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# Human Gene-Editing Research: Is the Future Here Yet?

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## HUMAN GENE-EDITING RESEARCH: IS THE FUTURE HERE YET?\*

NANCY M. P. KING\*\*

*Since the discovery of DNA, researchers have pursued the prospect of correcting genetic disorders using genetic interventions. The most recent development, gene editing, poses many scientific, medical, ethical, and policy challenges, especially when the goal is editing the genomes of embryos, creating changes that can be inherited by future generations. Genetic treatments for already-born persons are not controversial, but inheritable genetic changes raise concerns about dangerous outcomes, questions about how to prioritize among scientific and societal needs, and worries about pursuing genetic changes that are enhancements rather than treatments for disease. The history of genetic-intervention research and the development of gene-editing tools like CRISPR were complicated enough, even before the “CRISPR babies” controversy arose in late 2018. CRISPR and related editing technologies should be used for basic research in order to learn more about human development and disease, but there is considerable disagreement and reason to be cautious about clinical applications. Moreover, no global enforcement mechanism exists to detect and prevent deviations from policy. Improved transparency, robust ongoing discussion, and increased education in ethics and genetics for scientists, students, and the public may therefore be both achievable goals and best practices for this rapidly developing science.*

INTRODUCTION .....	1052
I. THE SCIENCE AND EARLY HISTORY OF GENE EDITING .....	1054
A. <i>Science and Ethics in a Fast-Moving Field</i> .....	1055
B. <i>Benefits, Harms, and Policy Tradeoffs</i> .....	1058

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1052	<i>NORTH CAROLINA LAW REVIEW</i>	[Vol. 97]
II.	A BRIEF HISTORY OF CRISPR NEWS AND POLICY.....	1063
III.	WHAT ARE THE ETHICAL AND POLICY ISSUES IN GENE EDITING? .....	1070
	A. <i>Is Germline Genome Editing Necessary, or Just Way Cool?</i> .....	1071
	B. <i>Appropriate Research Targets: Treatment or Enhancement?</i> .....	1077
	C. <i>Oversight and Governance, Domestic and Global</i> .....	1080
	D. <i>A Moratorium?</i> .....	1082
	E. <i>Access and Cost</i> .....	1083
IV.	CAN POLICY SHAPE SCIENCE? .....	1085
	A. <i>Is Germline Editing the Future?</i> .....	1085
	B. <i>Is Enhancement Inevitable?</i> .....	1086
	C. <i>Sticking to the Basics: A Proposal</i> .....	1087
	CONCLUSION.....	1090

## INTRODUCTION

Gene editing is the technical process of deleting segments of DNA from an organism’s genes, and sometimes substituting new DNA sequences, in order to eliminate deleterious mutations.<sup>1</sup> Advances in gene-editing technology have renewed hopes of correcting genetic defects in humans and rekindled debates about the many ethical, social, and policy consequences of genetic manipulation, especially when changes will be passed on through the germline, that is, to future generations. Gene-editing tools like CRISPR-associated protein 9 (“CRISPR-Cas9”) are potentially precise, accurate, easy, quick, and cheap. As a result, gene editing has also renewed long-standing debates about efforts to pursue human

1. Nonscientists will welcome the accessibility, comprehensive history, and sweeping survey of ethical and policy issues raised by gene editing in a highly readable book by one of the discoverers of CRISPR. See generally JENNIFER A. DOUDNA & SAMUEL H. STERNBERG, *A CRACK IN CREATION: GENE EDITING AND THE UNTHINKABLE POWER TO CONTROL EVOLUTION* (2017). For a shorter and equally accessible overview, see Jennifer Kahn, *The CRISPR Quandary*, N.Y. TIMES MAG. (Nov. 9, 2015), <https://www.nytimes.com/2015/11/15/magazine/the-crispr-quandary.html> [<https://perma.cc/9YW3-BCVQ> (dark archive)]. In addition, students of popular culture may appreciate two YouTube videos about CRISPR. See acapellascience, *CRISPR-Cas9 (“Mr. Sandman” Parody)* | *A Capella Science*, YOUTUBE (Oct. 8, 2016), <https://www.youtube.com/watch?v=k99bMtg4zRk> [<https://perma.cc/W9PK-PG39>]; LastWeekTonight, *Gene Editing: Last Week Tonight with John Oliver (HBO)*, YOUTUBE (July 1, 2018), <https://www.youtube.com/watch?v=AJm8PeWkiEU> [<https://perma.cc/4C2M-DE6V>].

germline alteration and enhancement. These debates reached fever pitch in late November 2018, when Chinese scientist Dr. He Jiankui claimed to the world that he had accomplished genome editing of two zygotes successfully brought to term as twin girls.<sup>2</sup> At first it was unclear whether the twins actually existed, but it became increasingly clear that Dr. He had lied, ignored ethics guidelines, and cut regulatory corners at best, and that the purported edits were probably ineffective and possibly dangerous.<sup>3</sup>

This Article examines the new gene-editing boom, considering briefly a range of issues—namely, the safety, efficacy, affordability, ethical and social acceptability, oversight, and control of this novel biotechnology. Part I, a very basic introduction to the science of gene editing, notes the similarities and differences between gene editing and its predecessor, gene transfer or gene addition, and a potential successor, base editing. This part continues by examining the policy furor that followed the first publications reporting about gene-editing research efforts in human embryos. It concludes that keeping up with the science and managing its oversight have become significant challenges for policymakers and bioethics scholars. Part II considers the prospect of human gene editing in its social and historical context, examining the most recent scientific developments and the policy debates engendered thereby, including the recent, unexpected, and highly controversial reported birth of gene-edited twins in China. Part III then discusses ethical and policy debates and future prospects for ethical consensus on whether, where, when, and how to move forward with human gene-editing research and clinical translation applied to embryos intended for birth. This part addresses somatic versus germline editing and gene editing's connection to and dependence on basic assisted reproduction technologies like in vitro fertilization

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2. See *infra* notes 83–98 and accompanying text.

3. Dr. He's claims were first brought to public attention in late November 2018. See Antonio Regalado, *Exclusive: Chinese Scientists Are Creating CRISPR Babies*, MIT TECH. REV. (Nov. 25, 2018), <https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/> [<https://perma.cc/9FLZ-3UJ4>] [hereinafter Regalado, *Chinese Scientists*]. Also on November 25, Dr. He released a YouTube video about his claims. The He Lab, *About Lulu and Nana: Twin Girls Born Healthy After Gene Surgery as Single-Cell Embryos*, YOUTUBE (Nov. 25, 2018), <https://www.youtube.com/watch?v=th0vnOmFltc> [<https://perma.cc/H3XM-EE97>]. For a summary of Dr. He's claims and responses to those claims, see Sharon Begley & Andrew Joseph, *The CRISPR Shocker: How Genome Editing Scientist He Jiankui Rose from Obscurity to Stun the World*, STAT (Dec. 17, 2018), <https://www.statnews.com/2018/12/17/crispr-shocker-genome-editing-scientist-he-jiankui/> [<https://perma.cc/ARU5-US4N>]; see also *infra* notes 86–98 and accompanying text.

(“IVF”) and preimplantation genetic diagnosis (“PGD”), including controversial arguments about the necessity of germline alteration. This part also addresses treatment versus enhancement and questions of governance and access. Part IV suggests the need to refocus emphasis on modeling and adhering to careful, meticulous, and responsible science, as taught and practiced in laboratories around the world, in both preclinical and translational research settings. Responsible science, fostered by good education in sound and ethical scientific practice, has the best chance—if there is any chance—of promoting the conduct of reason-grounded and thoughtful research, and of helping to ensure robust public discussion of and policy deliberation about ethically sound scientific progress.

#### I. THE SCIENCE AND EARLY HISTORY OF GENE EDITING

Gene editing has captured the public imagination since CRISPR first hit the news just a few years ago.<sup>4</sup> It is noteworthy, however, that most of the scientific, medical, ethical, and policy issues raised by gene editing echo questions and problems that have been discussed since Watson, Crick, and Franklin first identified the double helix.<sup>5</sup> This Article addresses some of the most significant implications of future human clinical applications of gene editing.<sup>6</sup>

4. See *supra* note 1.

5. Tracy Hampton, *Ethical and Societal Questions Loom Large as Gene Editing Moves Closer to the Clinic*, 315 JAMA 546, 546–48 (2016). The deoxyribonucleic acid (“DNA”) helix was identified in 1953. By the 1970s, the search for effective gene-based treatments for human genetic diseases had begun in earnest. Mary Carrington Coutts, *Human Gene Therapy*, 4 KENNEDY INST. ETHICS J. 63, 65 (1994) The first human patient-subject, Ashanti de Silva, received a gene-transfer (now often referred to as gene augmentation) intervention in 1990. *Id.* at 63. In 1999, Jesse Gelsinger became the first patient-subject to die as a result of a gene-transfer research intervention. Rick Weiss & Deborah Nelson, *Methods Faulted in Gene Test Death: Teen Too Ill for Therapy, Probe Finds*, WASH. POST, Dec. 8, 1999, at A1; Paul Gelsinger, *Jesse’s Intent*, GUINEA PIG ZERO (2000), <http://www.guineapigzero.com/jesses-intent.html> [<https://perma.cc/R5PG-8S3X>]. The first gene-transfer intervention was approved as a therapy in 2004 in China. Sue Pearson, Hepeng Jia & Keiko Kandachi, *China Approves First Gene Therapy*, 22 NATURE BIOTECHNOLOGY 3, 3–4 (2004). A few more gene-transfer interventions have been approved to date as therapies by the European Medicines Agency (“EMA”), see Nuala Moran, *First Gene Therapy Glybera (Finally) Gets EMA Approval*, BIOWORLD (Nov. 2, 2012), <http://www.bioworld.com/content/first-gene-therapy-glybera-finally-gets-ema-approval-1> [<https://perma.cc/5BQN-U4FT>], and the FDA, News Release, FDA, FDA Approves Novel Gene Therapy to Treat Patients with a Rare Form of Inherited Vision Loss (Dec. 19, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm> [<https://perma.cc/LSH7-YNEN>].

6. This Article draws on some of my previous work on gene editing and related novel biotechnologies, most notably Nancy M. P. King, Pat C. Lord & Douglas E. Lemley,

A. *Science and Ethics in a Fast-Moving Field*

Researchers have been attempting to “edit” genes, by deleting harmful genes and replacing them in the genome with nonmutated versions, since the 1990s.<sup>7</sup> The tools and techniques first used in gene editing, zinc finger nucleases (“ZFNs”) and transcription activator-like effector nucleases (“TALENs”), are complex and difficult to master; their slow progress thus attracted little notice.<sup>8</sup> But then came CRISPR (clustered regularly interspersed palindromic repeats), which was first discovered as an adaptive immune system in bacteria but was quickly modified to specifically target any DNA sequence.<sup>9</sup> Since mid-2014, the explosion of scientific, medical, and public

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*Editing the Genome: Prospects, Progress, Implications, and Cautions*, 5 CURRENT GENETIC MED. REP. 35, 35–43 (2017). It is unfortunately not possible, however, to address all or even most of the relevant issues without taking up excessive space and trying readers’ patience. Many significant ethical and policy issues arise from applications of gene editing (and gene drives) to plants and animals. These issues include not only agricultural and animal husbandry applications but also basement biohacking and the potential weaponization of genetically altered organisms. All this and more is well beyond the scope of this Article, yet others have given these topics expert treatment. See generally NAT’L ACADS. OF SCIS., ENG’G, & MED., GENE DRIVES ON THE HORIZON (2016) (summarizing the scientific discoveries related to gene drives and considerations for their responsible use); Sharon Begley, *Monsanto Licenses CRISPR Technology to Modify Crops—with Key Restrictions*, STAT (Sept. 22, 2016), <https://www.statnews.com/2016/09/22/monsanto-licenses-crispr/> [<https://perma.cc/G3MS-FKG3>]. Nor do I address the prospect of using gene editing and related technologies to create human-animal chimeras, such as “humanized” pigs capable of growing human organs suitable for transplantation, which raises issues that are related to but distinguishable from those addressed in this Article and that deserve thorough examination. See, e.g., David Shaw et al., *Creating Human Organs in Chimaera Pigs: An Ethical Source of Immunocompatible Organs?*, 41 J. MED. ETHICS 970, 970–74 (2015); Fergus Walsh, *US Bid to Grow Human Organs for Transplant Inside Pigs*, BBC NEWS (June 6, 2016), [www.bbc.com/news/health-36437428](http://www.bbc.com/news/health-36437428) [<https://perma.cc/PD7N-TT6L>].

7. See Jens Boch, *TALEs of Genome Targeting*, NATURE BIOTECHNOLOGY 135, 135–36 (2011); Sundar Durai et al., *Zinc Finger Nucleases: Custom-Designed Molecular Scissors for Genome Engineering of Plant and Mammalian Cells*, 33 NUCLEIC ACIDS RES. 5978, 5978 (2005).

8. Even so, close to a dozen protocols involving ZFNs have been submitted to the Recombinant DNA Advisory Committee (“RAC”) for review to date. See, e.g., *Gene Transfer Protocol Report: A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) Mediated Targeted Integration of SB-FIX in Adult Subjects with Severe Hemophilia B*, GEMCRIS (Jan. 23, 2018), [https://www.gemcris.od.nih.gov/Contents/GC\\_CLIN\\_TRIAL\\_RPT\\_VIEW.asp?WIN\\_TYPE=R&CTID=1446](https://www.gemcris.od.nih.gov/Contents/GC_CLIN_TRIAL_RPT_VIEW.asp?WIN_TYPE=R&CTID=1446) [<https://perma.cc/7ER8-X557>]. Moreover, TALEN, although nowhere near approval as a therapy, has been used to treat an infant outside the United States, apparently successfully. See Andrew Pollack, *A Cell Therapy Untested in Humans Saves a Baby with Cancer*, N.Y. TIMES, Nov. 6, 2015, at B3.

