful Merger Completion with OvaScience, Inc.*, BIOSPACE.COM (Dec. 7, 2018), <https://www.biospace.com/article/releases/millendo-therapeutics-announces-successful-merger-completion/>.

71. *Dahhan*, 321 F. Supp. 3d at 250–51 (discussing the number of patients).

had on the resulting children.⁷² It is possible that the children have mitochondrial (or even nuclear) DNA from the stem cells that they will pass on to their offspring.⁷³ It is also quite possible that the introduction had no impact at all on the resulting children.⁷⁴ Yet, if AUGMENT had its intended effect of boosting the efficacy of the intended mother's mitochondria, it could well alter the cell's mitochondrial DNA in ways that would be passed to offspring along the female line.⁷⁵

These three developments—the introduction of donor cytoplasm, MRT, and AUGMENT—all involve changes that could be transmitted to offspring, thus altering the germline (as least of the mitochondrial DNA) in ways that would not occur naturally.⁷⁶ All three were done by fertility clinics who simply decided to try the techniques without human trials or advance regulatory approval.⁷⁷ None of the three involved public funding, and all were done with the intention of using a technique that could be (or was) offered to paying customers before any kind of testing indicating safety or efficacy was established.⁷⁸ There is no indication that use of the procedure caused harm to any of the resulting children, though there is also no way at this point to know for sure, and it is still too early to inquire about future generations.⁷⁹ These cases, however, provide a model for innovation in ART. In some of the cases,

72. See Andy Coghain, *First Baby Born with IVF that Uses Stem Cells to Pep Up Old Eggs*, NEW SCIENTIST (May 8, 2015), <https://www.newscientist.com/article/dn27491-first-baby-born-with-ivf-that-uses-stem-cells-to-pep-up-old-eggs/> (stating that even though a baby was born after Augment treatments, it was impossible to prove that the treatment was the reason for the success. Furthermore, “[t]here’s lack of evidence of efficacy, efficiency, and safety’ and ‘manipulation of the embryo at that very sensitive time could cause more problems for the nuclear genome, which is why safety data is critical.’”).
73. *Id.* (discussing similar research that had been conducted in 2001, which resulted in the babies carrying extra mitochondria from the donor cell).
74. *Dahhan*, 321 F. Supp. 3d at 250 (discussing data showing no increase in pregnancy rates).
75. The changes would not, however, introduce any genetic material from sources other than the intended parents. See Lewis, *supra* note 36, at 1280 (describing use of woman’s own mitochondria).
76. See PREVENTING MITOCHONDRIAL DISEASE, *supra* note 41 (stating that mtDNA and nDNA found in an egg constitutes the germline that the eventual offspring will carry and transmit to any of their future children. Therefore “any changes made to DNA by using such treatments are essentially irreversible”).
77. See Daar, *supra* note 36 (observing that after the FDA said in 2001 that any further use of cytoplasmic injection would require an Investigational New Drug application, the practice ceased throughout the United States); see Lewis, *supra* note 36, at 1280; see Cha, *supra* note 51.
78. See Daar, *supra* note 36; see Lewis, *supra* note 36, at 1280; see Cha, *supra* note 51.
79. See Coghain, *supra* note 72.

animal testing preceded the initial use, but the first human experimentation occurred because fertility doctors simply decided, like Dr. He in China, to try it on patients.⁸⁰ In considering CRISPR, it is important to assess how likely innovation in the use of new techniques is to occur in the future.

II. INNOVATION AND THE CHANGING ART LANDSCAPE

Innovation in ART has gone through a series of changes reflecting the intersection of the regulatory landscape in the United States and the available sources of ART funding. Development of CRISPR will take place in a very different funding environment than Saint Barnabas's experimentation with cytoplasm transfer in the nineties.⁸¹ These changes will involve the growing consolidation of fertility practices with increasing returns to scale, the use of brokers and platforms to expand geographical research, the growing ability to exploit international differences in price and regulation, the greater availability of private funding from billionaire philanthropists and private equity investors, and finally what may be changing demand for ART from better organized patient populations and older women seeking to extend their fertility.⁸² This section will examine that changing landscape before turning to CRISPR itself.

A. Old Story: Complacent Cartels

At one time, federal funding constituted the major source of biomedical funding, with a large part of that funding going to universities for basic research.⁸³ Much of the federal oversight of biomedical developments was tied to the research funding.⁸⁴ In addition, commercialization of the products of that research tended to take place in one of two ways. Either the research contributed to medical procedures, which typically depended on insurance reimbursement to win acceptance.⁸⁵ The insurance companies, in turn, insisted on transparency and accountability in assessing the suitability of the

80. Greely, *supra* note 1, at 116.

81. See Carbone & Madeira, *supra* note 36, at 94 (describing St. Barnabas's procedures).

82. *Id.*

83. See Kenneth Sutherlin Dueker, *Biobusiness on Campus: Commercialization of University-Developed Biomedical Technologies*, 52 FOOD & DRUG L.J. 453, 457 (1997).

84. See Note, *Guiding Regulatory Reform in Reproduction and Genetics*, 120 HARV. L. REV. 574, 579 (2006).

85. Robert J. Levine, *Federal Funding and the Regulation of Embryonic Stem Cell Research: The Pontius Pilate Maneuver*, 9 YALE J. HEALTH POL'Y L. & ETHICS 552, 561 (2009) ("Because insurance coverage for ART is quite limited, reimbursement requirements fail to promote quality care.").

procedures.⁸⁶ Alternatively, the research might contribute to drug development, with drugs dependent on FDA preclearance to be sold in the American market.⁸⁷ For approval, the FDA requires compliance with research protocols establishing safety and efficacy through closely monitored clinical trials.⁸⁸

ARTs have largely developed outside of this process. The Dickey-Wicker Amendment, which has been attached to every Department of Health and Human Services appropriations bill since 1996, bans federal funding for embryo research.⁸⁹ At least initially, insurance coverage was limited.⁹⁰ While the drugs used in the ART require FDA approval, fertility techniques originally did not.⁹¹

As a result, fertility clinics sometimes seemed to be the “wild west” of medicine.⁹² IVF clinics operated with private research funds and few external forces existed to slow the work of the clinics.⁹³ Further, once the clinics were established, they enjoyed strong public support that limited legislative ability to restrict their activities.⁹⁴ Regulation of the industry has involved a tacit compromise: “no laws are passed that even tangentially sanction embryo destruction and no laws are passed that intrude on the profitability of fertility treatments.”⁹⁵ That compromise serves the interests of both sides.⁹⁶ Religious groups like the Catholic Church, which opposes IVF altogether, consistently

86. *Id.*

87. *See* Dueker, *supra* note 83, at 455 (describing how the biggest business beneficiary of university basic research was the pharmaceutical industry).

88. *See Unapproved Drugs*, FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs> (last visited Mar. 8, 2020).

