

# COUNSELING AFTER CRISPR

Bret D. Asbury\*

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## ABSTRACT

*This Article explores the implications of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) gene editing and its emergent ability to treat human diseases by altering prenatal DNA. After surveying current scientific capabilities, this Article narrows its scope to focus on how this rapidly evolving technique will impact prenatal genetic counseling, an area in which there has been both federal and state legislation in recent years and one in which the most spirited debates relating to human genome editing are likely to emerge. Whereas recent scholarly debates surrounding prenatal genetic counseling have addressed how genetic counselors can and should assist potential parents in deciding whether to bring genetically anomalous fetuses to term, the arrival of CRISPR—a relatively simple and cost-effective method of editing genomes that has the potential to mitigate or eliminate many fetal genetic abnormalities—presents a new set of questions for prenatal genetic counselors.*

*As CRISPR’s ability to alter human genomes expands and becomes more refined, a number of ethical, financial, and regulatory challenges will emerge. This Article describes these novel challenges and sets forth a framework for how prenatal genetic counseling can best meet them. In doing so, it focuses on three questions. First, under what medical circumstances might it be appropriate for a prenatal genetic counselor to raise the possibility of a genetic intervention? Second, what role, if any, should state and federal legislation play in promoting awareness of genetic interventions? Third, to what extent might it be appropriate medically, ethically, and financially to subsidize access to gene therapy?*

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\*Associate Dean for Faculty Research and Associate Professor, Drexel University Thomas R. Kline School of Law. A.B., Princeton University, J.D., Yale Law School. The author would like to thank Lauren McGinley and Conor McCabe for superb research assistance, Kevin Woodson and the participants in the 2017 John Mercer Langston Writing Workshop for helpful and insightful comments, and the Drexel University Thomas R. Kline School of Law and Deans Roger Dennis and Dan Filler for their generous research support.

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## I. INTRODUCTION

On August 2, 2017, *Nature* published the results of the first known attempt to create genetically modified human embryos in the United States.<sup>1</sup> The underlying experiment, led by Shoukhrat Mitalipov of Oregon Health and Science University,<sup>2</sup> demonstrated that it is possible to correct inherited, disease-causing human genes safely and efficiently—to edit out and rewrite mutations in the genetic code of human embryos prior to their implantation in the womb. Mitalipov’s breakthrough in correcting a genetic mutation that can cause heart failure<sup>3</sup> did not go unnoticed: the *Nature* article drew immediate attention from

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1. See Hong Ma et al., Correction of a Pathogenic Gene Mutation in Human Embryos, 548 NATURE 413 (2017).

2. See Steve Connor, *First Human Embryos Edited in U.S.: Researchers Have Demonstrated They Can Efficiently Improve the DNA of Human Embryos*, MIT TECH. REV. (Jul. 26, 2017) <https://www.technologyreview.com/s/608350/first-human-embryos-edited-in-us/?set=608342> [<https://perma.cc/GDJ9-H9SU>]. Prior to this announcement, there were only three other known instances of attempts to edit human embryos, all in China and none as successful as this one. *Id.*

3. Ma et al., *supra* note 1, at 1. The study successfully edited out a mutation in a gene called MYBPC3, which can cause hypertrophic cardiomyopathy, or HCM. “HCM is a myocardial disease characterized by left ventricular hypertrophy, myofibrillar disarray and myocardial stiffness; it has an estimated prevalence of 1:500 in adults and manifests itself clinically with heart failure.” *Id.* (citation omitted).

dozens of media sources,<sup>4</sup> including the *New York Times*<sup>5</sup> and *Washington Post*.<sup>6</sup> Though the embryos in Mitalipov's experiment were not implanted into a womb for gestation, this groundbreaking application of human gene therapy suggests that the birth of the first human being to have had a disease edited out this way is inevitable,<sup>7</sup> and likely to occur sooner than any of us had ever imagined.

Professor Mitalipov's successful gene editing is but the latest illustration of mankind's ongoing attempt to shape evolution. Humans have long sought to control their environments and enhance their quality of life through biological engineering. But whereas prior efforts to control biology—which have included selective breeding of crops and livestock, efforts to eradicate naturally occurring diseases, and widespread inoculation and vaccination—were often imprecise, time-consuming, and cumbersome, scientists now have the ability to target undesirable traits at the genetic level with unprecedented efficiency, be it with respect to plants, animals, or, now, human beings. The emergence in 2012 of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)<sup>8</sup>—the relatively simple and inexpensive method of precisely editing genomes employed by Professor Mitalipov<sup>9</sup>—has led to an explosion in research and scholarship devoted to gene editing,<sup>10</sup> with ramifications ranging from agriculture and medicine, to industrial production and environmental management.<sup>11</sup>