9. Kahn, *supra* note 1.

interest has resulted in thousands of scholarly publications,<sup>10</sup> floods of articles in the popular press,<sup>11</sup> and extensive debate about a broad range of bioethics and public policy issues, including but not limited to questions about safety and efficacy, about whether it is appropriate to edit the human germline,<sup>12</sup> and about whether it is possible to establish global governance over what appears to be a potentially species-altering technology.<sup>13</sup> Federal and international panels and commissions have addressed the science and ethics of CRISPR.<sup>14</sup> And public discussion of the possibility and desirability of making inheritable genetic alterations to eliminate genetic disease, and of genetically enhancing humans, which has been simmering for nearly fifty years, has now reached boiling point.

10. See, e.g., Barry L. Stoddard & Keith Fox, Editorial, *CRISPR in Nucleic Acids Research*, 44 NUCLEIC ACIDS RES. 4989, 4989–90 (2016), corrected at 44 NUCLEIC ACIDS RES. 8512, 8512 (2016) (correcting an omission of a reference from a previous issue to properly explain that “the number of studies citing ‘CRISPR + Cas9,’ as indexed in PubMed, has exploded from four papers in 2012 to a projection of over 2000 publications in 2016”); Amanda B. Keener, *Gene Editing: From Roots to Riches*, SCIENTIST (Oct. 1, 2016), <http://www.the-scientist.com/?articles.view/articleNo/47156/title/Gene-Editing--From-Roots-to-Riches/> [<https://perma.cc/5ZZ9-NNHZ>].

11. See, e.g., Kendal K. Morgan, *CRISPR Comes to the Clinic*, GENOME MAG., Summer 2017, at 40, 43, 45; Alice Park, *Life, the Remix*, TIME, July 4, 2016, at 42, 44–48; Michael Specter, *The Gene Hackers*, NEW YORKER, Nov. 16, 2015, at 52, 54; Nathaniel Comfort, *Can We Cure Genetic Diseases Without Slipping into Eugenics?*, NATION (July 16, 2015), <http://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/?print=1> [<https://perma.cc/C9FL-2QT5>]; Mike Feibus, *CRISPR Gene Editing Tool: Are We Ready to Play God?*, USA TODAY (July 24, 2017, 9:00 AM), <https://www.usatoday.com/story/tech/columnist/2017/07/24/crispr-gene-editing-tool-we-ready-play-god/490144001/> [<https://perma.cc/5WHE-X3W7>].

12. See *About Human Germline Gene Editing*, CTR. FOR GENETICS & SOC’Y, <http://www.geneticsandsociety.org/article.php?id=8711> [<https://perma.cc/6VC6-4N6N>].

13. See Gary E. Marchant & Wendell Wallach, *Coordinating Technology Governance*, ISSUES SCI. & TECH., Summer 2015, at 43, 43–45.

14. There have been two international summits on human genome editing to date. See Press Release, Nat’l Acad. of Scis. Eng’g & Med., Second International Summit on Human Genome Editing to Be Held in Hong Kong (May 8, 2018), <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=05082018> [<https://perma.cc/Z9V4-K7SY>]. In addition, the National Academies of Science, Engineering, and Medicine convened international scholarly meetings over several years and issued an influential report in 2017. See generally NAT’L ACADS. OF SCIS., ENG’G, & MED., HUMAN GENOME EDITING: SCIENCE, ETHICS, AND GOVERNANCE (2017) [hereinafter NASEM, HUMAN GENOME EDITING] (“Recognizing both the promise and concerns related to human genome editing, the National Academy of Sciences and the National Academy of Medicine convened the Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations to carry out the study that is documented in this report.”). And the second issue of the CRISPR Journal featured a compendium of position statements from around the world. See *infra* text accompanying note 82.

The prospect of genetic modification, and the fears and hopes it engendered, were first addressed in the 1970s in connection with the Asilomar moratorium on recombinant DNA research.<sup>15</sup> Discussion of the ethical, legal, and social implications (“ELSI”) of genetic research expanded in the 1990s when recombinant DNA research in humans began to attempt correction of genetic defects and the Human Genome Project began its work of finding and mapping all human genes.<sup>16</sup> Attention to the implications of gene-based treatment and enhancement largely faded from view, however, after the mapping project was completed and progress in clinical research slowed.

Despite the growth of multidisciplinary in the biosciences, collaboration between scientists and bioethics scholars has remained challenging because of the rapid development of specialized knowledge and the resultant information gaps and language barriers. This means that ethical and policy thinking can at times lag behind biotechnological developments or misunderstand or mischaracterize them.<sup>17</sup> However, waiting to address the implications of a novel biotechnology until it is more fully developed often means chasing after what has rapidly become regarded as inevitable.<sup>18</sup> Indeed, the global response to Dr. He’s work may exemplify both the inherent

15. At the Asilomar Conference, the American scientific community voluntarily and temporarily halted all recombinant DNA research until risks of harm were further assessed and oversight mechanisms were created. *See generally* Paul Berg, *Asilomar 1975: DNA Modification Secured*, 455 NATURE 290 (2008) (noting the successes of the conference and considering whether an Asilomar-type conference could “help resolve some of the controversies now confronting scientists and the public”); Michael Rogers, *The Pandora’s Box Congress*, ROLLING STONE, June 19, 1975, at 36 (narrating the historic conference through vignettes).

16. Eric D. Green, James D. Watson & Francis S. Collins, *Twenty-Five Years of Big Biology*, 526 NATURE 29, 29–31 (2015).

17. When five percent of the federal funding for the Human Genome Project was set aside for study of its ethical, legal, and social implications, bioethics scholarship went mainstream. *See* Jean E. McEwen et al., *The Ethical, Legal, and Social Implications Program of the National Human Genome Research Institute: Reflections on an Ongoing Experiment*, 15 ANN. REV. GENOMICS & HUM. GENETICS 481, 481–82 (2014). Yet it also became known for examining the potential of biotechnologies that had not yet come to fruition and thus was sometimes regarded as standing in the way of science. Steven Pinker, *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> [<https://perma.cc/5AHD-HQNM> (dark archive)].

18. Germline gene editing has been so characterized. *See, e.g.*, Stephen S. Hall, *Red Line: Will We Control Our Genetic Destinies?*, SCI. AM., Sept. 2016, at 54, 56–58; Antonio Regalado, *Engineering the Perfect Baby*, MIT TECH. REV., May–June 2015, at 26, 32 [hereinafter Regalado, *Engineering the Perfect Baby*].

limitations of guidance development and the failures of education and enforcement.<sup>19</sup>

### B. *Benefits, Harms, and Policy Tradeoffs*

Two overarching policy questions that scientists, scholars, and society began to address during the Asilomar moratorium have reemerged as a result of CRISPR-Cas9: First, should our concerns be focused only on safety and efficacy, or also on metaphysical matters like the integrity of human genetic inheritance?<sup>20</sup> And second, should the debates and decisions be led by scientists who are experts in the technology; by policymakers, bioethics scholars, and the general public; or by the individuals and families affected by genetic disorders, and their advocates?<sup>21</sup> In the current debate about inheritable genetic modifications, more than a few prominent scientists have agreed that science alone cannot answer ethics questions; instead, they acknowledge the need for broad and robust

19. See discussion *infra* Part II; see also Antonio Regalado, *Rogue Chinese CRISPR Scientist Cited US Report as His Green Light*, MIT TECH. REV. (Nov. 27, 2018), <https://www.technologyreview.com/s/612472/rogue-chinese-crispr-scientist-cited-us-report-as-his-green-light/> [<https://perma.cc/EG4N-VPU3>].

20. George J. Annas, Lori B. Andrews & Rosario Isasi, *Protecting the Endangered Human: Toward an International Treaty Prohibiting Cloning and Inheritable Alterations*, 28 AM. J.L. & MED. 151, 151–53 (2002) [hereinafter Annas et al., *Protecting the Endangered Human*]; George Annas, *Scientists Should Not Edit Genomes of Human Embryos*, B.U. SCH. PUB. HEALTH (Apr. 30, 2015), <https://www.bu.edu/sph/2015/04/30/scientists-should-not-edit-genomes-of-human-embryos/> [<https://perma.cc/U4NW-UXQM>] [hereinafter Annas, *Human Embryos*].

21. See, e.g., Ruha Benjamin, *Interrogating Equity: A Disability Justice Approach to Genetic Engineering*, in INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: COMMISSIONED PAPERS 48, 48–51 (2015), [www.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga\\_170455.pdf](http://www.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_170455.pdf) [<https://perma.cc/MU37-9JRV>]; Alta Charo, *The Legal/Regulatory Context*, in INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: COMMISSIONED PAPERS, *supra*, at 13, 13–19; Erika Check Hayden, *Tomorrow's Children*, 530 NATURE 402, 403–05 (2016); J. Benjamin Hurlbut, *Limits of Responsibility: Genome Editing, Asilomar, and the Politics of Deliberation*, HASTINGS CTR. REP., Sept.–Oct. 2015, at 11, 11–14; Eric T. Juengst, *Crowdsourcing the Moral Limits of Human Gene Editing?*, HASTINGS CTR. REP., May–June 2017, at 15, 15–23; Daniel Sarewitz, *Science Can't Solve It*, 522 NATURE 413, 413–14 (2015); Sharon F. Terry, *Societal Implications: The Role of Advocacy Organizations*, in INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: COMMISSIONED PAPERS, *supra*, at 36, 36–38; Charis Thompson, *Governance, Regulation, and Control: Public Participation*, in INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: COMMISSIONED PAPERS, *supra*, at 44, 44–47; Antonio Regalado, *Patients Favor Changing the Genes of the Next Generation with CRISPR*, MIT TECH. REV. (Dec. 2, 2015), <https://www.technologyreview.com/s/544141/patients-favor-changing-the-genes-of-the-next-generation-with-crispr/> [<https://perma.cc/M6GD-6U2X>].

public debate.<sup>22</sup> But whether that ethics debate should be framed as a balance of the risks of harm against potential benefits only for individuals and their progeny, or whether it should expand to address the implications of multiple individual, inheritable changes for the human species as a whole,<sup>23</sup> is still at issue. At the same time, the research is advancing rapidly and has already taken some unprecedented directions.<sup>24</sup>

Scientists and the public alike recognize that potentially astounding health benefits could follow from editing the human germline. But there are real concerns as well. Introducing permanent inheritable changes might introduce unintended errors that could damage not only individual patient-subjects but also their future offspring for generations. This concern arose when gene-transfer research<sup>25</sup> began in 1990.<sup>26</sup> Gene transfer seeks to correct deleterious genetic mutations by introducing multiple copies of nonmutated versions of the responsible gene into the body.<sup>27</sup> The principal risk of harm comes from the possibility of “off-target effects”—that is, that copies could insert into the wrong place in the genome, causing a different and potentially deleterious mutation.<sup>28</sup> That potential harm is only to the individual so treated; however, it is common to monitor

22. See, e.g., Eric S. Lander, *Brave New Genome*, 373 NEW ENG. J. MED. 5, 5–8 (2015).

23. See Annas et al., *Protecting the Endangered Human*, *supra* note 20, at 153; Annas, *Human Embryos*, *supra* note 20.

24. Chinese researchers in particular have surged ahead in both embryo research and clinical applications, and He Jiankui was not the first to surprise the scientific community. See discussion *infra* Part II.

25. Gene-transfer research was first misleadingly labeled “gene therapy.” See Nancy M. P. King, *Rewriting the “Points to Consider”: The Ethical Impact of Guidance Document Language*, 10 HUM. GENE THERAPY 133, 133 (1999). It has now been renamed “gene augmentation” or “gene-addition” research to distinguish it from gene editing. See Thierry VandenDriessche & Marinee K. Chuah, *CRISPR-Cas9 Flexes Its Muscles: In Vivo Somatic Gene Editing for Muscular Dystrophy*, 24 MOLECULAR THERAPY 414, 414–16 (2016).

26. Coutts, *supra* note 5, at 63. The first human clinical gene-transfer experiment that intended to develop a genetic treatment enrolled children with adenosine deaminase deficiency, a severe combined immunodeficiency disorder. Francesca Ferrua & Alessandro Aiuti, *Twenty-Five Years of Gene Therapy for ADA-SCID: From Bubble Babies to an Approved Drug*, 28 HUM. GENE THERAPY 972, 972–74 (2017). The first patient-subject in that experiment, Ashanti DeSilva, is still alive and well. See *id.* at 978.

27. See LEROY WALTERS & JULIE GAGE PALMER, *THE ETHICS OF HUMAN GENE THERAPY* 18, 23, 26, 166–69 (1997); Nancy M. P. King, *Accident & Desire: Inadvertent Germline Effects in Clinical Research*, HASTINGS CTR. REP., Mar.–Apr. 2003, at 23, 24 [hereinafter King, *Accident & Desire*]; VandenDriessch & Chuah, *supra* note 25.

28. The principal concern is that an off-target insertion will cause cancer. See, e.g., Salima Hacin-Bey-Abina et al., *Efficacy of Gene Therapy for X-Linked Severe Combined Immunodeficiency*, 363 NEW ENG. J. MED. 355, 363 (2010).

adult male patient-subjects in many gene-transfer clinical trials by testing their semen to determine whether there are any potential germline effects and to advise them against unprotected sex until monitoring is completed.<sup>29</sup>

Gene editing, in contrast, does not flood the organism with new copies of genes.<sup>30</sup> Instead, it either removes mutated or damaged sequences from genes, or removes them and replaces them with undamaged versions.<sup>31</sup> One of the reasons that gene editing has generated such scientific excitement is that it seems to be significantly more precise, and potentially more accurate, as well as more effective and more reliably permanent, than gene addition at its best.<sup>32</sup>

The key to gene editing is the creation of double-strand breaks in the DNA double helix. Gene editing before CRISPR used ZFNs and TALENs; these methods, which are still in use, required very precise and painstaking construction of the proteins that break DNA, called nucleases, to hit the right places where the DNA should be broken (called cleavage sites).<sup>33</sup> The discovery of CRISPR has rapidly led to technologies that are much simpler and easier to use.<sup>34</sup>

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29. The risk of germline effects from somatic cell gene-transfer interventions historically arose only by accident. *See, e.g.*, Katherine A. High, *Gene Therapy for Hemophilia: The Clot Thickens*, 25 HUM. GENE THERAPY 915, 918 (2014). The semen of some male gene-transfer research subjects was found to contain copies of the viral vector used to insert the transgene into their somatic cells. *Id.* at 918 fig.3 (collecting well-publicized incidents of such occurrence). This discovery led to monitoring of male patient-subjects; in gene-transfer trials using systemic administration of the vector-transgene combination, semen is collected and tested to look for copies of the (deactivated) viral vector used to carry the transgene into the body's cells. *Id.* at 918. Persistence of vector has always been temporary and has never appeared to include transgene or to affect sperm. *Id.* This low risk of germline effects nonetheless raised concerns and has influenced study design, altering the choice of vector in some gene-transfer protocols and the route of administration of the vector-transgene combination in others, in order to reduce the likelihood of germline transmission. *See id.* at 917–19; King, *supra*, at 23–26. In this author's opinion, concern about germline effects may have contributed to Jesse Gelsinger's death in a phase one gene-transfer protocol, because the FDA changed the route of administration of the gene-transfer intervention from injection into the peripheral circulation to injection into a vein leading directly to the liver, reasoning that the former route was systemic and thus more likely to risk germline effects. Targeting the liver proved more dangerous, however, as it provoked an overwhelming immune response that led to Gelsinger's death.