89. Philip J. Nickel, *Ethical Issues in Human Embryonic Stem Cell Research*, in *FUNDAMENTALS OF THE STEM CELL DEBATE: THE SCIENTIFIC, RELIGIOUS, ETHICAL, AND POLITICAL ISSUES* 62, 74 (Monroe et al. eds., 2008).

90. *See* June Carbone & Naomi Cahn, *Embryo Fundamentalism*, 18 WM. & MARY BILL RTS. J. 1015, 1034 (2010) (noting that health insurance policies rarely cover IVF).

91. *See* generally Lewis, *supra* note 36 (describing FDA assertion of jurisdiction).

92. *See, e.g.*, Judith Daar, *Federalizing Embryo Transfers: Taming the Wild West of Reproductive Medicine?*, 23 COLUM. J. GENDER & L. 257, 258 (2012).

93. *Guiding Regulatory Reform in Reproduction and Genetics*, *supra* note 84, at 587.

94. *Id.* at 584 (observing that the “strong public acceptance of IVF that ensued, coupled with an entrenched economic force in the form of a private fertility industry, may have then solidified the early deadlock into a long-term deregulatory norm that has persisted to this day.”).

95. Carbone & Cahn, *supra* note 90, at 1015.

96. *See id.* at 1032 (“Legislative and regulatory oversight of assisted reproduction has been characterized by moral posturing and regulatory gridlock.”).

object to laws that implicitly or explicitly authorize ART.⁹⁷ As a result, the ability to get laws passed addressing ART practices, like surrogacy, has historically required restrictions on their applicability to same-sex couples—restrictions vigorously opposed by many of the laws’ proponents.⁹⁸ The major regulation Congress has been able to get through for IVF itself involves reporting requirements—the clinics must report their success rates.⁹⁹

The wild west moniker, however, which reflects the lack of more direct regulation and is descriptive of early clinics is in many ways misleading.¹⁰⁰ Establishing the initial fertility clinics in the United States did require an entrepreneurial spirit, and with the creation of a new line of medical practices, ethical abuses occurred, notably the use of donor sperm from the fertility doctors performing the procedures.¹⁰¹ Further, once the industry was established, it involved a cartel-like structure more like cosmetic surgery than

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97. See, e.g., Joseph Card. Ratzinger, *Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation Replies to Certain Questions of the Day*, CONGREGATION FOR THE DOCTRINE OF THE FAITH (Feb. 22, 1987), http://www.vatican.va/roman_curia/congregations/cfaith/documents/rc_con_cfaith_doc_19870222_respect-for-human-life_en.html (determining that both heterologous and homologous artificial fertilization are unacceptable); John M. Haas, *Begotten Not Made: A Catholic View of Reproductive Technology*, U.S. CONF. CATH. BISHOPS, <http://www.usccb.org/issues-and-action/human-life-and-dignity/reproductive-technology/begotten-not-made-a-catholic-view-of-reproductive-technology.cfm> (“One reproductive technology which the Church has clearly and unequivocally judged to be immoral is in vitro fertilization or IVF.”) (last visited Feb. 29, 2020).
98. Carbone & Cahn, *supra* note 90, at 1045 (describing surrogacy provisions limiting applicability to different sex couples).
99. The United States Fertility Clinic Success Rate and Certification Act of 1992, 42 U.S.C. §§ 263a-1–263a-7 (1994). Congress does find it easier to restrict technologies that have not yet shown promise. See Russell A. Spivak et al., *Germ-Line Gene Editing and Congressional Reaction in Context: Learning from Almost 50 Years of Congressional Reactions to Biomedical Breakthroughs*, 30 J.L. & HEALTH 20, 30 (2017) (detailing existing legislation on genetic alterations); Paul Enriquez, *Editing Humanity: On the Precise Manipulation of DNA in Human Embryos*, 97 N.C. L. REV. 1147, 1240 (2019) (summarizing legal regulation of genetic alterations in embryos).
100. See, e.g., Daar, *supra* note 92 (calling it an “urban myth”). She emphasizes instead that American reproductive practice, like all others areas of medicine, “is subject to quality control through a variety of mechanisms, most notably licensure of physicians by state-based medical boards, application of practice standards established by professional societies, and private tort litigation.” *Id.* at 262.
101. See, e.g., Jody Lynee Madeira, *Uncommon Misconceptions: Holding Physicians Accountable for Insemination Fraud*, 37 L. & INEQ. 45, 45 (2019) (describing doctors using their own sperm without informing patients).

cancer treatment.¹⁰² However, a critical barrier to entry into the fertility business is the need to recruit trained medical professionals, including reproductive endocrinologists who require twelve years of secondary education to be properly certified.¹⁰³ Fertility practices are then “subject to quality control through a variety of mechanisms, most notably licensure of physicians by state-based medical boards, application of practice standards established by professional societies, and private tort litigation.”¹⁰⁴ Without widespread insurance coverage or other third party subsidies, these practices catered to high end patients able to pay out-of-pocket for high end procedures.¹⁰⁵ Debora Spar describes the clinics as competing to serve wealthy clients, with relatively high value, high profit services, rather than competing on price or seeking to expand volume.¹⁰⁶

Within these decentralized clinics,¹⁰⁷ doctors might try new techniques, such as Saint Barnabas’s use of cytoplasm transfer. Maureen Ott, one of the women who gave birth using cytoplasm transfer, commented, “[w]e wanted a baby so badly that we felt it was important to pursue every option available.”¹⁰⁸ Clinic patients supported (and presumably paid for) experimentation

102. See Carbone & Madeira, *supra* note 36, at 77 (noting the decentralized, small practice nature of most IVF centers).
103. *How to Become a Fertility Specialist*, DOCTORLY.ORG, <http://doctorly.org/how-to-become-a-fertility-specialist/> (last visited Feb. 25, 2020); See DEBORA SPAR, A BABY BUSINESS: HOW MONEY, SCIENCE, AND POLITICS DRIVE THE COMMERCE OF CONCEPTION 33 (2006) (observing that the lengthy training necessary to be able to do IVF creates barriers to entry); David Sable, *How Entrepreneurs Will Move IVF into the Future*, FORBES (Feb. 3, 2018), <https://www.forbes.com/sites/davidsable/2018/02/03/how-entrepreneurs-will-move-ivf-into-the-future/#41ae87a6554a> (describing how fertility clinics focus on providing higher quality care rather than expanded access).
104. Daar, *supra* note 92, at 262.
105. See Judith F. Daar, *Accessing Reproductive Technologies: Invisible Barriers, Indelible Harms*, 23 BERKELEY J. GENDER L. & JUST. 18, 37 (2008) (observing that insurance mandates have relatively little effect on fertility treatment usage because those with insurance coverage are the patients most likely to be able to afford fertility treatments on their own).
106. SPAR, *supra* note 103, at 34 (describing trade-offs in business models between high volume, lower priced, routine services versus high-end, high profit, lower volume customized services).
107. *Fertility Clinics*, CAPSTONE PARTNERS, <http://capstoneheadwaters.com/sites/default/files/Capstone%20Fertility%20Clinics%20Report%20Q1%202017.pdf#page=4> (last visited Mar. 8, 2020) (observing that the U.S. Fertility Clinic industry is highly fragmented and is comprised mainly of small regional clinics).
108. June Carbone, *Toward A More Communitarian Future? Fukuyama As the Fundamental Secular Humanist*, 101 MICH. L. REV. 1906, 1920 (2003) (quoting *Healthy Baby Born After World’s First Successful Cytoplasmic Transfer*, BUS. WIRE (July 18, 1997), WL, Business Wire Plus Database).