Though CRISPR has already proven effective in editing the genes of numerous plants and laboratory animals to eliminate undesirable traits, its transformative potential extends far beyond flora and fauna—there is now a growing consensus that scientists will soon have the ability to manipulate human

4. See, e.g., James Gallagher, *Human Embryos Edited To Stop Disease*, BBC NEWS (Aug. 2, 2017), <http://www.bbc.com/news/health-40802147> [<https://perma.cc/7SZL-4A75>]; Kim Painter, *U.S. Scientists Fix Disease Genes in Human Embryos for 1st Time*, USA TODAY (Aug. 2, 2017), <https://www.usatoday.com/story/news/2017/08/02/us-scientists-fix-disease-genes-human-embryos-1st-time/104223394/> [<https://perma.cc/HZ95-EYRB>]; Kelly Servick, *First U.S.-based Group To Edit Human Embryos Brings Practice Closer to Clinic*, SCIENCE (Aug. 2, 2017), <http://www.sciencemag.org/news/2017/08/first-us-based-group-edit-human-embryos-brings-practice-closer-clinic> [<https://perma.cc/3QGK-FPF8>].

5. See Pam Belluck, *In Breakthrough, Scientists Edit a Dangerous Mutation from Genes in Human Embryos*, N.Y. TIMES (Aug. 2, 2017), <https://www.nytimes.com/2017/08/02/science/gene-editing-human-embryos.html> [<https://perma.cc/C6GF-SRM3>].

6. See Ariana Eunjung Cha, *First Human Embryo Editing Experiment in U.S. 'Corrects' Gene for Heart Condition*, WASH. POST (Aug. 2, 2017), [https://www.washingtonpost.com/news/to-your-health/wp/2017/08/02/first-human-embryo-editing-experiment-in-u-s-corrects-gene-for-heart-condition/?utm\\_term=.d3ee7e659b4d](https://www.washingtonpost.com/news/to-your-health/wp/2017/08/02/first-human-embryo-editing-experiment-in-u-s-corrects-gene-for-heart-condition/?utm_term=.d3ee7e659b4d) [<https://perma.cc/4K2K-2326>].

7. See *id.*; Connor, *supra* note 2.

8. An explanation of CRISPR and its origins, as well as a discussion of other modern methods of gene editing, appears in the following Part.

9. Connor, *supra* note 2.

10. From 2011 to 2016, the number of scientific papers published with CRISPR in their title or abstract increased by 1,493%. *STAT's Stats of the Year: 2016 by the Numbers*, STAT (Dec. 28, 2016), <https://www.statnews.com/2016/12/28/stat-stats-year-in-numbers/> [<https://perma.cc/H37M-GC8N>].

11. Nuffield Council on Bioethics, *Genome Editing: An Ethical Review 4* (2016) [hereinafter *Nuffield Review*].

genomes to treat or cure diseases such as congenital heart defects, cystic fibrosis, muscular dystrophy, sickle-cell disease, hemophilia, HIV, and certain cancers.<sup>12</sup> This nascent ability raises many difficult ethical questions relating to the dangers, efficacy, and reproductive implications of genetic intervention in humans. Chief among them is how the ability to edit human genomes to treat and cure disease should inform the manner in which medical professionals and pregnant women understand and address fetal genetic abnormalities. This is especially the case where aborting the pregnancy remains an option and where the implications of any genetic intervention will last a lifetime, and possibly extend to future generations.

Under current best practices, women learning of a potential fetal abnormality rely heavily on prenatal genetic counseling to assist them as they consider whether to abort or proceed with the knowledge that their child will likely face significant medical challenges. In its ideal form, this relationship is characterized by the counselor's explanation of both the risk that a genetic abnormality actually exists and the implications of bringing a genetically anomalous embryo or fetus to term. The counselor must do so pursuant to genetic counseling's long-held commitment to nondirectiveness, which requires that she offer neutral information, rather than advise a woman whether or not to terminate her pregnancy.

But as will be discussed below,<sup>13</sup> genetic counselors frequently fail to abide by this norm. Instead, they often undermine informed choice by offering selective information and directive advice based on their perceptions about the anticipated genetic condition and the ability of the mother to manage it. The content and framing of the information counselors choose to share with expectant mothers can be of crucial importance. As shown in a prior article,<sup>14</sup> genetic terminations are distinct from other types of abortions in that they result in elevated rates of grief, depression, and post-traumatic stress.<sup>15</sup> And though some of these symptoms might be unavoidable, others arise as a direct result of the receipt of insufficient information.