30. *See* Rodolphe Barrangou & Jennifer A. Doudna, *Applications of CRISPR Technologies in Research and Beyond*, 34 NATURE BIOTECHNOLOGY 933, 933–36 (2016).

31. *See id.* at 934 (offering a short primer on CRISPR).

32. *See generally id.* (overviewing the wide variety of advantages CRISPR brings, both generally and as applied to specific industries and research fields).

33. *See id.* at 933. For excellent discussions of all three biotechnologies, see generally Thomas Gaj, Charles A. Gersbach & Carlos F. Barbas III, *ZFN, TALEN, and*

CRISPR-Cas9 is the first and most popular of the new gene-editing tools to be discovered and developed to date.<sup>35</sup> It is stable, simple, facile, affordable, specific, and highly versatile, able to target any DNA sequence, to remove mutated sequences, and even to replace them with nonmutated sequences.<sup>36</sup> In comparison with the imprecision of gene addition or augmentation, gene-editing techniques appear to more precisely control the integration of new genetic information, thereby decreasing (though not completely eliminating) the possibility of harmful insertional mutagenesis and other off-target effects.<sup>37</sup> And CRISPR-Cas9 is so easy to use that kits can be purchased online, enabling many scientists and students to

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*CRISPR/Cas9-Based Methods for Genome Engineering*, 31 TRENDS BIOTECHNOLOGY 397 (2013); Rajat M. Gupta & Kiran Musunuru, *Expanding the Genetic Editing Tool Kit: ZFNs, TALENs, and CRISPR-Cas9*, 124 J. CLINICAL INVESTIGATION 4154 (2014); and Keener, *supra* note 10.

34. In 1993, Francisco Mojica identified multiple copies of palindromic repetitive bases, interspaced with unique DNA spacers, in the DNA of a microbe. Eric S. Lander, *The Heroes of CRISPR*, 164 CELL 18, 18 (2016). Its structural similarity to another clustered repeat sequence with spacers that had previously been identified in a common bacterium suggested biological significance across species. Yoshizumi Ishino et al., *Nucleotide Sequence of the IAP Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in Escherichia Coli, and Identification of the Gene Product*, 169 J. BACTERIOLOGY 5429, 5432 (1987). These repetitive genetic sequences came to be known as CRISPR. Mojica's work outlining CRISPR's likely function as an adaptive defense mechanism, able to cut foreign DNA in order to cripple the ability of an invading virus to replicate and damage the host, was published in early 2005. See Francisco J.M. Mojica et al., *Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements*, 60 J. MOLECULAR EVOLUTION 174, 180–81 (2005). Over the next decade, CRISPR's mechanism of action was examined and elucidated further. See Samuel H. Sternberg & Jennifer A. Doudna, *Expanding the Biologist's Toolkit with CRISPR-Cas9*, 58 MOLECULAR CELL 568, 568 (2015). It has now been developed into a highly specific gene-editing tool.

35. See Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCIENCE 819, 819–20, 822 (2013); Giedrius Gasiunas et al., *Cas9-crRNA Ribonucleoprotein Complex Mediates Specific DNA Cleavage for Adaptive Immunity in Bacteria*, 109 PROC. NAT'L ACAD. SCI. 2579, 2579, 2585 (2012); Martin Jinek et al., *A Programmable Dual-RNA-Guided Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816, 816, 820 (2012); Morgan L. Maeder & Charles A. Gersbach, *Genome-Editing Technologies for Gene and Cell Therapy*, 24 MOLECULAR BIOLOGY 430, 434–35 (2016).

36. See Jennifer A. Doudna & Emmanuelle Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*, 346 SCIENCE 1077 *passim* (2014); Young-II Jo et al., *CRISPR-Cas9 System as an Innovative Genetic Engineering Tool: Enhancements in Sequence Specificity and Delivery Methods*, 1856 BIOCHIMICA ET BIOPHYSICA ACTA 234, 234–36 (2015); Yue Mei et al., *Recent Progress in CRISPR-Cas9 Technology*, 43 J. GENETICS & GENOMICS 63, 63–64, 71, 73 (2016).

37. Maeder & Gersbach, *supra* note 35, at 433–34.

explore gene editing in almost any laboratory setting, or even at home.<sup>38</sup>

Newer CRISPR models and related technologies are rapidly being developed and tested. Such refinements are continually underway to make gene-editing systems simpler, smaller, and more precise.<sup>39</sup> In particular, editing RNA (using Cas13 instead of Cas9) has some advantages over editing DNA.<sup>40</sup> Unlike DNA editing, RNA editing is temporary.<sup>41</sup> An RNA edit is therefore reversible if it goes wrong in any way, and it can be applied to correct transient conditions, such as damage caused by inflammation resulting from an infection.<sup>42</sup> RNA edits are also effective when cells are not actively dividing, whereas DNA edits are linked to cell division.<sup>43</sup> This difference means that RNA editing, unlike DNA editing, can be applied to brain and muscle cells, as well as to cell types found in other tissues.<sup>44</sup> Finally, RNA edits affect individual bases in the sequences of base pairs that make up genes—and because single-base mutations cause a number of human genetic diseases, RNA editing could have the potential to treat those diseases precisely and effectively (though not permanently).<sup>45</sup>

Another widely heralded improvement is base editing. Instead of engineering double-strand breaks of DNA, that is, removing an entire

38. Park, *supra* note 11, at 45; *see also infra* text accompanying note 128. For more information on biohacking in general, see Joe Brophy, *God's Name in Vein: Biohacker Injects Himself with DNA Sequence Made from Bible and Koran Verses*, THE SUN (Dec. 21, 2018, 12:58 AM), <https://www.thesun.co.uk/news/8014880/biohacker-injects-dna-sequence-bible-koran-verses/> [<https://perma.cc/LD67-XQ3W>].

39. *See, e.g.*, Janice S. Chen et al., *Enhanced Proofreading Governs CRISPR-Cas9 Targeting Accuracy*, 550 NATURE 407, 407–10 (2017).

40. *See, e.g.*, Jon Cohen, 'Base Editors' Open New Way to Fix Mutation: Novel CRISPR-Derived Technologies Surgically Alter a Single DNA or RNA Base, 358 SCIENCE 432, 432–33 (2017); David B.T. Cox et al., *RNA Editing with CRISPR-Cas13*, 358 SCIENCE 1019, 1019–27 (2017).

41. Julia Belluz & Umair Irfan, *2 New CRISPR Tools Overcome the Scariest Parts of Gene Editing*, VOX (Oct. 25, 2017, 1:00 PM), <https://www.vox.com/2017/10/25/16527370/crispr-gene-editing-harvard-mit-broad> [<http://perma.cc/M3YD-U5ZH>].

42. *Id.*

43. *Id.*

44. *Id.*

45. *Id.* But *see* Jon Cohen, *Powerful CRISPR Cousin Accidentally Mutates RNA While Editing DNA Target*, SCIENCE (Apr. 17, 2019, 4:10 PM), <https://www.sciencemag.org/news/2019/04/powerful-crispr-cousin-accidentally-mutates-rna-while-editing-dna-target> [<https://perma.cc/56QW-CCRR>] (“[T]he weaknesses of base editors have become increasingly apparent, and a new study shows they can also accidentally mutate the strands of RNA that help build proteins or perform other key cellular tasks.”).

step in the ladder of the double helix and then either allowing the ends to reconnect without the missing step or inserting a repaired replacement, base editing targets individual base pairs without breaking the strand.<sup>46</sup> Paired combinations of just four proteins make up all human DNA, and thousands of human diseases are known to be caused by mutations in just one base pair of matched proteins in one gene.<sup>47</sup> For example, a mistake that puts one adenosine-thymidine (“A-T”) pair where a guanine-cytosine (“G-C”) pair should be causes half of known human genetic diseases.<sup>48</sup> Therefore, using base editing to change A-T pairs to G-C pairs could permanently and precisely correct a great many deleterious mutations.<sup>49</sup> Base editing with an enzyme specially synthesized for this purpose is being studied in cell cultures and in small animal models,<sup>50</sup> and has been pronounced successful in human embryos with Marfan syndrome in a paper by Chinese researchers.<sup>51</sup>

Is it possible for ethics and policy to keep up with the breakneck pace of this science? Maybe; but it sure ain’t easy.

## II. A BRIEF HISTORY OF CRISPR NEWS AND POLICY

Gene editing made headlines in March 2015 when a group of senior scientists and scholars led by Jennifer Doudna published recommendations arising from a California conference that invited comparison with the 1970s Asilomar moratorium on recombinant DNA research.<sup>52</sup> They recommended a moratorium on “germline genome modification for clinical application in humans, while societal, environmental, and ethical implications of such activity are

46. Belluz & Irfan, *supra* note 41; see also Nicole M. Gaudelli et al., *Programmable Base Editing of A-T to G-C in Genomic DNA Without DNA Cleavage*, 551 NATURE 464, 464–65 (2017); Alexis C. Komor et al., *Programmable Editing of a Target Base in Genomic DNA Without Double-Stranded DNA Cleavage*, 533 NATURE 420, 420–24 (2016); Brian S. Plosky, *CRISPR-Mediated Base Editing Without DNA Double-Strand Breaks*, 62 MOLECULAR CELL 477, 477–78 (2016).

47. Belluz & Irfan, *supra* note 41.

48. Gaudelli et al., *supra* note 46, at 464.

49. *Id.*

50. See, e.g., Yuanwu Ma et al., Letter to the Editor, *Highly Efficient and Precise Base Editing by Engineered dCas9-Guide tRNA Adenosine Deaminase in Rats*, 4 CELL DISCOVERY 1, 1–3 (2018).

51. Yanting Zeng et al., *Correction of the Marfan Syndrome Pathogenic FBNI Mutation by Base Editing in Human Cells and Heterozygous Embryos*, 26 MOLECULAR THERAPY 2631, 2631–32 (2018).

52. David Baltimore, *A Prudent Path Forward for Genomic Engineering and Germline Gene Modification*, 348 SCIENCE 36, 36–38 (2015).

discussed among scientific and governmental organizations.”<sup>53</sup> They called for discussion of information and education about the science and its implications, asked that a “globally representative group” be convened to make policy recommendations, and sought support for “transparent research to evaluate . . . genome engineering technology” to examine “its potential applications for germline gene therapy.”<sup>54</sup> At around the same time, the International Society for Stem Cell Research (“ISSCR”) issued a similar position statement.<sup>55</sup> And a week later, another group of scientists published a sterner call for a moratorium accompanied by international dialogue “to assess whether, and under what circumstances—if any—future research involving genetic modification of human germ cells should take place.”<sup>56</sup>

Almost immediately thereafter, *Protein & Cell* published the results of a Chinese experiment attempting CRISPR-Cas9 modification of nonviable human embryos with the apparent aim of determining the feasibility of moving to therapeutic genome editing in viable human embryos.<sup>57</sup> The Chinese researchers’ findings of both off-target insertions and mosaicism—that is, successful editing of some but not all of the embryos’ cells, resulting in a “mosaic” pattern of edited and unedited cells—were troubling; so was their failure to conduct more basic research first.<sup>58</sup>

At the end of April 2015, the National Institutes of Health (“NIH”) announced that it would not fund any use of gene-editing technology in human embryos.<sup>59</sup> And in the summer and fall of 2015, several additional position statements appeared.<sup>60</sup> A joint statement by the American Society of Gene and Cell Therapy (“ASGCT”) and

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53. *Id.* at 37.

54. *Id.*

55. Statement, Int’l Soc’y for Stem Cell Research, The ISSCR Statement on Human Germline Genome Modification (Mar. 19, 2015), <http://www.isscr.org/docs/default-source/guidelines/isscr-statement-on-human-germline-genome-modification.pdf?sfvrsn=2> [<https://perma.cc/TPC9-5XV6>].

56. Edward Lanphier et al., *Don’t Edit the Human Germ Line*, 519 NATURE 410, 411 (2015).

57. Puping Liang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Trippronuclear Zygotes*, 6 PROTEIN & CELL 363, 363 (2015).

58. *Id.* at 366.

59. Statement, Nat’l Insts. of Health, Statement on NIH Funding of Research Using Gene-Editing Technologies in Human Embryos (Apr. 29, 2015) (on file with the North Carolina Law Review).

60. See *infra* text accompanying notes 61–63.

the Japan Society of Gene Therapy (“JSGT”)<sup>61</sup> joined the more cautious side of the discussion. Echoing the initial statement from Doudna’s group, statements by the Hinxton Group<sup>62</sup> and the International Bioethics Committee of the United Nations<sup>63</sup> raised cautions but did not call for a halt on gene-editing research that could affect the human germline.

The Doudna group’s call for global attention came to fruition in early December 2015, with the First International Summit on Human Genome Editing.<sup>64</sup> On December 3, the summit issued a statement that closely tracked the Doudna group’s recommendations: basic and preclinical research should go forward, somatic cell gene editing should go forward in clinical application, germline gene editing should not head toward the clinic, and an ongoing international forum should be created to continue discussion of the ELSI of gene editing.<sup>65</sup>

That forum, the Committee on Human Gene Editing of the National Academies, was created immediately after the summit. The committee held international meetings examining the state of the science, the potential for clinical benefit, the risks of harm, and the ELSI of human gene-editing technologies.<sup>66</sup> It also considered and assessed existing standards, oversight mechanisms, and safeguards

61. Theodore Friedmann et al., *ASGCT and JSGT Joint Position Statement on Human Genomic Editing*, 23 *MOLECULAR THERAPY* 1282, 1282 (2015).