with an untested technique.¹⁰⁹ Yet, such clinics do not have the resources for large scale or carefully controlled studies establishing the safety and efficacy of these procedures.¹¹⁰ Dr. Jamie Grifo, who participated in the Saint Barnabas procedures, explained, in response to a question as to why the clinic did not do animal testing, “[a]nimal colonies cost a fortune to maintain,” he said and “we have no research dollars.”¹¹¹

Nonetheless, the clinics are sensitive to negative publicity. Just as they did not have the funds for animal testing or large scale human trials, neither did they have the funds to challenge the FDA’s assertion of jurisdiction, even though the legal basis for jurisdiction is questionable.¹¹² Once the FDA required preclearance for the use of such techniques, they stopped being done in the United States.¹¹³ Over the next two decades, however, the environment for fertility research changed dramatically.

B. New Story: Privatization and Globalization

Over the last twenty years, the environment for ART innovation has changed substantially. Many of the changes involve the changing health care landscape and the increasing role of private funding across the board. Some of the changes, however, have affected ARTs with particular force. These changes have produced increasing returns to scale, encouraged the consolidation of fertility and other medical services, and increased the geographic reach of fertility services.¹¹⁴ Other changes have seen an increase in the role and availability of private funding, including both philanthropic efforts and private equity funding encouraging commercialization of techniques.¹¹⁵ Taken together, they provide a more promising landscape for future genetic

109. *Id.*

110. *Id.* at 1921.

111. Nigel Hawkes, *Baby Race That May Be Too Fast for Safety*, *TIMES*, Oct. 10, 1998, at 4.

112. *See, e.g.*, Lewis, *supra* note 36, at 1257; Richard A. Merrill & Bryan J. Rose, *FDA Regulation of Human Cloning: Usurpation or Statemanship?*, 15 *HARV. J.L. & TECH.* 85, 102 (2001); Enriquez, *supra* note 99, at 1147, 1148 (questioning the constitutionality of the FDA restrictions).

113. Indeed, for a time, Dr. Grifo moved his research to China. *See* Antonio Regalado & Karby Leggett, *Fertility Breakthrough Raises Questions About Link to Cloning*, *WALL ST. J.*, Oct. 13, 2003, at 1A (reporting that a team of Chinese and American doctors were expected to announce that they had created the first human pregnancy using a DNA-swapping technology that would prefigure the later use of MRT).

114. Hamid Yunis & Bella North, *Spotlight on Private Equity in the Fertility Sector*, *NAT’L L. REV.* (May 23, 2019), <https://www.natlawreview.com/article/spotlight-private-equity-fertility-sector>.

115. *Id.*

modification technologies—if they prove effective in solving the reproductive issues that arise from genetically transmitted diseases.

1. Private Funding

While federal funds once supplied the vast bulk of research funding, this is no longer true. By the nineties, private funding began to eclipse federal dollars in biomedical research generally.¹¹⁶ More recently, private equity and venture capital investors have begun to pay greater attention to the fertility industry.¹¹⁷ This private funding takes two principal forms.

The first is called “billionaire philanthropy.”¹¹⁸ With growing income inequality, concentrated charitable contributions can have more clout, particularly in controversial areas of research.¹¹⁹ For example, philanthropist Katharine McCormack funded development of the birth control pill, the Susan Thompson Buffett Foundation contributed to the development of safer IUDs, and the Bill and Melinda Gates Foundation has funded international contraceptive efforts.¹²⁰ They have done so, in part, because of the inconsistent political will to fund such efforts, given religious opposition and cultural division.¹²¹ In addition, private philanthropists and patient groups have attempted to jumpstart funding in neglected areas, often ones that affect their families.¹²² Research in Parkinson’s disease, autism, asthma, prostate cancer and other common diseases received boosts in funding when private donors decided to concentrate efforts in those areas.¹²³ Private donors also seek to support research that is “too obscure, too experimental, or too uncertain” to

116. *Guiding Regulatory Reform in Reproduction and Genetics*, *supra* note 84, at 579.

117. Yunis & North, *supra* note 114.

118. Kelsey Piper, *How Billionaire Philanthropy Provides Reproductive Healthcare When Politicians Won’t*, VOX (Sept. 17, 2019, 8:10 AM), <https://www.vox.com/future-perfect/2019/9/17/20754970/billionaire-philanthropy-reproductive-health-care-politics>.

119. *See id.*

120. *Id.*

121. *Id.*

122. *See* Alice Dickow, *Does Anyone Care? A Case Study of Funding Research on Rare Diseases*, INSIDE PHILANTHROPY (Oct. 18, 2018), <https://www.insidephilanthropy.com/home/2018/10/18/does-anyone-care-a-case-study-of-funding-research-on-a-rare-diseases>.

123. *How Four Philanthropists Are Innovating Medical Research*, BRIDGESPAN GRP. (Sept. 26, 2013), <https://www.bridgespan.org/insights/blog/give-smart/how-philanthropists-innovate-medical-research>.

attract other funding.¹²⁴ With rare diseases, family and friend fundraising efforts often make more of a difference than other sources.¹²⁵ These private funding sources, while small in comparison with industry-based or public funds, typically come with fewer strings attached.¹²⁶

The second source of private funding comes from venture capital and private equity firms.¹²⁷ Venture capital firms typically invest in start-ups, helping to get such companies off the ground.¹²⁸ Venture capital investors acquire an equity interest in the company, hoping to benefit from their investment when the company takes off, is sold, or goes public.¹²⁹ By contrast, private equity firms pool money from multiple investors and acquire shares in private companies (or in public companies that they hope to take private).¹³⁰ Large institutional investors are more common in the private equity world, and they often plan to hold the shares they acquire for relatively short periods.¹³¹ Both venture capital and private equity firms seek to profit from their investments, and often pressure the companies in which they invest to grow quickly and/or rapidly increase their profitability.¹³²

In the past, outside investment of this type has not played an important role in the development of fertility treatments, but venture capital and private equity firms increasingly see the fertility industry as a new opportunity.¹³³ Industry analysts emphasize the opportunity for consolidation as the industry experiences increasing returns to scale.¹³⁴ They emphasize women's later age of childbearing and increasing demand for such services.¹³⁵ Analysts also

124. Michael Anft, *When Scientific Research Can't Get Federal Funds, Private Money Steps In*, CHRON. PHILANTHROPY (Feb. 8, 2015), <https://www.philanthropy.com/article/When-Scientific-Research/151777#>.

125. Dickow, *supra* note 122.

126. *See How Four Philanthropists Are Innovating Medical Research*, *supra* note 123.