The frequent failure of prenatal genetic counseling to remain nondirective in practice has spurred federal and state legislation aimed at providing current, evidence-based information about prenatally diagnosed conditions to potential parents and their medical providers. Congress took action in 2008 by passing the bipartisan Prenatally and Postnatally Diagnosed Conditions Awareness Act

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12. See National Academy of Sciences & National Academy of Medicine, *Human Genome Editing: Science, Ethics, and Governance* 70-71 (2017) [hereinafter *HUMAN GENOME EDITING*] (providing examples of human diseases that might be treated through use of gene editing); Jennifer Doudna, *Embryo Editing Needs Scrutiny*, 528 *NATURE* 7581, Suppl., S6 (2015) (noting that gene editing strategies “could eventually be used to treat or cure human disease”).

13. See Part II.B, *infra*.

14. See Bret D. Asbury, *Fostering Informed Choice: Alleviating the Trauma of Genetic Abortions*, 25 *CORNELL J.L. & PUB. POL'Y* 293 (2015).

15. See *id.* at 307-12.

(PPDCAA),<sup>16</sup> and in the past decade eighteen states have passed similar legislation, seven of which have done so in the past three years.<sup>17</sup> But despite the recent flurry of attention in this area, none of this legislation has addressed what may soon become the most crucial question of all: how and to what extent should potential mothers be made aware of genetic interventions that might cure or mitigate the genetic abnormality of the fetuses they carry.

This glaring oversight is potentially catastrophic. Given the nearly limitless potential of CRISPR and other methods of modern gene editing to treat, cure, and avoid disease,<sup>18</sup> actual or potential genetic interventions will soon be at the forefront of treating prenatally diagnosed conditions. Legislation aimed at providing expectant mothers and their medical providers with useful, current information that does not touch on genetic interventions will therefore soon be markedly ill-suited for its most basic purpose. More broadly, given that genetic counseling routinely fails to deliver sufficient information to allow women to make informed reproductive choices even absent the possibility of genetic interventions, it follows that the routinization of gene therapy as yet another option for consideration will exacerbate this problem. Because informed choice is at the heart of the state and federal legislation in this area, its collective failure to touch on genetic interventions is both striking and problematic.

This Article sets forth the first argument delineating how prenatal genetic counseling should frame and discuss CRISPR and other transformative techniques of gene editing to foster informed reproductive decisions. It does so in three parts. Part I provides an overview of CRISPR—describing both its predecessors and the other modern techniques of gene editing—and discusses current and emergent applications of gene editing to plants, animals, the environment, and humans. Part II explores the challenges prenatal genetic counselors face as they attempt to adapt to a world in which the genetic alteration of embryos and fetuses may be both feasible and optimal, while balancing their nondirective aspirations with their broader desire to act in the best interest of the mother. Part III provides preliminary responses to the challenges set forth in Part II, describing under what circumstances prenatal genetic counselors should raise the possibility of gene editing and suggesting approaches for providing broader access to gene therapy. Part III also considers how appropriate federal or state legislation might better ensure that expectant mothers receive gene editing information in a manner that does not rely on genetic counseling, respects their autonomy, and enables them to make adequately informed choices. A final Part concludes.

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16. Prenatally and Postnatally Diagnosed Conditions Awareness Act, Pub. L. No. 110-374, § 2(1)–(3), 122 Stat. 4051, 4051 (2008).

17. See Part II.A, *infra*.

18. See Part I.C.2, *infra*.

## II. A PRIMER ON GENE EDITING AND CRISPR

Before delving into the legal, regulatory, and policy implications of modern gene editing on reproduction, it is first necessary to provide an overview of where this rapidly developing field of biology currently stands. This Part traces the development of CRISPR back to the 1970s, the dawn of modern gene editing, then describes its existing and potential applications across several species. As will be shown below, genetic editing has already made crops more nutritious, produced animals better suited for laboratory research, and treated several human diseases. And given gene editing's rapid development since CRISPR emerged in 2012, breakthroughs such as Professor Mitalipov's successful treatment of human embryos<sup>19</sup> will likely continue to emerge apace in areas ranging from the development of alternatives to fossil fuels, to the eradication of mosquito-borne diseases, to the reintroduction of extinct animal species. Understanding the impact gene editing can have on reproductive decision-making requires a basic understanding of the breadth, depth, and transformative nature of CRISPR and its peer technologies across the biological spectrum. Though condensed by necessity, this Part attempts to provide just that.