62. Statement, Hinxton Grp., Statement on Genome Editing Technologies and Human Germline Genetic Modification (Sept. 10, 2015) (on file with the North Carolina Law Review).

63. See generally Int’l Bioethics Comm., UNESCO, Rep. of the Int’l Bioethics Comm. on Updating its Reflection on the Human Genome and Human Rights, U.N. Doc. SHS/YES/IBC-22/15/2 REV.2 (Oct. 2, 2015) (discussing various ethical challenges posed by gene editing of the human genome without calling for an outright ban on the practice in the future).

64. See STEVEN OLSON, NAT’L ACADS. OF SCIS., ENG’G, & MED., INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: A GLOBAL DISCUSSION 6–7 (2015). For a sampling of the broad range of views included in the summit, see generally INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: COMMISSIONED PAPERS, *supra* note 21.

65. Statement, Nat’l Acads. of Scis. Eng’g & Med., On Human Gene Editing: International Summit Statement (Dec. 3, 2015), <http://www.nap.edu/21913> [<https://perma.cc/PFE6-Y9X2>]; see also Sara Reardon, *Global Summit Reveals Divergent Views on Human Gene Editing*, 528 *NATURE* 173, 173 (2015). See generally INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: COMMISSIONED PAPERS, *supra* note 21 (presenting various issues on which the summit took a position).

66. *Consensus Study*, NAT’L ACADEMIES SCI., ENGINEERING & MED., <http://www.nationalacademies.org/gene-editing/consensus-study/index.htm> [<http://perma.cc/5HFT-AEYC>].

worldwide.<sup>67</sup> Its final report, *Human Genome Editing: Science, Ethics, and Governance*, appeared in February 2017.<sup>68</sup> The report's widely anticipated recommendations have generally been interpreted as opening the doors to the future a little wider, in two respects. First, the report recommends limiting human clinical trials of somatic gene editing to prevention and treatment applications "at this time" and calls for public discussion and policy debate on enhancement applications, thus setting the stage for enhancement research in the future.<sup>69</sup> Second, it recommends permitting human germline gene editing, but only for compelling purposes—that is, when there are no reasonable alternatives and the intervention is intended to prevent or treat serious disease or disability.<sup>70</sup> The report thus even more clearly sets the stage for germline interventions in the not-too-distant future, depending on what counts as a reasonable alternative.<sup>71</sup> It also requires rigorous and comprehensive oversight and long-term multigenerational follow-up and recommends transnational cooperation and ongoing public reassessment.<sup>72</sup>

The summer of 2017 saw a number of additional developments. The American College of Medical Genetics and Genomics published a points-to-consider document on genome editing in clinical genetics;<sup>73</sup> it concluded that "genome editing in the human embryo is premature" and strongly encouraged "broad public debate," continued research to resolve technological problems, and resisting pressure for premature clinical application.<sup>74</sup> Shortly thereafter, the American Society of Human Genetics led a large group of genetics and medical organizations that published a comprehensive joint position statement on human-germline genome editing, which divided the ethical issues into those arising from its failure and those arising from its success,<sup>75</sup> and concluded that "at this time," germline gene editing intended for human pregnancy is "inappropriate," but in vitro

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67. *Id.*

68. NASEM, HUMAN GENOME EDITING, *supra* note 14.

69. *Id.* at 133–39.

70. *Id.* at 134.

71. *Id.* at 134–35.

72. *Id.*

73. ACMG Bd. of Dirs., Am. Coll. of Med. Genetics & Genomics, *Genome Editing in Clinical Genetics: Points to Consider—A Statement of the American College of Medical Genetics and Genomics*, 19 GENETICS MED. 723, 723–24 (2017).

74. *Id.* at 724.

75. Kelly E. Ormond et al., *Human Germline Genome Editing*, 101 AM. J. HUM. GENETICS 167, 167–76 (2017).

human germline-editing research should go forward and should be publicly funded.<sup>76</sup> Echoing the *Human Gene Editing* report, the position statement further argued that human clinical applications of germline editing should not proceed unless there is a compelling medical and ethical rationale, good preclinical evidence, and a transparent public process.<sup>77</sup>

Finally, the first human-embryo editing in the United States came to light in the summer of 2017. Oregon Health Sciences University's ("OHSU") Shoukrat Mitalipov and his team edited viable human zygotes, which they created using healthy oocytes and sperm containing a genetic mutation that causes hypertrophic cardiomyopathy, and which thus had a 50/50 chance of carrying the mutation.<sup>78</sup> They edited these zygotes with a CRISPR-Cas9 package that included a normal synthetic copy of the mutated gene so that the mutation could be replaced with the synthetic copy.<sup>79</sup> Their published results claimed a high degree of success with few off-target effects and almost no mosaicism, but did contain a surprising wrinkle: the normal gene was not the synthetic version but a copy of the normal version found in the oocyte genome.<sup>80</sup> These results have been questioned as improbable.<sup>81</sup> It seems likely that a definitive answer will emerge only

76. *Id.* at 172–73.

77. *Id.* at 173–74.

78. Hong Ma et al., *Correction of a Pathogenic Gene Mutation in Human Embryos*, 548 NATURE 413, 413–16 (2017).

79. *Id.*

80. *Id.* at 416–18. Not surprisingly, there was considerable discussion triggered by this revelation in the science-oriented popular press about the ethics of gene editing human embryos, with some particularly skeptical. See, e.g., Eliza Barclay, *Scientists Successfully Used CRISPR to Fix a Mutation that Causes Disease. This Is Huge.*, VOX (Aug. 2, 2017, 3:50 PM), <https://www.vox.com/science-and-health/2017/8/2/16083300/crispr-heart-disease> [<http://perma.cc/R24J-EHT9>]; Sharon Begley, *U.S. Scientists Edit Genome of Human Embryo, but Cast Doubt on Possibility of 'Designer Babies.'* STAT (Aug. 2, 2017), [www.statnews.com/2017/08/02/crispr-designer-babies/?utm](http://www.statnews.com/2017/08/02/crispr-designer-babies/?utm) [<http://perma.cc/L8M3-ZKSP>]; Jessica Berg, *Editing Human Embryos with CRISPR Is Moving Ahead—Now's the Time to Work Out the Ethics*, CONVERSATION (July 28, 2017, 11:40 AM), <https://theconversation.com/editing-human-embryos-with-crispr-is-moving-ahead-nows-the-time-to-work-out-the-ethics-81732> [<http://perma.cc/PC4W-99G3>]; Emily Mullin, *Gene Editing Study in Human Embryos Points Toward Clinical Trials*, MIT TECH. REV. (Aug. 2, 2017), <https://www.technologyreview.com/s/608482/gene-editing-study-in-human-embryos-points-toward-clinical-trials/> [<http://perma.cc/R24J-EHT9>]; Kelly Servick, *First US-Based Group to Edit Human Embryos Brings Practice Closer to Clinic*, SCIENCE (Aug. 2, 2017, 1:00 PM), <https://www.sciencemag.org/news/2017/08/first-us-based-group-edit-human-embryos-brings-practice-closer-clinic> [<http://perma.cc/7PEP-3CQ5>].

81. Skeptical researchers argue that the editing process may simply have deleted a portion of DNA that included the mutation, and that Mitalipov's team detected the one remaining normal maternal gene, not two copies of it, but the team has responded that

if there is continued research by other teams attempting to duplicate OHSU's results.

All things considered, it should be clear by now that human genome editing is of enormous social and policy interest, but keeping track of the position papers, reports, guidances, and commentaries is as much of a challenge as keeping up with the science. There is even a journal devoted entirely to CRISPR, and its second issue contains a useful compilation and review of the many statements relating to the ethical and policy implications of the science—but that list appeared in print in early 2018<sup>82</sup> and already needs updating. Most notably, the Second International Summit on Human Genome Editing took place in Hong Kong on November 27–29, 2018.<sup>83</sup> It included a hastily rearranged session featuring He Jiankui, whose claim of having brought gene-edited twins to live birth had shocked the world just days before.<sup>84</sup> The repercussions of Dr. He's work are still being felt, and new and amended policy and guidance documents are being published and prepared.<sup>85</sup>

In brief, Dr. He, a Chinese national who studied in the United States while developing his embryo-editing plans, claims to have edited the genomes of twin girls at fertilization in order to increase their resistance to HIV infection.<sup>86</sup> Dr. He has also claimed that another pregnancy resulting from his research was underway as of

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two copies of the maternal gene have been detected and that as-yet-unpublished work confirms that gene repair preferentially seeks the healthy maternal gene. Ewen Callaway, *Did CRISPR Really Fix a Genetic Mutation in These Human Embryos?*, NATURE (Aug. 8, 2018), <https://www.nature.com/articles/d41586-018-05915-2> [<http://perma.cc/Q9BU-4KPX>].

82. Carolyn Brokowski, *Do CRISPR Germline Ethics Statements Cut It?*, 1 CRISPR J. 115, 115–23 (2018).

83. The summit website includes agenda information, slide presentations, videos, and a concluding statement. *Second International Summit on Human Genome Editing*, NAT'L ACADEMIES SCI., ENGINEERING & MED., [http://www.nationalacademies.org/genome-editing/2nd\\_summit/](http://www.nationalacademies.org/genome-editing/2nd_summit/) [<http://perma.cc/RYX5-GJAS>].

84. Regalado, *Chinese Scientists*, *supra* note 3.

85. For example, eight European specialty societies have published a statement in response to Dr. He's work. Hildegard Büning et al., *Consensus Statement of European Societies of Gene and Cell Therapy on the Reported Birth of Genome-Edited Babies in China*, 29 HUM. GENE THERAPY 1337, 1337–38 (2018). Other work is still underway. See, e.g., Sharon Begley, *After 'CRISPR Babies,' International Medical Leaders Aim to Tighten Gnome Editing Guidelines*, STAT (Jan. 24, 2019), [https://www.statnews.com/2019/01/24/crispr-babies-show-need-for-more-specific-rules/?utm\\_content=buffer3335a&utm\\_medium=social&utm\\_source=twitter&utm\\_campaign=twitter\\_organic](https://www.statnews.com/2019/01/24/crispr-babies-show-need-for-more-specific-rules/?utm_content=buffer3335a&utm_medium=social&utm_source=twitter&utm_campaign=twitter_organic) [<https://perma.cc/BMV7-HFVT>].

86. Marilyn Marchione, *Chinese Researcher Claims First Gene-Edited Babies*, ASSOCIATED PRESS (Nov. 26, 2018), <https://www.apnews.com/4997bb7aa36c45449b488e19ac83e86d> [<http://perma.cc/6NXX-GE76>].

late November 2018.<sup>87</sup> These claims were recently substantiated by Chinese authorities,<sup>88</sup> but there is still no peer-reviewed publication of Dr. He's research at the time of this writing, and scientists who reviewed the slides he presented at the summit in Hong Kong are skeptical about his data.<sup>89</sup> Dr. He presented his claims to the world in a YouTube video,<sup>90</sup> and reporter Antonio Regalado broke the story of his work in the *MIT Technology Review* shortly before the summit began.<sup>91</sup>

Apparently, Dr. He recruited couples in which the man has HIV infection and the woman does not and told them that he was conducting HIV vaccine research.<sup>92</sup> Dr. He collected sperm and ova from the man and woman, washed the sperm before fertilizing the ovum with it—which is well known to render transmission of HIV to the embryo virtually impossible—and then sought to edit out a gene that plays a role in helping HIV enter cells, ostensibly to increase the resulting child's resistance to HIV infection.<sup>93</sup> Crucially, Dr. He admitted that the edit was not successful in one of the embryos, and it is unclear whether it was completely or even partially successful in the other.<sup>94</sup> In addition, it is probable that disabling or deleting the gene in question decreases resistance to other, more common infections.<sup>95</sup>

87. Ashley P. Taylor, *Second CRISPR-Modified Pregnancy May Be Underway*, SCIENTIST (Nov. 28, 2018), <https://www.the-scientist.com/news-opinion/second-crispr-modified-pregnancy-may-be-underway-65151> [<http://perma.cc/V8BG-MQPV>].

88. Phoebe Zhang, *China Confirms Birth of Gene-Edited Babies, Blames Scientist He Jiankui for Breaking Rules*, S. CHINA MORNING POST (Feb. 4, 2019, 11:47 AM), <https://www.scmp.com/news/china/science/article/2182964/china-confirms-gene-edited-babies-blames-scientist-he-jiankui> [<https://perma.cc/TDE7-DA9K>].

89. See Katarina Zimmer, *CRISPR Scientists Slam Methods Used on Gene-Edited Babies*, SCIENTIST (Dec. 4, 2018), <https://www.the-scientist.com/news-opinion/crispr-scientists-slam-methods-used-on-gene-edited-babies--65167> [<http://perma.cc/Z3VY-MVQK>]; see also Amy Dockser Marcus, *Scientists Skeptical About Gene-Edited Baby Experiment*, WALL ST. J. (Dec. 12, 2018, 7:00 AM), <https://www.wsj.com/articles/gene-edited-babies-experiment-raises-concerns-11544616000> [<http://perma.cc/K6FR-WMBT>]. See generally Sean P. Ryder, #CRISPRbabies: Notes on a Scandal, 1 CRISPR J. 355, 355–57 (2018) (noting that there are enough uncertainties about Dr. He's work to "raise clear scientific objections"); Ed Yong, *The CRISPR Baby Scandal Gets Worse by the Day*, ATLANTIC (Dec. 3, 2018), <https://www.theatlantic.com/science/archive/2018/12/15-worrying-things-about-crispr-babies-scandal/577234/> [<http://perma.cc/F3XT-WH9P>] (detailing fifteen "worrying things" about Dr. He's research).