127. Rebecca Robbins, *Investors See Big Money in Infertility. And They're Transforming the Industry*, STAT (Dec. 4, 2017), <https://www.statnews.com/2017/12/04/infertility-industry-investment/>.

128. *Id.*

129. *Private Equity vs. Venture Capital: What's the Difference?*, INVESTOPEDIA <https://www.investopedia.com/ask/answers/020415/what-difference-between-private-equity-and-venture-capital.asp#targetText=private%20equity%20is%20investment%20capital,potential%20for%20long%2Dterm%20growth>. (last updated Mar. 19, 2020).

130. *Id.*

131. *Id.*

132. *See id.*

133. *See Yunis & North*, *supra* note 114.

134. *Fertility Clinics*, *supra* note 107.

135. *Id.*

note the improving success rates of existing fertility treatments and the possibilities for technological innovation.¹³⁶ In addition, investors see potential gains from increased collaboration, better advertising, international opportunities, and more sophisticated development strategies.¹³⁷

Ultimately, increased private funding, both philanthropic and investment driven, may involve less direct oversight than government funding. But particularly when the funding comes from commercial investors, it may include pressure to quickly ramp up new products or unneeded or untested procedures.¹³⁸

2. Pressures for Consolidation

Driving some of the investment opportunities is the growing consolidation in the fertility industry. The pressure to consolidate comes in large part from increasing returns to scale.¹³⁹ Consolidation is occurring across the health care industry, and some of these trends affect fertility clinics as well.¹⁴⁰ Chief among these forces are the Electronic Records Act and accompanying privacy regulations, which involve not only transition costs, but also continuing compliance monitoring of the privacy requirements.¹⁴¹ In addition, innovation itself may increase consolidation to the extent it requires investment in new and more expensive machinery, more varied treatments, or inclusion of larger groups of specialists in providing care.¹⁴²

Changing insurance requirements also affect the returns to scale.¹⁴³ Fifteen states mandate at least some coverage of IVF, though they do not neces-

136. *Id.*

137. *See* Yunis & North, *supra* note 114.

138. Aaron Harris, *Why VCs Sometimes Push Companies to Burn Too Fast*, YCOMBINATOR (Nov. 21, 2016), <https://blog.ycombinator.com/why-vc-sometimes-push-companies-to-burn-too-fast/> (describing short-term time frames for venture capital investors); Robbins, *supra* note 127 (observing that some clinics have resisted private equity investors because of the fear that these investors emphasize increased volume to the detriment of patient care).

139. Carbone & Madeira, *supra* note 36, at 81.

140. *See id.* at 80 (observing that doctors have been selling private practices to larger hospital associations with increasing concentration since the nineties).

141. Paul R. Brezina et al., *How Obamacare Will Impact Reproductive Health*, 31 SEMINARS REPROD. MED. 189, 194 (2013) (discussing the high cost of the transition to electronic records and the need for continuing record maintenance and compliance monitoring).

142. Carbone & Madeira, *supra* note 36, at 81–83 (observing that larger groups enjoy greater discounts in acquiring new equipment).

143. *See id.* at 92–93.

sarily contain the full range of fertility treatments.¹⁴⁴ Market pressures, however, have been gradually increasing insurance coverage, particularly for the high-end employees most likely to delay childbearing.¹⁴⁵ In 2013, sixty-five percent of businesses with over 500 employees covered an initial evaluation by a fertility specialist, with twenty-seven percent paying for IVF and forty-one percent paying for IVF related drugs.¹⁴⁶

Greater insurance coverage, in turn, changes the dynamics of fertility practices.¹⁴⁷ The most direct impact is the increased demand for services.¹⁴⁸ Insurance companies also limit the services they will reimburse and the prices that they will pay for these services.¹⁴⁹ Debora Spar explains that greater insurance coverage—or even the *threat* of insurance—shifts fertility business models toward an emphasis on attracting a larger volume of patients who want more routine (and lower priced) services that insurers will reimburse.¹⁵⁰

An additional factor that may influence the future development of the industry is increased integration of fertility services with genomic information.¹⁵¹ In an era of personalized medicine, doctors have become increasingly aware of genetic factors that may increase the risk of infertility or of the transmission of genetic traits that increase the risk of disease in offspring.¹⁵² For patients with diagnosed disorders, insurance companies may cover a larger part of the cost of the testing and treatments associated with reproduction.¹⁵³ At least one industry analyst has suggested the development of specialized fertility centers designed specifically to integrate patient care with reproductive services.¹⁵⁴

144. Tara Siegel Bernard, *Insurance Coverage for Fertility Treatments Varies Widely*, N.Y. TIMES (July 25, 2014), <http://www.nytimes.com/2014/07/26/your-money/health-insurance/insurance-coverage-for-fertility-treatments-varies-widely.html> (noting that “[o]f the states that mandate coverage, only eight—Arkansas, Connecticut, Hawaii, Illinois, Maryland, Massachusetts, New Jersey and Rhode Island—require some level of coverage for in vitro fertilization”).

145. See Carbone & Madeira, *supra* note 36, at 90.

146. Bernard, *supra* note 144.

147. See Carbone & Madeira, *supra* note 36, at 87.

148. SPAR, *supra* note 103, at 34.

149. *Id.*

150. *Id.*

151. See David Sable, *The Seven Trends that Define the Future of IVF*, FORBES (Feb. 28, 2015, 4:53 PM), <http://www.forbes.com/sites/davidsable/2015/02/28/the-seven-trends-that-define-the-future-of-ivf/>.

152. See Carbone & Madeira, *supra* note 36, at 89–90.

153. *Id.*

154. David Sable, *Embryologist-Owned IVF Labs and Other Keys to the Future of Preventive Medicine*, FORBES (July 18, 2019, 11:11 AM), <https://www.forbes.com>.

These changes in fertility markets may simultaneously increase the size of existing clinics and contribute to greater segmentation of the markets. Larger clinics already serve more populous states with greater insurance coverage, while most clinics remain relatively small and focused on custom services for patients who pay out of pocket.¹⁵⁵ This segmentation may continue to increase further in the future.¹⁵⁶

3. Patient Recruitment and Globalization

The pressure to increase volume has increased the need to advertise fertility services and the desire to increase clinics' geographic reach.¹⁵⁷ Industry changes include both efforts to increase access and demand, and the creation of platforms that match patients and services.¹⁵⁸ These platforms contribute to greater market segmentation.¹⁵⁹ Some platforms, for example, seek to recruit wealthy patients to the United States for services, while sending poorer Americans to less expensive clinics abroad.¹⁶⁰ They may also exploit jurisdictional differences in regulation.¹⁶¹ For example, advertising the ability to engage in embryo sex selection is a practice banned in many countries.¹⁶²

Some industry analysts have invested in efforts to market "one-stop-shop fertility care, starting long before a woman is ready to conceive."¹⁶³ The idea is to recruit younger patients, persuade them to monitor their fertility

com/sites/davidsable/2019/07/18/embryologist-owned-ivf-labs-and-other-keys-to-the-future-of-preventive-medicine/#6b05589c5c21.

155. SPAR, *supra* note 103, at 58 (observing that most clinics "are either very high volume or very high tech").

156. *See id.* at 58–60.

157. *See Fertility Market Overview*, HARRIS WILLIAMS & CO. (May 2015), http://www.harriswilliams.com/sites/default/files/content/fertility_industry_overview_-_2015.05.19_v10.pdf (commenting on the highly fragmented nature of the U.S. market and efforts to increase consolidation and geographic reach).

158. *See* Carbone & Madeira, *supra* note 36, at 106; *see* Sable, *supra* note 151.

159. *See* Carbone & Madeira, *supra* note 36, at 106.

160. *See id.*; *see Our Centers and Staff*, FERTILITY INSTS., <http://www.fertility-docs.com/about-us/clinics-and-staff.php> (last visited Apr. 1, 2020); *see International Programs*, FERTILITY INSTS., <http://www.fertility-docs.com/programs-and-services/international-programs.php> (last visited Apr. 1, 2020).

161. Carbone & Madeira, *supra* note 36, at 100.

162. Meredith Leigh Birdsall, *An Exploration of "The 'Wild West' of Reproductive Technology": Ethical and Feminist Perspectives on Sex-Selection Practices in the United States*, 17 WM. & MARY J. WOMEN & L. 223, 226 (2010) (describing that "more and more couples from other countries are coming to the United States for sex-selection procedures to which they are denied at home").

163. Robbins, *supra* note 127.

through new apps and other devices, encourage them to consider freezing or donating their eggs, and proactively identify potential barriers to reproduction.¹⁶⁴ A private equity firm in New York has created a national network of fertility clinics and frozen egg banks, called “Prelude Fertility.”¹⁶⁵ It plans to use social media to encourage younger patients to become more aware of fertility issues and to begin to plan for them years in advance.¹⁶⁶

In the meantime, existing agencies act as matchmakers between fertility service patients and providers.¹⁶⁷ Clinics that recruit gamete donors and provide surrogacy services already operate on a national and international basis.¹⁶⁸ Some countries ban surrogacy while others offer the services at lower prices.¹⁶⁹ Even within the United States, the fifty states vary widely in the regulation of surrogacy.¹⁷⁰ Agencies exist that recruit broadly, matching patients and providers.¹⁷¹ These agencies contribute to the increasing volume of fertility patients; they also make it easier to evade regulatory restrictions.¹⁷²

Taken together, these efforts reflect a growing demand for fertility services, with some designed to increase the demand even more. As that occurs, new platforms have arisen that consolidate fertility services within a framework that seeks to meet customer needs—at least for patients able to pay. This new world of globalized, privatized reproductive medicine provides the framework for considering the future of genetic alteration.

164. *Id.*

165. Amanda Cantrell, *This Venture Capital Fund Wants to Get You Pregnant*, INSTITUTIONAL INV. (May 15, 2019) <https://www.institutionalinvestor.com/article/b1ff3x6hcl5wbb/This-Venture-Capital-Fund-Wants-to-Get-You-Pregnant>.

166. Robbins, *supra* note 127.

167. Tamar Lewin, *Coming to U.S. for Baby, and Womb to Carry It*, N.Y. TIMES (July 5, 2014), <http://www.nytimes.com/2014/07/06/us/foreign-couples-heading-to-america-for-surrogate-pregnancies.html>.

168. *See, e.g., id.* (describing increase in international visitors coming to the United States for surrogacy treatments).

169. *See, e.g.,* Lisa C. Ikemoto, *Reproductive Tourism: Equality Concerns in the Global Market for Fertility Services*, 27 L. & INEQ. 277, 282 (2009) (“The most troubling aspects of reproductive tourism arise from the use of third parties who furnish gametes and from surrogates who gestate babies for others. In fact, the strongest critics of these practices use the term ‘trafficking’ rather than ‘tourism.’”).

170. *See* June Carbone & Jody Lyneé Madeira, *The Role of Agency: Compensated Surrogacy and the Institutionalization of Assisted Reproduction Practices*, 90 WASH. L. REV. ONLINE 7, 14 (2015).

171. *Id.* at 25.

172. I. Glenn Cohen, *Circumvention Tourism*, 97 CORNELL L. REV. 1309, 1311 (2012) (describing rise of medical tourism designed to circumvent regulatory obstacles).

III. CRISPR AND THE FUTURE OF GENETIC MODIFICATION

In thinking about CRISPR's potential to usher in germline genetic modifications, it is important to think about why a patient would want access to the technology, and the circumstances in which doctors and scientists would be tempted to make it available. In short, just like the development of surrogacy and gamete donation, the development of CRISPR technology is likely to reflect underlying supply and demand motivations.

Approaching CRISPR this way sets up three questions. First, why would Dr. He ever choose the patients he did for the first use of CRISPR to edit a child's genome?¹⁷³ Second, what is the prospect for using CRISPR to enhance the reproductive efforts of patients who would otherwise be infertile? Third, is CRISPR a likely option for patients who could not otherwise produce genetically related offspring without the risk of transmitting a disease? These three uses (and potential uses) of CRISPR may develop in different environments, with different implications for CRISPR's impact on the future of genomic germline modification.

A. What was Dr. He Thinking?

Dr. He's choice of patients for the first experimentation with CRISPR in the reproductive context is curious—and unjustifiable. As Hank Greely has observed, the problems with the experiment are not just about germline editing.¹⁷⁴ Greely concluded that even if the experiment had involved only somatic cells, with no germline alterations, it would have been “‘criminally reckless’ as well as ‘grossly premature, and deeply unethical.’”¹⁷⁵ The reasons go to the basic protocols underlying scientific research.¹⁷⁶

The first involves balancing the costs and benefits to the research subjects. The first use of a new technique in a human is always inherently dangerous because the consequences may not be knowable in advance.¹⁷⁷ These risks are magnified in embryos where the impact can affect the child's development over the course of a lifetime, and the genetic modifications can be passed, perhaps in unpredictable ways, to offspring.¹⁷⁸ As of yet, CRISPR use has not been determined to be safe and effective in somatic cells—the

173. Greely uses the term “genome” to refer to changes in multiple genes. In addition, he prefers the term “edit” to “change” to distinguish intentional alterations from naturally occurring ones. Greely, *supra* note 1, at 165.

174. *Id.* at 151.

175. *Id.*

176. *Id.* at 153.