90. The He Lab, *supra* note 3.

91. See Regalado, *Chinese Scientists*, *supra* note 3.

92. See Marchione, *supra* note 86.

93. Regalado, *Chinese Scientists*, *supra* note 3; see also Marchione, *supra* note 86.

94. See Marchione, *supra* note 86; Zimmer, *supra* note 89; see also Ryder, *supra* note 89, at 355.

95. See Marchione, *supra* note 86; Zimmer, *supra* note 89.

Moreover, the embryos were not infected or diseased in any way; such an edit constitutes prevention, or enhancement, rather than treatment (and of course, there are many other, far less invasive ways to prevent HIV infection).<sup>96</sup> Thus, bringing these edited embryos to live birth violates every guidance document and every ethical and policy standard in place around the world. Questions also abound about the validity of regulatory approvals Dr. He claims to have obtained and the clarity, completeness, and accuracy of the consent form signed by the couple.<sup>97</sup> The Chinese government has condemned Dr. He's work and suspended all his activities.<sup>98</sup>

And yet, Dr. He has managed to claim the spotlight and rekindle fierce debate about clinical applications of CRISPR.<sup>99</sup> Scientific and policy developments therefore seem to be leading inexorably—and pretty swiftly—toward an expansive research portfolio and clinical applications of gene editing. So now it is time to ask: Why not?

### III. WHAT ARE THE ETHICAL AND POLICY ISSUES IN GENE EDITING?

Editing the human germline might be an accidental attribute of a genuinely successful gene-editing treatment, or it might be gene editing's true goal. Does the difference matter? Well, yes, if it points toward enhancement applications and thereby complicates consequent policy implications. Questions of oversight and governance, access and cost, and even more basically, whether and if so how tightly future clinical applications of the technology should be controlled, all need to address how far it is okay to go.

96. Yong, *supra* note 89; *see also* Catherine Offord, *Claim of First Gene-Edited Babies Triggers Investigation*, SCIENTIST (Nov. 26, 2018), <https://www.the-scientist.com/news-opinion/claim-of-first-gene-edited-babies-triggers-investigation-65139> [<http://perma.cc/5RTP-K6F4>].

97. *See* Yong, *supra* note 89; *see also* Xiaomei Zhai et al., *Chinese Bioethicists Respond to the Case of He Jiankui*, HASTINGS CTR. (Feb. 7, 2019), <https://www.thehastingscenter.org/chinese-bioethicists-respond-case-jiankui/> [<https://perma.cc/8VT3-3428>].

98. Offord, *supra* note 96; Antonio Regalado, *The Chinese Scientist Who Claims He Made CRISPR Babies Is Under Investigation*, MIT TECH. REV. (Nov. 26, 2018), <https://www.technologyreview.com/s/612466/the-chinese-scientist-who-claims-he-made-crispr-babies-has-been-suspended-without-pay/> [<http://perma.cc/X6CE-C2F3>].

99. *See supra* notes 84–85 and accompanying text.

A. *Is Germline Genome Editing Necessary, or Just Way Cool?*

Avoiding disease by means of genetic intervention requires knowing which genes are involved in disease causation. Once genes have been identified, treatments are generally sought for affected individuals and designed to be applied to somatic cells—that is, to edit the DNA in the affected cells of the individual’s body. Somatic cell genetic correction has been the goal of human genetic manipulation since its beginning.<sup>100</sup> Correction of the genetic defects in all or most of the affected somatic cells of an individual with a known genetic disorder would, by definition, be a treatment—even a cure—for that person.<sup>101</sup> Gene-editing research designed to correct genetic defects in the somatic cells of adults or children is less likely to pose a risk of inadvertent germline effects than is gene-addition research.<sup>102</sup> Thus, it is far less problematic, as long as standards of safety and efficacy are met.<sup>103</sup>

A representative gene-editing example is Sangamo Therapeutics’ trial of an *in vivo* gene-editing intervention for Hunter syndrome, or mucopolysaccharidosis type II, using ZFNs.<sup>104</sup> The first patient-

100. See generally WALTERS & PALMER, *supra* note 27, at 17–59 (describing the science and ethics of somatic cell gene therapy, which affects the research subject or patient but not future generations, and which still represents the only type of genetic research intervention or genetic treatment permissible in humans).

101. See *id.*

102. Sharon Begley, *They’re Going to CRISPR People. What Could Possibly Go Wrong?*, STAT (June 23, 2016), <https://www.statnews.com/2016/06/23/crispr-humans-penn-clinical-trial/> [<http://perma.cc/DUD7-XBBT>].

103. See, e.g., Kaiwen Ivy Liu et al., *A Chemical-Inducible CRISPR-Cas9 System for Rapid Control of Gene Editing*, 12 NATURE CHEMICAL BIOLOGY 980, 980–82 (2016); see also Begley, *supra* note 102. Nonetheless, it matters whether the gene-editing tool used simply snips out the defective sequence and allows the DNA to rejoin without it—a process known as nonhomologous end joining—or whether the defective sequence is replaced with a nonmutated sequence, which is known as homologous recombination or homology directed repair. Nonhomologous end joining is now known to be less precise than homology-directed repair; it also raises the interesting possibility that merely deleting the mutated sequence could also delete potentially beneficial genetic information and thus be as harmful as it is helpful. See, e.g., Moises Velasquez-Manoff, Opinion, *The Upside of Bad Genes*, N.Y. TIMES (June 17, 2017), <https://www.nytimes.com/2017/06/17/opinion/sunday/crispr-upside-of-bad-genes.html> [<http://perma.cc/67WS-EVUW>].

104. Jocelyn Kaiser, *A Human Has Been Injected with Gene-Editing Tools to Cure His Disabling Disease. Here’s What You Need to Know*, SCIENCE (Nov. 15, 2017), <http://www.sciencemag.org/news/2017/11/human-has-been-injected-gene-editing-tools-cure-his-disabling-disease-here-s-what-you> [<http://perma.cc/PE4J-PLYX>]. More recently, University of Pennsylvania researchers began a trial using CRISPR-Cas9 to alter the T cells of adult patient-subjects with cancer. See Shawna Williams, *Two Patients Treated with CRISPRed Cells in Immunotherapy Trial*, SCIENTIST (Apr. 16, 2019), <https://www.the-scientist.com/news-opinion/two-patients-treated-with-crispred-cells-in-immunotherapy-trial-65744>

subject, an adult man, was enrolled in November 2017, and no safety concerns appear to have emerged after enrollment of several more adult patient-subjects in this dose-escalation trial.<sup>105</sup> However, the results have been disappointing,<sup>106</sup> as is often the case the first time a new potential treatment is studied in human patient-subjects.

Importantly, the experimental gene-editing intervention in this trial cannot cross the blood-brain barrier,<sup>107</sup> so it cannot actually edit DNA in all the affected somatic cells. Because of the difficulty of reaching and effectively correcting all the affected cells in many genetic disorders, studying possible gene-editing treatments in affected patient-subjects is of great importance, but somatic cell gene editing in adults, and even in children, may not be as effective as interventions timed to prevent development of genetic disorders or to halt damage at an early stage. Treating an already-born person with somatic cell gene editing may not be perfectly effective if it is not possible to edit most or all of the affected DNA. If only some of the affected cells in the body are successfully edited, this results in mosaicism—a mosaic mixture of affected and corrected cells. Depending on the nature of the condition and the degree of correction, some mosaicism may be enough to effectively treat the condition, and in other cases, the effect may not be sufficient. In contrast, editing an early embryo can improve correction and avoid mosaicism, because the embryo has fewer cells needing correction, and all of the cells in an early embryo are rapidly dividing and can thus perpetuate the correction throughout development. Therefore, early intervention seems a logically superior route, as long as the risk of genetic disease is known.

Once a couple has given birth to a child diagnosed with a genetic disorder, the child's parents and their close relatives can learn more about their own relevant genetic makeup and can use various means

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[<https://perma.cc/M53N-3NW2>]. Both the treatment-oriented headline and the very preliminary public announcement about this research demonstrate current overexcitement about CRISPR's potential.

105. Kaiser, *supra* note 104; Marilyn Marchione, *Early Results Boost Hopes for Historic Gene Editing Attempt*, ASSOCIATED PRESS (Sept. 5, 2018), <https://www.apnews.com/2543a04b925c443b9ad3987f4209e68e> [<http://perma.cc/6MQY-YXAW>]; Andrew McConaghie, *No Safety Concerns So Far in Sangamo's Groundbreaking Gene-Editing Trial*, PHARMAPHORUM (Feb. 7, 2018), <https://pharmaphorum.com/news/no-safety-concerns-far-sangamos-groundbreaking-gene-editing-trial/> [<http://perma.cc/SW4U-RRAH>].

106. Ron Leuty, *Why This East Bay Biotech Company Shed Half Its Value*, S.F. BUS. TIMES (Feb. 7, 2019), <https://www.bizjournals.com/sanfrancisco/news/2019/02/07/sangamo-genome-editing-mps-hurler-hunter.html> [<https://perma.cc/4C65-A3L7> (dark archive)].

107. Kaiser, *supra* note 104.

to prevent the birth of additional affected children. Interestingly, current debates about germline gene editing tend to skip over discussion of some of those means. For example, long before the beginnings of the Human Genome Project, Ashkenazi Jewish communities worldwide began collating family histories to try to identify individuals whose offspring might be at risk of being affected by Tay-Sachs disease, a devastating neurodegenerative genetic disorder more common in persons with Ashkenazi Jewish ancestry than in the general population.<sup>108</sup> Couples seeking to marry might be counseled to find another partner, to forgo procreation, or to adopt. As a result, the global incidence of Tay-Sachs disease has decreased substantially.<sup>109</sup> Scientific advances have made even more options available to carrier couples, most notably including IVF to create a small number of embryos, PGD to test them for Tay-Sachs mutations, and selecting unaffected embryos to implant and bring to term.<sup>110</sup>

Preventing germline transmission of genetic disease through the selection of healthy embryos is widely available in affluent countries. Assisted reproduction technology (“ART”) has expanded rapidly in recent decades, and IVF with PGD has become almost standard for those in need of reproductive health services, especially couples affected by genetic disorders who wish to give birth to a genetically related but unaffected child.<sup>111</sup> However, IVF and PGD are relatively costly services, with prices ranging from four to six figures, depending on location and insurance coverage.<sup>112</sup> In the United States, these procedures are largely the province of the private sector, are not comprehensively regulated, and are far from always paid for by

108. The Jewish Genetic Disease Consortium maintains a web resource on Tay-Sachs Disease that includes extensive information on the disorder, carrier screening for couples, and options for couples who screen positive. *Tay-Sachs Disease*, JEWISH GENETIC DISEASE CONSORTIUM, <https://www.jewishgeneticdiseases.org/diseases/tay-sachs-disease/> [http://perma.cc/H3CW-X6W9].

109. Marvin R. Natowicz & Elizabeth M. Prencz, *Heterozygote Screening for Tay-Sachs Disease: Past Successes and Future Challenges*, 8 CURRENT OPINION PEDIATRICS 625, 627 (1996); Roberto Rozenberg & Lygia da Veiga Pereira, *The Frequency of Tay-Sachs Disease-Causing Mutations in the Brazilian Jewish Population Justifies a Carrier Screening Program*, 119 SAO PAULO MED. J. 146, 146 (2001).

110. *Learning About Tay-Sachs Disease*, NAT’L HUM. GENOME RES. INST., <https://www.genome.gov/10001220/learning-about-taysachs-disease/> [http://perma.cc/43S2-H29Y]; see also Natowicz & Prencz, *supra* note 109, at 626.

111. Robert Klitzman, *How Much Is a Child Worth? Providers’ and Patients’ Views and Responses Concerning Ethical and Policy Challenges in Paying for ART*, 12 PLOS ONE, e0171939, Feb. 16, 2017, at 1, 2.

112. *Id.* at 1–2.

private health insurance or included in government-funded health care.

It is usually possible—not always, but almost always—to use IVF and PGD to select an unaffected embryo instead of editing an affected embryo. Regardless of whether the goal is to select an unaffected embryo or to edit one that is affected, it is necessary to use IVF to create one embryo or several, and then to use PGD to determine whether any are affected by the genetic disorder of concern (or are carriers). Selecting and implanting an unaffected embryo is thus a key alternative to editing an affected embryo. If editing an individual at a later stage—as an adult, a child, or even a fetus—is not enough, either because of mosaicism or because later editing cannot reverse early damage that occurs before the editing process is undertaken, then it might seem logical to regard embryo editing as nothing other than an alternative to embryo selection. The earlier the editing process begins in development, the more likely it is that all of the body’s cells will be corrected, including those of the (immature) gametes. This effectively makes germline editing a “side effect” of effective treatment.

The gene-editing debate has thus reintroduced an important question<sup>113</sup>. If IVF and PGD are commonly used to select disease-free offspring, are there any good reasons to pursue gene editing of embryos (or of gametes<sup>114</sup>) aside from the rare instances when no unaffected embryo can be selected because all of a couple’s embryos will be affected? Most commentators have answered no,<sup>115</sup> some have

113. Terence R. Flotte, *Therapeutic Germ Line Alteration: Has CRISPR-Cas9 Technology Forced the Question?*, 26 HUM. GENE THERAPY 245, 245 (2015).

114. Hall, *supra* note 18; Regalado, *Engineering the Perfect Baby*, *supra* note 18, at 27–30; *see also* George Church, *Compelling Reasons for Repairing Human Germlines*, 377 NEW ENG. J. MED. 1909, 1910 (2017); Antonio Regalado, *A New Way to Reproduce*, MIT TECH. REV., Sept.–Oct. 2017, at 33, 35–38 [hereinafter Regalado, *A New Way to Reproduce*].