177. *Id.*

178. *Id.*

logical initial step in human use.¹⁷⁹ Further, researchers are concerned about identifiable risks associated with CRISPR use in embryos including the possibility that the CRISPR tool could unintentionally make changes in the wrong places, producing potentially dangerous “‘off target’ effects.”¹⁸⁰ The desired edits could also have unpredictable effects, altering human function in undesirable ways.¹⁸¹ CRISPR could succeed in altering some, but not all, of the child’s target cells, which might undermine the intended benefit.¹⁸² Finally, CRISPR could “cause large deletions or duplications in DNA, with unpredictable (but almost certainly not good) effects.”¹⁸³

Weighed against these considerable risks are the limited potential benefits from Dr. He’s procedure. The twins’ father was HIV positive carrying the risk of HIV infection.¹⁸⁴ Nonetheless, there are established ways of limiting the risk of HIV infection or treating it after birth.¹⁸⁵ Moreover, even if the genetic alteration worked exactly as it was intended, there can be no certainty that it would confer HIV immunity.¹⁸⁶ The potential risks, therefore, almost certainly outweighed the potential benefits for the resulting children—and violated appropriate research protocols.¹⁸⁷

Dr. He’s use of CRISPR therefore hardly provides a model for future use. But it is worth considering what may have motivated the parents’ participation. While sperm washing (that is, separation of the sperm from semen) virtually eliminates the risk of infection, these services are not necessarily available for HIV positive prospective parents in China.¹⁸⁸ The investigation into Dr. He’s activities indicated that “HIV carriers are not allowed to have assisted reproduction.”¹⁸⁹ The Chinese couples involved in the experiment could thus have viewed participation as their only way to gain access to IVF and possibly, therefore, their only way to have children at all or children

179. See Diane Nicol et al., *Key Challenges in Bringing CRISPR-Mediated Somatic Cell Therapy into the Clinic*, 9 *GENOME MED.* 85 (2017) (describing safety issues associated with CRISPR).

180. Greely, *supra* note 1, at 153.

181. *Id.* at 153–54.

182. *Id.* at 153. This appears to have happened in the case of the Chinese twins, with uncertain results.

183. *Id.* at 153–54.

184. *Id.* at 116.

185. *Id.* at 155–56 (maintaining that with use of the proper techniques, the risk of infection at conception “disappears entirely”).

186. Greely, *supra* note 1, at 156.

187. *Id.* at 163, 168. These protocols include not only the balancing of risks and benefits, but provisions for appropriate follow-up care, informed consent, advance authorization and other provisions.

188. *Id.* at 165.

189. *Id.*

without a risk of HIV transmission. While this raises additional ethical concerns, principally about Dr. He's potential conflicts of interest,¹⁹⁰ it also raises a different way to think about the potential future use of CRISPR. What if, instead of thinking of CRISPR principally as a way to prevent disease transmission, it also became a way to facilitate fertility treatments? And how would patients and medical professionals react if they saw CRISPR as the last chance for a couple to have genetically related children? Dr. He's patients may well have been motivated by such considerations, which reflect legal regulation in China as much if not more than the medical advances offered by the CRISPR technique.

B. CRISPR and the Fertility Industry

Imagine the following scenario: A woman in her twenties receives a devastating cancer diagnosis. The doctors advise her that the cancer treatments are likely to damage or destroy her eggs, making it unlikely that she will be able to bear children in the future. She decides to retrieve and freeze as many eggs as she can before the cancer treatments. Ten years later, she is cancer free and ready to start a family. She thaws some of the eggs, fertilizes them with her husband's sperm, and tries to become pregnant. With the first attempts, she does not become pregnant. Then, she succeeds in becoming pregnant, but miscarries. She now has only one batch of eggs left. Five survive the thawing. By the time she is ready for the insemination, only three are still viable. PGD indicate that all three of the remaining embryos have serious genetic issues, with two embryos having two copies of the gene for sickle cell anemia and therefore a high likelihood of producing the disorder. By the time this occurs, CRISPR has been successfully used to edit the somatic cells associated with sickle cell, and embryo trials have been successful in editing and removing the sickle cell genes from embryos. Should CRISPR be used to edit the sickle genes to eliminate the possibility that the embryos will develop into children with the disease?

Currently, doctors are unable to use CRISPR without running afoul of the FDA's requirement that fertility clinics receive FDA approval before doing so.¹⁹¹ Researchers who want to apply for such approval will generally not receive approval within time to benefit the patients, particularly if the researchers waited until after the eggs were thawed and fertilized to request approval.¹⁹² At least at present, there are not enough patients in the position

190. *Id.* (observing that this would have meant that Dr. He approached vulnerable patients to propose an experiment from which he expected to benefit). On the other hand, it might also mean that the twins would not have existed but for the experiment, suggesting greater benefits than if the parents could easily access sperm washing technology.

191. *See supra* text accompanying note 36.

192. Caroline Praderio, *There's a Dark Side to Egg Freezing That No One is Talking About*, INSIDER (Mar. 22, 2017, 3:49 PM), <https://www.insider.com/egg->

of the cancer survivor to justify the costs ordinarily associated with the type of clinical trials necessary to secure FDA approval.¹⁹³

Therefore, when faced with the immediate needs of a patient, a fertility clinic might decide to perform the procedure abroad.¹⁹⁴ Then, assuming that the procedure is proved safe and effective, the clinic might want to continue to offer the option to other patients. The easiest way to do so would be to set up a clinic that routinely offered the procedure in another country with little regulation.¹⁹⁵ When PGD was first offered, select clinics, in the United States and abroad, often advertised their willingness to use the technique as a way of increasing success rates for high risk patients.¹⁹⁶ Today, clinics also advertise their willingness to use the technique as a means of sex selection, another controversial practice banned in many jurisdictions.¹⁹⁷ It is thus easy to imagine clinics offering the following packages of services:

- (1) An increasing number of clinics today offer egg freezing services.¹⁹⁸ The average woman who freezes her eggs does so around the age of 37, an age when women's fertility is already beginning to wane.¹⁹⁹ Industry critics worry that women who rely on frozen eggs may find themselves with too few viable ones to achieve a pregnancy.²⁰⁰

freezing-failure-risks-2017-3.; *See supra* text accompanying note 36. The rider would prevent FDA funding, which would affect approval for this process.

193. *See, e.g.*, Carbone & Madeira, *supra* note 36, at 95, 97 (describing how OvaScience developed its fertility procedures abroad because of a lack of funding to conduct the trial necessary to win FDA approval).

194. For a description of how that was done with the first MRT procedure, see Cohen, *supra* note 49.

195. Michelle J. Bayefsky, *Comparative Preimplantation Genetic Diagnosis Policy in Europe and the USA and its Implications for Reproductive Tourism*, 3 REPROD. BIOMEDICINE & SOC'Y ONLINE 41, 42, 45 (2016).

196. Birdsall, *supra* note 162, at 228.

197. *Id.* (describing that more and more couples from other countries are coming to the United States for sex-selection procedures that they are denied at home).

198. Praderio, *supra* note 192 ("The number of women who froze their eggs at US fertility clinics grew by more than 700% between 2009 and 2013.").

199. Kylie Baldwin, *Six Things You Should Know If You Are Considering Freezing Your Eggs*, CONVERSATION (Apr. 3, 2018, 8:37 AM), <https://theconversation.com/six-things-you-should-know-if-you-are-considering-freezing-your-eggs-94039#targetText=however%2C%20the%20average%20age%20at,eggs%20before%20you%20are%2036>.

200. Praderio, *supra* note 192.

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- (2) PGD can increase IVF success by allowing doctors to select healthier embryos for implantation. Reliance on PGD means that the ability to identify genetic defects is likely to increase in importance.²⁰¹
 - (3) The delay in starting families, with or without egg freezing,²⁰² may increase the number of patients who lack healthy gametes.²⁰³ They may wish to use PGD to screen the resulting embryos, and to use CRISPR to edit the genomes of their limited supply of embryos (or of the supply of gametes beforehand) to increase the likelihood of producing a healthy infant.
 - (4) If doctors are engaged in genetic manipulation anyway, in order to increase reproductive success, they may consider additional alterations. For example, suppose that one of the cancer patient's eggs has a gene associated with premature aging, limiting the child's potential lifespan.²⁰⁴ If the doctors are planning to edit that gene to prevent premature aging anyway, they might also add a gene associated with longer lifespan.²⁰⁵ With greater genomic knowledge and experience, fertility doctors could easily develop a menu of options for genetic modification.²⁰⁶

While the number of women in the position to use such techniques today is small, that could increase in the future.²⁰⁷ If the combination of better screening and human genome editing were available, it might persuade even more women to freeze eggs at younger ages. In addition, given the expense of IVF, if it became relatively safe and inexpensive to use CRISPR, patients

201. In addition, in some cases, it might make sense to screen the gametes before fertilization. See MACINTOSH, *supra* note 27, at 13–14 (discussing advantages of editing gametes rather than embryos).
202. Quoc Trung Bui & Claire Cain Miller, *The Age That Women Have Babies: How a Gap Divides America*, N.Y. TIMES (Aug. 4, 2018), <https://www.nytimes.com/interactive/2018/08/04/upshot/up-birth-age-gap.html>.
203. Over time, however, scientists expect to be able to create an unlimited supply of new gametes from stem cells. See Greely, *supra* note 22, at 259 (estimating that the ability to create an unlimited supply of new gametes may occur at about the same time as CRISPR technology becomes more reliable).
204. See Sandra Rodríguez-Rodero et al., *Aging Genetics and Aging*, 2(3) AGING & DIS. 186 (Apr. 28, 2011), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3295054/> (observing that alteration in a single gene produces a remarkable difference in lifespans).
205. See MACINTOSH, *supra* note 27, at 19–20 (discussing possibility of human germline modifications that increase lifespan).
206. *Id.* at 21 (discussing how the concept of “normality” might change over time).
207. Patti Neighmond, *Women Can Freeze Their Eggs For the Future, But At a Cost*, NAT'L PUB. RADIO (Oct. 16, 2014), <https://www.npr.org/sections/healthshots/2014/10/16/356727823/freezing-a-womans-eggs-can-be-emotionally-and-financially-costly>.

might prefer to use the gametes and embryos they have, rather than undergo additional rounds of intrusive procedures like egg extraction, even if they could produce additional gametes without difficulty.²⁰⁸ Thus, once doctors begin editing embryos to limit the risk of serious diseases, they might also consider manipulating or altering other genes (such as the genes that influence height or athletic performance).²⁰⁹

All of this assumes that CRISPR technology proves safe and effective and that increasing genomic knowledges makes the interventions more predictable. Once that occurs, the desire to use CRISPR to assist patients who could otherwise not reproduce could become substantial. An industry organized to increase the effectiveness of fertility treatments, by encouraging fertility tourism if necessary, raises the question of whether a dividing line between acceptable and unacceptable uses of CRISPR can be enforced. That, in turn, requires considering the role of CRISPR in preventing serious diseases.

C. CRISPR and the Prevention of Disease

The least controversial part of CRISPR would be its use to prevent a disease or the transmission of disease-causing genes to subsequent generations. Yet, germline genetic editing to prevent the transmission of diseases, unlike such editing to facilitate fertility treatments, is much less likely to become a routine part of reproductive medicine.²¹⁰ There are just too many alternatives for most couples carrying genes they do not wish to transmit to their offspring.²¹¹

At one time, many individuals knew that members of their families were at increased risk for diseases like sickle cell disease anemia but did not necessarily have many ways to address the possibility of transmission. Today, they do. If individuals carry a single copy of the gene associated with such

208. See Rachel Gurevich, *How Much Does IVF Really Cost?*, VERYWELLFAMILY, <https://www.verywellfamily.com/how-much-does-ivf-cost-1960212> (last visited Mar. 8, 2020) (indicating the price of IVF); *In Vitro Fertilization (IVF)*, MAYO CLINIC, <https://www.mayoclinic.org/tests-procedures/in-vitro-fertilization/about/pac-20384716?page=0&citems=10> (last visited Mar. 8, 2020) (indicating that IVF is invasive); *but cf. The Egg Retrieval Process*, EXTEND FERTILITY, <https://extendfertility.com/services/egg-freezing/the-egg-retrieval/> (last visited Mar. 8, 2020) (indicating that IVF is only minimally invasive).

209. Greely, *supra* note 22, at 262 (noting the advantages for competitive skiers of alleles that produce high levels of hemoglobin).

210. See Macintosh, *supra* note 8, at 276 (explaining the level of support for this technology amongst polled citizens and how governments across the world continue to ban germline genetic editing to prevent the transmission of diseases).

211. See *id.* at 274.

autosomal recessive diseases,²¹² they would be carriers, but they would not ordinarily suffer from the disease themselves.²¹³ If, on the other hand, both mother and father passed on copies of the gene to their offspring, the offspring would experience the disease.²¹⁴ Couples who know that they are carriers of the gene are accordingly eager not to bear children who would inherit two copies of the gene. Similarly, adults who have inherited the gene for Huntington's disease from a single parent are likely to develop the disease later in life.²¹⁵ If they are to have children, they may wish to ensure that they do not pass on the autosomal dominant gene to their children. In this case, it does not matter whether the other parent can transmit the gene or not; receiving a single copy from one parent is enough to cause the disease.²¹⁶ In both of these cases, however, PGD together with IVF is ordinarily enough to ensure that the parents do not pass on the disease to their children.²¹⁷ These parents are not necessarily infertile in any way. They may be able to produce large numbers of embryos, and fertility specialists can choose the embryos to implant that do not pass on a disease causing gene.²¹⁸ For many couples, this is sufficient to allow them to bear healthy children, and indeed groups like the Ashkenazi Jewish communities that have embraced such techniques have seen a dramatic drop in the incidence of hereditary diseases such as Tay Sachs without use of genome editing.²¹⁹

Genetic screening mechanisms such as PGD cannot eliminate the transmission of such diseases entirely, however. For example, suppose a prospective parent has inherited two copies of the Huntington's gene, one from each parent. All of the individual's gametes will contain the Huntington's gene and, therefore, absent germline editing, so will all of the individual's children, even if the second parent does not have the gene.²²⁰ Similarly, with a recessive gene such as the one for sickle cell anemia, it is possible that two people who each inherited two copies of the gene may still wish to have children. However, if each parent has two copies of the sickle cell gene, then all the genes they pass on to their children will also have the gene.²²¹ In addition, in some cases, such as the risk of HIV transmission, gene editing

212. MACINTOSH, *supra* note 27, at 14.

213. *Id.*

214. *Id.*

215. *Id.* at 13.