115. *See, e.g.*, Hampton, *supra* note 5, at 547–48; *see also, e.g.*, Friedmann et al., *supra* note 61, at 1282; Elisabeth Hildt, *Human Germline Interventions—Think First*, FRONTIERS GENETICS, May 2016, at 1, 1–3; Lander, *supra* note 22, at 5–7; *supra* text accompanying notes 66–72 (addressing the National Academies of Science, Engineering, and Medicine’s cautious opposition to germline gene editing). In responding “no” to this question, numerous other scientists and bioethics scholars have condemned He Jiankui’s gene-editing experiments as both unnecessary and potentially dangerous. *See supra* notes 86–99 and accompanying text. Further, Francis Collins, Director of the National Institutes of Health, added his censure in a strongly worded statement. Statement, Francis S. Collins, Dir., Nat’l Insts. of Health, Statement on Claim of First Gene-Edited Babies by Chinese Researcher (Nov. 28, 2018), <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-claim-first-gene-edited-babies-chinese-researcher> [http://perma.cc/

emphasized caution, without ruling out the future possibility;<sup>116</sup> and a few have responded, “Of course; why not?”<sup>117</sup>

Robust and reliable understanding of whether editing very early embryos or gametes can provide complete correction and target specificity is still in very short supply. Given our limited knowledge of the relationships among genes and between genes and the environment, genetic alteration of embryos or gametes might have completely unexpected consequences, which can be avoided simply by selecting an unaffected embryo. It thus seems only prudent to limit human clinical applications of gene editing to instances of true necessity, when an unaffected embryo cannot be selected. Recently, however, noted medical scientist George Daley has argued that many couples with low fertility may not be able to use IVF to create enough embryos to identify one that is unaffected to implant and bring to term.<sup>118</sup> This could potentially expand the “necessary” application of embryo editing considerably.<sup>119</sup>

But these are all safety questions. Some additional questions that should be asked may also highlight assumptions on which the whole field of ART is based. These questions touch on some potentially broader issues of social policy and ethics: Should every couple be able to pursue giving birth to children who are genetically related to both

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S28Y-QG4F]; see also Jon Cohen, *Francis Collins Ponders Fallout from CRISPR Baby Study*, SCIENCE (Nov. 30, 2018, 11:50 AM), <https://www.sciencemag.org/news/2018/11/epic-scientific-misadventure-nih-head-francis-collins-ponders-fallout-crispr-baby-study> [<http://perma.cc/Q3GG-UYW6>].

116. See, e.g., Dana Carroll, *A Perspective on the State of Genome Editing*, 24 MOLECULAR THERAPY 412, 412–13 (2016); Flotte, *supra* note 113, at 245; Raheleh Heidari, David M. Shaw & Bernice Elger, *CRISPR and the Rebirth of Synthetic Biology*, 23 SCI. ENGINEERING ETHICS 354, 355–57 (2016); Matthew H. Porteus & Christina T. Dann, *Commentary, Genome Editing of the Germline: Broadening the Discussion*, 23 MOLECULAR THERAPY 980, 981–82 (2015); Jeremy Sugarman, *Ethics and Germline Gene Editing*, 16 EMBO REPS. 1, 1 (2015); Xiamoei Zhai, Vincent Ng & Reidar Lie, *No Ethical Divide Between China and the West in Human Embryo Research*, 16 DEVELOPING WORLD BIOETHICS 116, 117, 119 (2016).

117. See, e.g., Church, *supra* note 114, at 1910–11; Hall, *supra* note 18, at 57–58; Julian Savulescu et al., *The Moral Imperative to Continue Gene Editing Research on Human Embryos*, 7 PROTEIN CELL 476, 477 (2015); James Gallagher, *Embryo Engineering a Moral Duty, Says Top Scientist*, BBC NEWS (May 13, 2015), [www.bbc.com/news/uk-politics-32633510](http://www.bbc.com/news/uk-politics-32633510) [<https://perma.cc/K5F5-DUBZ>]; Pinker, *supra* note 17. Notably, George Church was the only scientist quoted as not condemning He Jiankui for his human genome-editing CRISPR experiment. See Marchione, *supra* note 86; Yong, *supra* note 89.

118. George Q. Daley, Robin Lovell-Badge & Julie Staffann, *Perspective, After the Storm—A Responsible Path for Genome Editing*, 380 NEW ENG. J. MED. 897, 898–99 (2019).

119. *Id.*

parents? Should that effort overshadow adoption or the use of donated gametes? Should couples who have religious or personal objections to discarding any embryo be able to create only a single embryo, and correct it if needed, rather than creating more than one in order to identify and select one that is unaffected?

And finally, and most central here, is it reasonable to regard the complexities and uncertainties of creating germline effects as acceptable side effects of embryo editing under the circumstances, in comparison to its potential benefits, even in instances of true need? How can germline effects be adequately studied in future generations from the perspectives of both science and ethics? How should genetically altered offspring be regarded? Are they lifelong research subjects? For how many generations?<sup>120</sup> Could editing the germline alter the human genetic inheritance? What does that mean? Should we do so? What sort of policy process should be in place to address these questions? Is it possible to reach international agreement on whether to permit, and if so, how to regulate human germline alteration?<sup>121</sup>

Although the germline effects of editing embryos, zygotes, or even gametes were initially posited as a side effect of effective treatment, it may ultimately be impossible to distinguish between germline alteration as a side effect and as a goal. If widespread use of IVF and PGD alone could remove most genetic diseases from the human genetic inheritance, then shouldn't embryo editing be reserved for disorders that can be removed from the human genetic inheritance only by choosing not to procreate or by editing embryos or gametes? Perhaps because the same considerations and concerns exist about germline gene editing regardless of its status as side effect or goal, few efforts are made to preserve a distinction. Instead, most popular arguments in favor of embryo editing start and end with the goal of eradicating devastating genetic diseases forever.<sup>122</sup>

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120. Friedmann et al., *supra* note 61, at 1282.

121. WALTERS & PALMER, *supra* note 27, at 90–91; Mark S. Frankel & Audrey R. Chapman, *Facing Inheritable Genetic Modifications*, 292 *SCIENCE* 1303, 1303 (2001); Juengst, *supra* note 21, at 15, 19; *see* discussion *infra* Section III.D.

122. Survey research very much depends on exactly how questions are asked, and to whom. *See, e.g.*, CARY FUNK & MEG HEFFERON, PEW RESEARCH CTR., PUBLIC VIEWS OF GENE EDITING FOR BABIES DEPEND ON HOW IT WOULD BE USED 2–3 (2018). It is quite understandable that when people are asked about using gene editing to eliminate their own diseases from the population, they will find it easier to imagine themselves as healthy than to imagine that their parents selected an unaffected embryo instead of using gene editing on theirs. *See* Mullin, *supra* note 80.

When analysis of the ethical appropriateness of embryo editing equates editing with selection or fails to compare, consider, or even mention embryo selection, this increases the perceived acceptability of gene editing.<sup>123</sup> It also helps to promote what some have argued is the real goal of embryo editing: genetic enhancement.<sup>124</sup> Arguments in favor of genetic enhancement are further assisted by the conceptual fuzziness of the line between treatment and enhancement.

*B. Appropriate Research Targets: Treatment or Enhancement?*

Whether germline genetic alteration should be limited to treatment for genetic disorders or should encompass enhancements as well is yet another debate that has been going on for many decades.<sup>125</sup> Discussion of the similarities and differences among prevention, treatment, and enhancement is a debate that is older and broader than genetics, even though it has considerable significance in genetic intervention. Consider just two examples: vaccines *enhance* immune system function in order to *prevent* infection; erythropoetin is a *treatment* used to restore red blood cell production after cancer chemotherapy causes anemia, but it is also used to increase the blood's oxygen-carrying capacity in order to *prevent* altitude sickness or *enhance* aerobic efficiency in healthy individuals. Many other such examples exist, including administering human growth hormone ("HGH") as a treatment for children who have lower than normal HGH levels, while also giving HGH to uncomplicatedly short children with normal HGH levels to enhance the height they inherited from their parents. Many such "off label" uses of interventions developed as treatments have been proposed and undertaken in the history of medicine and medical research.<sup>126</sup>

123. See, e.g., Cohen, *supra* note 115.

124. See, e.g., Robert Sparrow, *A Not-So-New Eugenics: Harris and Savulescu on Human Enhancement*, HASTINGS CTR. REP., Jan.–Feb. 2011, at 32, 32–33; see also Eric T. Juengst et al., *Is Enhancement the Price of Prevention in Human Genome Editing?*, 1 CRISPR J. 1, 1–2 (2018).

125. See WALTERS & PALMER, *supra* note 27, at 110–11.

126. The history of human gene-transfer research reveals numerous hopes for genetic enhancement, including but not limited to discussions about the feasibility of extending treatment uses of gene-transfer interventions to enhancement purposes. For example, could a gene-transfer intervention for cancer-caused cachexia be used to increase muscle mass in athletes (which, if done, would constitute difficult-to-detect "gene doping")? Could delivering additional corrected copies of the mutated gene responsible for Prader-Willi syndrome, a genetic disorder that includes insatiable appetite, to healthy overweight people suppress their appetites and result in weight loss? Might industry be interested in helping to develop a gene-transfer intervention to spur rapid regrowth of hair after

Examples like these demonstrate the difficulty of cleanly distinguishing between enhancement and treatment. The terms themselves are ambiguous and context dependent; treatment in one setting is enhancement in another. Moreover, as treatment interventions become more common, what is regarded as a condition in need of treatment is highly likely to expand into territory previously regarded as reserved for enhancement only, in the same way that the indications for use of an approved treatment virtually always expand over time.<sup>127</sup>

Discussion of the ethical and policy debates about human enhancement, from everyday examples to the extremes of the anti-aging movement and transhumanism, is far beyond the scope of this Article. Several aspects of genetic enhancement nonetheless deserve mention.

First, assessing and balancing the risks of harm and potential benefits in enhancement research poses a particular challenge. It is far easier, and much less morally problematic, to weigh potential benefits and risks of harm in human research when the potential benefits are understood as a return to normal functioning—a treatment—than when the research subject is a healthy patient for whom “better than normal” is the goal. Despite this difficulty, biohackers have sought to enhance themselves.<sup>128</sup> Enhancing human embryos should certainly be given far more serious consideration.

But what if genetic enhancement is just at the far end of a continuum that represents the generally praiseworthy, or at least not automatically contemptible, desire to better ourselves? Humans

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chemotherapy so that it could also be used off-label for correction of male pattern baldness? All of these speculative possibilities have been discussed in meetings of the NIH Recombinant DNA Advisory Committee.

127. ERIC T. JUENGST & DANIEL MOSELEY, STANFORD ENCYCLOPEDIA OF PHILOSOPHY, HUMAN ENHANCEMENT 12 (Edward N. Zalta et al. eds., Spring 2016 ed. 2016), <https://plato.stanford.edu/entries/enhancement/> [<https://perma.cc/7T6J-5FEX>]; Juengst, *supra* note 21, at 21; Eric T. Juengst, *Can Enhancement Be Distinguished from Prevention in Genetic Medicine?*, 22 J. MED. & PHIL. 125, 126 (1997); Tristan Keys et al., *Faith in Science: Professional and Public Discourse on Regenerative Medicine*, in AFTER THE GENOME: A LANGUAGE FOR OUR BIOTECHNOLOGICAL FUTURE 11, 32–33 (Michael J. Hyde & James A. Herrick eds., 2013).

128. See, e.g., Josiah Zayner, *The First Attempt at Human CRISPR Gene Editing*, SCI., ART, BEAUTY (Oct. 13, 2017), <http://www.josiahzayner.com/2017/10/the-first-human-to-attempt-crispr-gene.html> [<https://perma.cc/8RM5-AXM6>]; Sarah Zhang, *A Biohacker Regrets Publicly Injecting Himself with CRISPR*, ATLANTIC (Feb. 20, 2018), <https://www.theatlantic.com/science/archive/2018/02/biohacking-stunts-crispr/553511/> [<https://perma.cc/W86Z-VM2Z>].

already enhance themselves and their children in a wide variety of relatively modest ways: eyeglasses and laser surgery for myopia, education and Ritalin for academic achievement, meditation and even controlled administration of hallucinogens for moral enhancement, and caloric restriction for life extension. Inheritable genetic enhancements may hold the potential to change the balance of characteristics in a society more pervasively and permanently than other enhancement technologies currently available to individuals and families. Individual choices to ensure that one's children and grandchildren are blond haired and blue-eyed, taller than average, more trusting and compassionate, possessing higher IQs, or needing less sleep potentially have a wide range of possible consequences across societies. Yet all parents seek to secure advantages for their children and pass them on across generations through the acquisition and inheritance of wealth, education, employment opportunities and experiences, contacts and connections, and other forms of social capital. Are genetic enhancements different in kind from other enhancements, or do they differ only in degree of precision, penetrance, and irreversibility?

Many of the enhancements just described would not be regarded as advantageous if everyone had them. Being tall, or blond haired and blue-eyed, matters little if everyone is tall, or blond haired and blue-eyed; these characteristics, and others that matter only if you have them and others do not, are, in economic or philosophical terms, *positional goods*.<sup>129</sup> Some enhancements, in contrast, may continue to be desirable nevertheless, at least within limits. For example, more education or greater intelligence, more stamina, less need for sleep, and staying healthier longer may all confer advantages over individuals who lack these characteristics, but each enhancement may still have value if everyone shares them; they are, philosophically speaking, *intrinsic goods*.<sup>130</sup> Even in circumstances where income-related disparities will surely limit access to any and all genetic enhancements, whether for individuals alone or also for their progeny, it is worth considering what kinds of enhancements are even worthy of consideration in a society that seeks to be both free and fair.

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129. FRED HIRSCH, *THE SOCIAL LIMITS TO GROWTH* 27 (rev. ed. 2005).

130. MICHAEL J. ZIMMERMAN, *STANFORD ENCYCLOPEDIA OF PHILOSOPHY*, INTRINSIC VS. EXTRINSIC VALUE 5–8 (Edward N. Zalta et al. eds., Spring 2015 ed. 2015), <https://plato.stanford.edu/entries/value-intrinsic-extrinsic/> [<https://perma.cc/VBG5-3PLY>].

Finally, even the most highly valued of intrinsic goods has a place on a continuum from enhancements that manipulate normal species functioning in minor ways, such as bringing short people up to the species norm or improving eyesight beyond 20/20 vision, to those that change normal species functioning more profoundly, such as tripling the human lifespan or enabling humans to photosynthesize in order to counter a shrinking food supply on an overheating planet. Inheritable genetic modifications, now potentially made much easier by gene editing, may be difficult to undo. Thus, even if genetic enhancement is currently no more than a philosopher's dream, contemplating the inheritable changes that could in the future be wrought by human germline gene editing may add at least a modicum of urgency to ongoing ethical and policy deliberations about human enhancement. We need to worry about this because it simply may not be possible to avoid embryo enhancement if embryo editing goes forward.