216. *Id.*

217. *Id.*

218. MACINTOSH, *supra* note 27, at 12.

219. See Nancy M.P. King, *Human Gene-Editing Research: Is the Future Here Yet?*, 97 N.C. L. REV. 1051, 1073 (2019).

220. MACINTOSH, *supra* note 27, at 13–14 (indicating that editing gametes may be more effective than editing embryos).

221. *Id.* at 14.

cannot eliminate the disease itself, but the addition of new genes might confer immunity.²²² In each of these cases, gene editing would be a way to prevent transmission to the developing fetus in circumstances where genetic screening could not do so.²²³

In dealing with genetic diseases, however, it is also possible that doctors could edit the genes after the children are born, rather than before conception or implantation. In many cases, somatic editing would be preferable.²²⁴ Ordinarily, in a child or adult, as opposed to embryo, it would be easier to target particular tissues, and avoid unplanned changes.²²⁵ In addition, if off-target changes did occur, they would not affect embryonic or fetal development, which might be particularly damaging, and they would not be passed on to offspring.²²⁶ On the other hand, embryo or gamete editing would be preferable if the troubling conditions occurred early enough that by the time of the child's birth, critical damage is already likely to have occurred, or the child's development is likely to have been adversely affected.²²⁷ In addition, some diseases may already be imbedded in a large percentage of the body's cells by the time of birth, making it much harder to use somatic cell editing to eliminate the effects.²²⁸

This means there are cases where human germline modification in gametes or embryos might be a valuable way of preventing the transmission of potentially devastating diseases. Cases like this, where germline editing is the best or only way of accomplishing such a result, however, are likely to be rare. First, most of these diseases are rare to begin with.²²⁹ Second, cases where PGD cannot be used to screen gametes or embryos, but germline edit-

222. This is what Dr. He attempted to accomplish. *See id.* at 15–16 (noting the tradeoffs involved in this type of genetic editing).

223. *See id.* at 16.

224. *See* Greely, *supra* note 22, at 258.

225. *Id.* at 260.

226. *Id.* at 261.

227. *Id.*

228. *Id.*

229. *See* Genetics Home Reference, *What Are Genome Editing and CRISPR-Cas9?*, NAT'L LIBR. MED. (Mar. 31, 2020), <https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting> (listing relevant diseases, including cystic fibrosis, hemophilia, and sickle cell disease); Ann Pietrangelo, *Cystic Fibrosis by the Numbers: Facts, Statistics, and You*, HEALTHLINE, <https://www.healthline.com/health/cystic-fibrosis-facts> (last updated Nov. 26, 2019) (“Cystic fibrosis is an uncommon genetic disorder.”); *Hemophilia*, CLEVELAND CLINIC, <https://my.clevelandclinic.org/health/diseases/14083-hemophilia> (last reviewed Jan. 20, 2020) (“Hemophilia is a rare, inherited bleeding disorder.”); *Sickle Cell Disease*, NAT'L ORG. RARE DISORDERS, <https://rarediseases.org/rare-diseases/sickle-cell-disease/> (last visited Apr. 1, 2020) (“Sickle cell disease (SCD) is a rare blood disorder . . .”).

ing is appropriate will be rarer still.²³⁰ Third, parents who have two copies of many of these genes will have the disease and many may not be well enough to bear or raise children.²³¹ Finally, in some of these cases, other remedies, such as somatic cell editing will be preferable.²³² This leaves a small community who may have an intense interest in this technology, but few prospects for scaling up its implementation to the point where it becomes routine.

Therefore, to the extent it makes sense to encourage the development of CRISPR as a disease prevention technology, it might make more sense to tie its development to the specialists developing disease specific therapies, including somatic genome editing. Patient groups wishing to manage reproduction would then want a choice of options that may include testing prospective partners, access to PGD and IVF, and genetic modification as a last resort. In this context, germline alterations should be thought of as part of disease treatment and management. Insurance companies in turn may want to extend coverage to reproductive techniques to avoid incurring the costs associated with covering children at greater risk for the disease. Further, specialists who work with these patient groups should be trained to counsel their patients on reproductive access. Development of gene editing technology should take place within the same framework as other treatments associated with managing diseases associated with genetic inheritance.

If CRISPR and other forms of germline editing are restricted to these groups, however, either legally or practically, then the major issue will be funding. A private globalized industry is unlikely to develop simply to help eliminate the transmission of these genes even though many ethicists would ideally like to see CRISPR use, if it is permitted at all, limited to these populations.²³³ Indeed, that may be likely unless CRISPR is tied to the ability to solve fertility issues that affect a broader population than simply those with genetic diseases. In short, use of CRISPR in the reproductive context to assist in disease prevention is likely to remain rare and relatively easy to regulate.

230. Indeed, the incidence of Tay-Sachs disease in the Jewish population in the United States has fallen by more than ninety percent since the seventies. *See* Ira Stoll, *How the Jews Nearly Wiped Out Tay-Sachs*, JEWISH TELEGRAPHIC AGENCY (Aug. 11, 2017), <https://www.jta.org/2017/08/11/united-states/how-the-jews-nearly-wiped-out-tay-sachs>.

231. *See* Genetics Home Reference, *supra* note 229; Katie Willard Virant, *Parenting with Chronic Illness*, PSYCHOL. TODAY (Jan. 14, 2019), <https://www.psychologytoday.com/us/blog/chronically-me/201901/parenting-chronic-illness> (explaining the challenges of parenting with chronic illness).

232. Greely, *supra* note 22, at 260 (describing for example, somatic cell treatments for sickle cell anemia).

233. Ed Yong, *The Designer Baby Era Is Not upon Us*, ATLANTIC (Aug. 2, 2017), <https://www.theatlantic.com/science/archive/2017/08/us-scientists-edit-human-embryos-with-crisprand-thats-okay/535668/>.

IV. CONCLUSION

The attention focused on the prospect of germline genomic modification is, at this point, largely unwarranted. Dr. He's experimentation with CRISPR in China was premature and deserves international condemnation. The more important focus should be on the development of CRISPR to effect somatic cell alterations that treat existing diseases. In looking to the future, the use of CRISPR to effect germline changes to eliminate the transmission of disease-causing genes to infants, while not ready for implementation right now, is likely to be a development that still has limited impact outside of those families plagued with hereditary diseases. Instead, the potentially far-reaching impact of CRISPR depends on whether it becomes a more important part of the fertility industry, that has been establishing globalized platforms that match patients with new technologies. Should CRISPR become part of efforts to increase the efficacy of reproduction, to increase the numbers of viable gametes, or to enhance the health of the resulting children, it will have much more far reaching implications than if its use is limited to preventing disease transmission. In that case, the questions are not so much about CRISPR itself, but about the channeling and development of reproductive medicine on a global basis.