*C. Oversight and Governance, Domestic and Global*

That gene editing provides an unparalleled opportunity to address significant questions about governance of new technologies, appropriate oversight, and issues of justice, both domestic and global, seems an understatement. That we are very far from being able to capitalize on that opportunity seems equally obvious. The reasons are legion: international scientific competition, a proliferation of regulatory and oversight mechanisms replete with gaps and overlaps, historical precedents like the “Wild West” of ART in the United States, and the accessibility and affordability of do-it-yourself CRISPR kits for at-home biohacking are just a few of the contributors to the patchwork picture.<sup>131</sup>

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131. See generally Marianne J. Legato et al., *Editing the Human Genome: Progress and Controversies*, 1 GENDER & GENOME 4, 5–7 (2016) (recounting a roundtable discussion on the progress of human gene editing and the reasons it is controversial). In addition, the European Union's recent determination that gene-edited organisms should be regarded as genetically modified organisms from a regulatory standpoint has added confusion and consternation to the mix. See Press Release, Court of Justice of the European Union, *Organisms Obtained by Mutagenesis Are GMOs and Are, in Principle, Subject to the Obligations Laid Down by the GMO Directive* (July 25, 2018), <https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-07/cp180111en.pdf> [<https://perma.cc/72JD-GHPN>]. Finally, organisms obtained by mutagenesis qualify as genetically modified and are therefore subject to the GMO Directive's obligations. *Id.*; see also Rodolphe Barrangou, *CRISPR Crazy: A Response to the EU Court Ruling*, 1 CRISPR J. 251, 251 (2018); Press Release, Court of Justice of the European Union, *supra*. One important, agreed-upon but largely nonregulatory limitation on human embryo research—the so-called fourteen-day rule—is applied widely but differently across national boundaries and plays a

To address this kind of complexity, which is not at all unprecedented, Marchant and Wallace have suggested applying a model called a “governance coordinating committee,” which can make use of a “soft law” approach to novel biotechnologies by serving a managerial “honest broker” function.<sup>132</sup> Is there a path forward for establishing a governance coordination committee for gene editing? Well, the summary statement from the organizers of the Second International Summit on Human Genome Editing

calls for an ongoing international forum to foster broad public dialogue, develop strategies for increasing equitable access to meet the needs of underserved populations, speed the development of regulatory science, provide a clearinghouse for information about governance options, contribute to the development of common regulatory standards, and enhance coordination of research and clinical applications through an international registry of planned and ongoing experiments.<sup>133</sup>

In addition, consider that the NIH has recently decided to yet again revise and reduce the role of the Recombinant DNA Advisory Committee (“RAC”) in the oversight of human gene-transfer research, having concluded that gene-transfer research no longer needs the scrutiny that should be afforded to novel biotechnologies. As part of this revision, “to use the RAC as a public forum to advise on issues associated with emerging biotechnologies, the RAC’s charter will be modified to change the committee’s focus from

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fundamental role in gene editing and related research. Insoo Hyun, Amy Wilkerson & Josephine Johnston, *Human-Embryo Research: Revisit the 14-Day Rule*, 533 NATURE 169, 170 (2016).

132. Marchant & Wallach, *supra* note 13, at 46, 48 (“Emerging technologies require a coordinated, holistic, and nimble approach, while not sacrificing diligence in overseeing discernible dangers. . . . It would be an illusion to think that a GCC, or any other body, could resolve these problems altogether. However, through advice, influence, and building rapport among stakeholders, a GCC could play a key role in modulating the development and deployment of new technologies. Today, no single institution is positioned to play such a role.”).

133. Statement, Organizing Comm. of the Second Int’l Summit on Human Genome Editing, On Human Genome Editing II (Nov. 29, 2018) [hereinafter Organizing Committee Statement], <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11282018b> [https://perma.cc/7WU2-DB2R]; *see also* Statement, Marcia McNutt, President, Nat’l Acad. of Scis., and Victor J. Dzau, President, Nat’l Acad. of Med., Statement on the Second International Summit on Human Genome Editing (Nov. 29, 2018) [hereinafter Presidents’ Statement], <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11282018c> [https://perma.cc/DD25-95HH].

research solely involving recombinant or synthetic nucleic acids to emerging biotechnologies research.”<sup>134</sup>

If the RAC is actually reformulated to provide a public forum that can advise broadly on scientific, safety, and ethical issues arising in research on emerging biotechnologies, perhaps there is some hope that it could continue to listen, deliberate, and influence the progress of gene-editing research and related biotechnologies. That would be desirable. It remains to be seen whether the NIH truly intends to make this change; however, its director, Francis Collins, has referenced it in his response to the He Jiankui scandal.<sup>135</sup> It is far from clear at the time of this writing what this model could really accomplish.<sup>136</sup> Even so, another proponent of responsible research progress instead of moratoria in this socially and politically sensitive area has also called for a comprehensive regulatory roadmap that would incorporate a wide variety of guidelines, controls, and checkpoints.<sup>137</sup>

#### D. A Moratorium?

Notably, in mid-March an international group of genome scientists and bioethics scholars published an article in *Nature* calling for a moratorium on “heritable genome editing.”<sup>138</sup> An accompanying editorial echoed the need for better regulation and broader discussion,<sup>139</sup> and the same issue published letters from NIH and the National Academies supporting a moratorium.<sup>140</sup>

The moratorium call is detailed, addressing the need to improve the efficiency of IVF and PGD as potentially preferable to clinical genome editing, endorsing the continuation of basic genome-editing

134. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, 83 Fed. Reg. 41,082, 41,083 (Aug. 17, 2018); *see also* Francis S. Collins & Scott Gottlieb, *The Next Phase of Human Gene-Therapy Oversight*, 379 NEW ENG. J. MED. 1393, 1395 (2018) (“The NIH envisions using the RAC as an advisory board on today’s emerging biotechnologies, such as gene editing, synthetic biology, and neurotechnology, while harnessing the attributes that have long ensured its transparency.”).

135. *See* Cohen, *supra* note 115; *see also* Organizing Committee Statement, *supra* note 133; Presidents’ Statement, *supra* note 133.

136. Nancy M. P. King, *RAC Oversight of Gene Transfer Research: A Model Worth Extending?*, 30 J.L. MED. & ETHICS 381, 386 (2002).

137. R. Alta Charo, *Rogues and Regulations of Germline Editing*, 380 NEW ENG. J. MED. 976, 976 (2019).

138. Eric Lander et al., *Adopt a Moratorium on Heritable Genome Editing*, 567 NATURE 165, 165–68 (2019).

139. Editorial, *Set Rules for Genome Editing*, 567 NATURE 145, 145 (2019).

140. Correspondence, 567 NATURE 175, 175 (2019).

research, and positing the global moratorium on clinical genome editing as voluntary and temporary. Not surprisingly, however, it was immediately controversial, with prominent scientists and scholars supporting both sides of the question for a wide range of reasons.<sup>141</sup> As at least two international expert groups,<sup>142</sup> with some members already clearly in both “slow down” and “move ahead” camps, have pledged to work together to define terms, discuss scientific and ethical issues, and set standards in germline genome-editing research, the controversy over global governance and research policy is sure to remain significant.

#### E. Access and Cost

Cost and access have been important concerns for all treatment technologies for as long as paying for health care has been an issue. Both domestically and on a global scale, new biotechnologies often come with immense price tags.<sup>143</sup> Gene-transfer, cell-based, and regenerative-medicine interventions are, generally speaking, very expensive; some efforts are being made to reduce costs through scale-up and standardization,<sup>144</sup> but the success of such efforts is uncertain.

141. Jon Cohen, *New Call to Ban Gene-Edited Babies Divides Biologists*, SCIENCE (Mar. 13, 2019, 2:00 PM), <https://www.sciencemag.org/news/2019/03/new-call-ban-gene-edited-babies-divides-biologists> [<https://perma.cc/9K5X-XJLA>]. And on April 24, in a letter sent to Alex Azar, United States Secretary of Health and Human Services, sixty-two scientists and bioethics scholars strongly supported a moratorium. See *Gene Therapy Leaders Urge Global Moratorium on Germline Editing*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Apr. 24, 2019), <https://www.genengnews.com/topics/genome-editing/gene-therapy-leaders-urge-global-moratorium-on-germline-editing/> [<https://perma.cc/E9VA-ZS96>].

142. There is a new WHO expert advisory committee to develop governance and oversight standards for human genome editing. *WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing*, WORLD HEALTH ORG., <https://www.who.int/ethics/topics/human-genome-editing/committee-members/en/> [<https://perma.cc/J3FD-CUX8>]. There is also an international commission, formed by the National Academies of Science and Medicine and the United Kingdom Royal Society. See Correspondence, *supra* note 140, at 175.

143. E.g., Nancy M. P. King & Christine E. Bishop, *New Treatments for Serious Conditions: Ethical Implications*, 24 GENE THERAPY 534, 536 (2017); Damien Garde, *The Cure for ‘Bubble Boy’ Disease Will Cost \$665,000*, STAT (Aug. 3, 2016), <https://www.statnews.com/2016/08/03/gene-therapy-price-gsk/> [<https://perma.cc/L8EX-6PKS>]; Meghana Keshavan, *We May Soon Have Our First \$1 Million Drug. Who Will Pay for It? And How?*, STAT (Oct. 13, 2017), <https://www.statnews.com/2017/10/13/gene-therapy-pricing/?utm> [<https://perma.cc/T5JF-QFCH>].

144. Joshua G. Hunsberger, Thomas Shupe & Anthony Atala, *An Industry-Driven Roadmap for Manufacturing in Regenerative Medicine*, 7 STEM CELLS TRANSLATIONAL MED. 564, 564–68 (2018).

It is possible that the speed and simplicity of CRISPR-Cas9 and other gene-editing tools may help to reduce gene editing's ultimate cost. Even significant cost reductions will not necessarily improve the affordability of future treatments, however, particularly for patients in resource-poor countries, unless gene editing proves far more curative and considerably cheaper than currently available treatments, thus making it feasible to ensure global accessibility. Countries that cannot afford to provide basic health care for the people residing within their borders are unlikely to provide novel biotechnologies, even at low cost. Countries that—like the United States—choose to condition access to health care on the ability to pay for it, with exceptions for only some of those with the least resources and the greatest need, are unlikely to remove or lower that barrier for particular new technologies, no matter how promising.

This is only to say that the cost problem in health care is pervasive; gene editing will simply be another new and expensive biotechnology. But because gene editing of embryos must necessarily be integrated into existing ART systems, which are already financially out of reach for many, disparities of access will surely be exacerbated unless our thinking about payment for such services changes profoundly.

And yet, it must be acknowledged that the issue of fair access to costly biotechnologies is a question of distributive justice that is confined to the rather small and circumscribed realm of rescue medicine. There are other, much broader distributive justice questions that should also be considered. We should ask: How should we distribute not only fair access to novel biotechnological treatments but also to preventive services and also to the support services that are often so necessary when treatments are not cures? How should we fairly apportion funding for health-related research between the development of novel biotechnologies and the search for effective prevention? Should we focus instead on identifying, addressing, and ameliorating the many social factors that give rise to health disparities but that have proven more challenging—and much less exciting—than pursuing cutting-edge science?<sup>145</sup> Should we even consider thinking beyond health, to engage more seriously in collective discussion about all the things that make up a good life, and about

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145. REBECCA DRESSER, *WHEN SCIENCE OFFERS SALVATION* 47 (2001).

what societies should do to make the lives of the people who live in them better?<sup>146</sup>

#### IV. CAN POLICY SHAPE SCIENCE?

Somatic cell gene editing is not new, although CRISPR-Cas9, its relatives, and the recent development of even newer and potentially more precise techniques, like base editing, have made it far easier. However, the editing of early embryos and gametes is necessarily controversial. There is still agreement that clinical research involving human embryos intended for reproduction must wait until much more is known, but calls for complete avoidance of germline gene editing are increasingly in the minority.

##### A. *Is Germline Editing the Future?*

The question whether deliberate germline gene editing should ever be permitted is a question about the nature of the need. IVF combined with PGD is a safe and effective already-existing alternative to gene editing of embryos or gametes in all but the few circumstances where a genetic disorder will necessarily appear in all of the embryos a couple can produce. Yet there are would-be parents who might prefer editing a single embryo over creating and testing multiple embryos, selecting and implanting one or two unaffected embryos, and discarding the rest.<sup>147</sup> And there are other would-be parents with a range of different reasons for seeking gene editing.<sup>148</sup>

146. Juengst, *supra* note 21, at 19. See generally MADISON POWERS & RUTH FADEN, SOCIAL JUSTICE: THE MORAL FOUNDATIONS OF PUBLIC HEALTH AND HEALTH POLICY (2008) (proposing that health is only one of six essential dimensions of well-being to which all people deserve access).

147. Nonetheless, what philosophers refer to as the “nonidentity problem”—that is, that selecting an unaffected embryo means choosing a different potential person, whereas editing an embryo means treating the same potential person—may be a distinction that is more illusory than meaningful. Interview with Janet Malek, Assoc. Professor, Baylor Coll. of Med. (Oct. 19, 2018).

148. See Daley et al., *supra* note 118, at 897–99 (addressing the needs of couples with low fertility). For instance, there are would-be fathers with genetic disorders who would choose to have their spermatogonial stem cells genetically altered and reimplanted into their testes so that they can reproduce “naturally.” See Church, *supra* note 114, at 1909–11. And there are same-sex couples who would choose to create bipaternal or bimaternal embryos, should that technology become available. See Zhi-Kun Li et al., *Generation of Bimaternal and Bipaternal Mice from Hypomethylated ESCs with Imprinting Region Deletions*, 23 CELL STEM CELL 665, 665 (2018). It is noteworthy that the He Jiankui scandal has not deterred some researchers from studying similar preventive interventions. See Antonio Regalado, *Despite CRISPR Baby Controversy, Harvard University Will Begin Gene-Editing Sperm*, MIT TECH. REV. (Nov. 29, 2018), <https://www.technologyreview.com/>

When editing, rather than selection, is chosen or necessary, germline alteration is then a side effect of editing embryos, zygotes, or gametes in order to ensure that the intervention is completely effective with little or no possibility of mosaicism. But affecting the germline is also a goal in itself, accomplished by either embryo selection or embryo editing. IVF, PGD, and embryo selection already work to eliminate deleterious conditions from the human germline, without gene editing's uncertain and unknown effects on future generations. Yet there is no groundswell of enthusiasm for making these standard technologies more widely available. The scientific excitement that accompanies genetic manipulation risks overwhelming the ability of professionals and the public to place these novel biotechnologies in perspective.<sup>149</sup>

As a result, it is highly likely that over time, more and more embryo editing could come to be regarded as necessary, along with its germline effects, whether inadvertent or desired. And only editing can create (and perpetuate) enhancements.

#### B. *Is Enhancement Inevitable?*

The prospect of genetic enhancement is far more feasible with gene editing than it has ever been with gene addition. The simple existence of the technology has given rise to an imaginative fervor that so far has outpaced serious discussion about what enhancement means and what its consequences might be—despite the greatly expanded problems of assessing safety and even of predicting the meaning of efficacy when enhancement rather than correction is at issue.<sup>150</sup>

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s/612494/despite-crispr-baby-controversy-harvard-university-will-begin-gene-editing-sperm/ [https://perma.cc/2KEA-CXFW].

149. There are undoubtedly ambitious scientists and entrepreneurs who are inspired rather than deterred by Dr. He's experience. See Antonio Regalado, *The DIY Designer Baby Project Funded with Bitcoin*, MIT TECH. REV. (Feb. 1, 2019), <https://www.technologyreview.com/s/612838/the-transhumanist-diy-designer-baby-funded-with-bitcoin/> [https://perma.cc/S4FV-WUMQ]. And though beyond the scope of this Article, editing gametes is definitely regarded by the scientific community as a viable strategy to be studied, and one highly reputable scientist, George Daley, Dean of Harvard Medical School, supports continuing research looking toward clinical applications, even after Dr. He. See Regalado, *A New Way to Reproduce*, *supra* note 114, at 35.

150. The regulatory requirements for research with human subjects require a reasonable balance between risks of harm and potential benefits. But as discussion of Dr. He's research demonstrates, when seeking to enhance a healthy human, it is at best somewhat challenging to assess the potential benefits of making someone "better than normal" and compare those elusive benefits to the risks of harm. See Rebecca Dresser,

Addressing the problem of unequal access to costly biotechnologies barely dents the ethical issues raised by this challenging future possibility. Gene editing represents a major scientific leap forward, rekindling public excitement about the possibility of significant amelioration of genetic disorders in the foreseeable future. Yes, it will take quite some time before many human clinical gene-editing trials using CRISPR-Cas9 are underway, but clinical translation seems likely to move more quickly than it has for other novel biotechnologies. After all, research in healthy human embryos was approved in two countries just a year after the first publication of gene-editing research in tripronuclear human embryos in China.<sup>151</sup> And the controversy over He Jiankui's work is likely to continue for some time.<sup>152</sup>

### C. *Sticking to the Basics: A Proposal*

Despite the push toward clinical applications of human embryo editing, it matters a great deal whether the translational pathway is expected to follow a straight line or not. It seems likely that genetic-modification research in human embryos will continue and expand, but basic and proof-of-principle research may be far more vital than speeding toward the clinic. Gene-editing research using human embryos to gain basic knowledge of embryonic development and infertility is currently underway. Researchers received approval early in 2016 to use CRISPR-Cas9 in healthy donated embryos in the United Kingdom and in Sweden; by September, National Public Radio announced that the Swedish team had started their work.<sup>153</sup>

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*Genetic Modification of Preimplantation Embryos: Toward Adequate Human Research Policies*, 82 MILBANK Q. 195, 207, 209 (2004); Yong, *supra* note 89.

151. See Michelle Taylor, *Japan Joins List of Countries that Allow Gene Editing in Human Embryos*, LABORATORY EQUIPMENT (Oct. 5, 2018, 2:06 PM), <https://www.laboratoryequipment.com/news/2018/10/japan-joins-list-countries-allow-gene-editing-human-embryos> [https://perma.cc/Z8HM-YURE].

152. In recent news identified for this Article, Dr. He continued to defend his research and stated that he was seeking publication of his data. Luke W. Vrotsos, *Chinese Researcher Who Said He Gene-Edited Babies Breaks Week of Silence, Vows to Defend Work*, HARV. CRIMSON (Dec. 7, 2018), <https://www.thecrimson.com/article/2018/12/7/harvard-profs-react-to-human-gene-edit/> [https://perma.cc/7XMC-XG9R]. *But cf.* Henry T. Greely, *He Jiankui, Embryo Editing, CCR5, the London Patient, and Jumping to Conclusions*, STAT (Apr. 15, 2019), <https://www.statnews.com/2019/04/15/jiankui-embryo-editing-ccr5/> [https://perma.cc/QE3G-KKQS] (“Not only was He ethically wrong in doing this work, but its scientific basis was even weaker than generally recognized.”).

153. Ewen Callaway, *Embryo Editing Gets Green Light*, 530 NATURE 18, 18 (2016); Ewen Callaway, *Embryo-Editing Research Gathers Momentum*, 532 NATURE 289, 289 (2016); Park, *supra* note 11, at 45; Rob Stein, *Breaking Taboo, Swedish Scientist Seeks to*

Since then, researchers in the United Kingdom and elsewhere have made significant contributions to basic knowledge of embryo development and disease modeling.<sup>154</sup> Recently, an expert panel convened by the Japanese Ministry of Education, Culture, Sports, Science, and Technology drafted guidelines recommending gene editing of human embryos for basic science research.<sup>155</sup> And a developmental biologist in the United States is using CRISPR to test the efficacy of editing deleterious mutations like retinitis pigmentosa out of human embryos in very early stages of development.<sup>156</sup>

Although basic embryo research using CRISPR might seem like nothing other than the first step on the pathway of clinical translation, it should instead be considered a goal in itself. CRISPR was discovered and developed because scientific curiosity led to scientific excitement about the ability to understand, refine, and manipulate a newly identified biological ability. The basic embryo research that CRISPR makes possible seeks to improve scientific understanding of human growth and development in ways that may not lead directly to clinical applications but that may have far greater capacity to improve the health of many in the long run. Renewed attention to basic principles of careful and deliberate knowledge-generating research can do a lot to slow the race to the clinic and help to ensure that what ultimately succeeds in moving from “bench to bedside” is safe and effective, because more is known about how and why it works.<sup>157</sup>

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*Edit DNA of Healthy Human Embryos*, NPR (Sept. 22, 2016, 5:07 AM), <http://www.npr.org/sections/health-shots/2016/09/22/494591738/breaking-taboo-swedish-scientist-seeks-to-edit-dna-of-healthy-human-embryos> [<https://perma.cc/7T6J-5FEX>].

154. See, e.g., Norah M. E. Fogarty et al., *Genome Editing Reveals a Role for OCT4 in Human Embryogenesis*, 550 NATURE 67, 67 (2017); Heidi Ledford, *CRISPR Used to Peer into Human Embryos' First Days*, NATURE (Sept. 20, 2017), <https://www.nature.com/news/crispr-used-to-peer-into-human-embryos-first-days-1.22646> [<https://perma.cc/EU5K-J5GN>].

155. David Cyranoski, *Japan Set to Allow Gene Editing in Human Embryos*, NATURE (Oct. 3, 2018), <https://www.nature.com/articles/d41586-018-06847-7> [<https://perma.cc/FXG4-ZTST>].

156. Rob Stein, *New U.S. Experiments Aim to Create Gene-Edited Human Embryos*, NPR (Feb. 1, 2019, 5:42 PM), <https://www.npr.org/2019/02/01/690822745/u-s-scientists-researching-gene-editing-in-human-embryos> [<https://perma.cc/XJ75-3Z5F>].

157. JONATHAN KIMMELMAN, GENE TRANSFER AND THE ETHICS OF FIRST-IN-HUMAN RESEARCH: LOST IN TRANSLATION 111 (2009); Steven Joffe & Franklin G. Miller, *Bench to Bedside: Mapping the Moral Terrain of Clinical Research*, HASTINGS CTR. REP., Mar.–Apr. 2008, at 30, 32, 36. It is noteworthy that the authors of the call for a moratorium on clinical germline editing have taken this position. See Lander et al., *supra* note 138, at 166 (“To be clear, our proposed moratorium does not apply to germline editing for research uses, provided that these studies do not involve the transfer of an embryo to a person’s uterus.”).

It is also important to recognize that the tremendous—and justified—scientific excitement about CRISPR and related gene-editing tools may ultimately result in only modest clinical benefit, precisely because the knowledge gains from basic and preclinical research are themselves broadly generalizable rather than targeted to treatment breakthroughs. This is the way all science generally works, and despite the rapid translation of scientific excitement about gene editing into the popular press, the science of gene editing works this way too.

Great clinical breakthroughs could indeed come from CRISPR; only time will tell. But progress is truly more likely if its pace is slow and steady and if detours and switchbacks are encouraged as learning opportunities. It may be too late to temper public expectations or broaden public deliberation about gene editing, but reinforcing scientific responsibility is a duty borne by all those who think about the relationship of science to society. When shared governance is nearly impossible to achieve or even conceive of in a global explosion of scientific excitement and increasingly accessible technology, sharing conversation plays a vital role in supporting and perpetuating a global commitment to harm prevention, practical wisdom, and reasoned reflection about medical progress.

One of the most important outcomes of the “gene-edited babies” controversy should be renewed attention to the relationship between good science and the ethical and social value of responsible scientific progress. Whether or not He Jiankui is appropriately characterized as a rogue scientist, many researchers and scholars have noted that ethically sound research means more than simple adherence to laws and regulations. Some have gone on to point out that critical reflection about the ethical underpinnings of human research and the promotion of open and robust discussion regardless of self-interest are essential.<sup>158</sup> After all, Dr. He appears to believe that his work is

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158. See, e.g., J. Benjamin Hurlbut & Jason Scott Robert, *CRISPR Babies Raise an Uncomfortable Reality—Abiding by Scientific Standards Doesn't Guarantee Ethical Research*, CONVERSATION (Dec. 3, 2018, 6:33 AM), <https://theconversation.com/crispr-babies-raise-an-uncomfortable-reality-abiding-by-scientific-standards-doesnt-guarantee-ethical-research-108008> [<https://perma.cc/9B3K-RWUR>]; Mark Yarborough, *Who Missed the Chance to Stop the CRISPR Babies Scientist? Look in the Mirror*, STAT (Nov. 30, 2018), <https://www.statnews.com/2018/11/30/missed-chance-stop-crispr-babies-scientist/> [<https://perma.cc/74M9-YR2E>]; see also Jon Cohen, *Stanford Says Its Researchers Did Not Help Chinese Biologist Who Gene Edited Babies*, SCIENCE (Apr. 16, 2019), <https://www.sciencemag.org/news/2019/04/stanford-says-its-researchers-did-not-help-chinese-biologist-who-gene-edited-babies> [<https://perma.cc/9A43-35B4>].

both ethical and necessary; the extent to which he may have misunderstood what seems clear to others is a cautionary commentary on ethics education in the sciences, at every level.<sup>159</sup> The integrity of scientific data and the ethics of translational research are interdependent.<sup>160</sup> Both depend upon public and policy conversations about what constitute common human values and why we hold them.<sup>161</sup> This is why careful, transparent attention to all its implications is essential to the success of all new science. As difficult and all consuming as that attention is, both for scientists and for the rest of society, the promise of gene editing deserves no less.

#### CONCLUSION

This Article has attempted, in a drastically condensed discussion, to describe the rapid development of gene editing and to highlight the scientific, medical, ethical, and policy challenges posed by editing the genomes of embryos destined to be born. Such edits are expected to be inherited by future generations. Although developing effective genetic treatments for already-born persons is universally desirable, inheritable genetic changes have been prohibited or, at best, regarded with extreme caution, for a variety of ethical, policy, and scientific reasons, including concern about the high likelihood of dangerous outcomes, desire to make use of less drastic means of eliminating genetic disease, and the hope of preserving the human genetic inheritance without introducing uncontrolled enhancements.

Careful and thoughtful ongoing research can make use of CRISPR and related editing technologies in order to learn more about human development and disease, and thus has a promising

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159. See, e.g., Sharon Begley, *He Took a Crash Course in Bioethics. Then He Created CRISPR Babies*, STAT (Nov. 27, 2018), <https://www.statnews.com/2018/11/27/crispr-babies-creator-soaked-up-bioethics/> [<https://perma.cc/TP6F-RBEP>]; Jon Cohen, *After Last Week's Shock, Scientists Scramble to Prevent More Gene-Edited Babies*, SCIENCE (Dec. 4, 2018, 5:25 AM), <https://www.sciencemag.org/news/2018/12/after-last-weeks-shock-scientists-scramble-prevent-more-gene-edited-babies> [<https://perma.cc/99SY-ZWE9>]; Vrotsos, *supra* note 152. Notably, Dr. He and several coauthors, including an American public relations specialist, authored an article in 2018 entitled "Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies." See *Retraction of: Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies by He J et al.*, CRISPR J 2018; *Fast Track*. DOI:10.1089/crispr/2018/0051, 2 CRISPR J. 65, 65 (2019). This document, the content of which is questionable in many ways, was published online by the CRISPR Journal before the news about the twins became public. *Id.* It never made it into the relevant issue of the journal, online or in print, and has since been taken down entirely. *Id.*

160. KIMMELMAN, *supra* note 157, at 94–95; Joffe & Miller, *supra* note 157, at 32.

161. See, e.g., DRESSER, *supra* note 145, at 116–17.

future. However, the desire to develop inheritable genetic modifications—including enhancements—is surprisingly strong, as He Jiankui’s work has demonstrated. Moreover, Dr. He’s work has shown that even if there were clear and universal agreement, there is no global enforcement mechanism able to detect deviations prospectively. Much depends upon continuing, clear, and complete discussion among scientists, bioethics scholars, and policymakers worldwide. Much also depends upon robust ethics education for scientists as well as for the public. But the real question is whether, after Dr. He, the genie can be put back in the bottle. Only time will tell.