## A. Background

Though definitions of "genome" vary, DNA (deoxyribonucleic acid) is the fundamental building block of the genomes of living organisms.<sup>20</sup> DNA consists of a long sequence of four nucleotides (adenine (A), cytosine (C), guanine (G), and thymine (T)), arranged in a particular order.<sup>21</sup> This ordering of nucleotides, or more familiarly, their *sequence*, largely determines the information encoded in a given organism's DNA.<sup>22</sup> Segments of this DNA sequence encode genes that, taken together, form the genome.<sup>23</sup> The human genome has about three billion nucleotides and contains 20,000 genes. All humans have two copies of each of these genes, one from each parent, which are arranged to form two sets of 23 chromosomes.<sup>24</sup>

The Nuffield Council on Bioethics defines genome editing as the "practice of making targeted interventions at the molecular level of DNA and RNA function

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19. See Connor, *supra* note 2.

20. See Beth Nicholson & K. Andrew White, *Functional long-range RNA – RNA interactions in positive-strand RNA viruses*, NATURE REVIEWS MICROBIOLOGY 493 (2014). doi:10.1038/nmicro3288. ("positive-strand RNA [(ribonucleic acid)] viruses are important human, animal and plant pathogens that are defined by their single-stranded positive-sense RNA genomes."); NUFFIELD REVIEW, *supra* note 11, at 5.

21. HUMAN GENOME EDITING, *supra* note 12, at 62.

22. NUFFIELD REVIEW, *supra* note 11, at 5.

23. HUMAN GENOME EDITING, *supra* note 12, at 46. These genes can be copied, or "transcribed" to form RNA, a second type of nucleotide polymer. *Id.* See also NUFFIELD REVIEW, *supra* note 11, at 6 (noting that the first step of gene expression is transcription of the DNA sequence into RNA).

24. HUMAN GENOME EDITING, *supra* note 12, at 62.

deliberately to alter the structural or functional characteristics of biological entities,” including “humans and animals, tissues and cells in culture, and plants, bacteria, and viruses.”<sup>25</sup> While selective breeding to produce desirable traits in agriculture and animal husbandry has been commonplace for thousands of years, specific efforts to target and manipulate the genetic code of organisms began in earnest in the 1970s.<sup>26</sup>

Modern methods of gene manipulation first focused on recombinant DNA technology, which allowed for the cutting and subsequent splicing together of DNA molecules from distinct genetic sources.<sup>27</sup> Though this approach was able to produce mice containing targeted and beneficial insertions of DNA from other species as early as the mid-1970s, transgenesis using recombinant DNA techniques was limited because it only allowed genes to be added (rather than added or subtracted) and, crucially, “offered no control over where the added genes would be inserted into the genome.”<sup>28</sup> This meant that the success or failure of early recombinant DNA gene therapies depended to some degree on luck, with success rates ranging from 1 in 100 to 1 in 1,000,000, depending on the chosen method of DNA insertion into a cell population.<sup>29</sup> This imprecision, combined with the concomitant enormous expense of early gene therapies, left researchers searching for more efficient approaches, which they began to uncover in the early 2000s.

The first of such approaches to gene editing, Zinc-finger nucleases (ZFNs), emerged in 2005 and the second, Transcription activator-like effector nucleases (TALENs), emerged five years later.<sup>30</sup> Both ZFNs and TALENs employ a DNA-cutting enzyme called FokI (from the bacteria *Flavobacterium okeanoikoites*), which they pair with an attached string of proteins engineered for the purpose of recognizing a defined sequence of nucleases in order to target, cut, and replace undesired DNA.<sup>31</sup> Despite the unprecedented precision and effectiveness of ZFNs and TALENs in locating and remedying flaws in an organism’s genetic code, both techniques faced challenges to their widespread adoption because designing, synthesizing, and optimizing proteins to specifically target flaws requires considerable effort (and resources).<sup>32</sup> Though ZFNs and TALENs proved far

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25. NUFFIELD REVIEW, *supra* note 11, at 4. RNA serves many purposes, but chief among them is to convert information stored in DNA into protein. See HUMAN GENOME EDITING, *supra* note 12, at 62.

26. See, e.g., George Church, *Encourage the Innovators*, 528 NATURE 7581 Suppl., S7 (2015); Doudna, *supra* note 12, at S6.

27. NUFFIELD REVIEW, *supra* note 11, at 7.

28. *Id.*

29. See HUMAN GENOME EDITING, *supra* note 12, at 66.

30. NUFFIELD REVIEW, *supra* note 11, at 8.

31. See Amy Maxmen & Denis Mallet, *Three Technologies that Changed Genetics*, 528 NATURE 7581, Suppl., S2 (2015).

32. See *id.*; see also Jennifer A. Doudna & Emmanuelle Charpentier, Review Summary, *The New Frontier of Genome Engineering with CRISPR-Cas9*, 346 SCIENCE 1077, 1077 (2014) (noting that “difficulties of protein design, synthesis, and validation remain a barrier to widespread adoption of [ZFNs and TALENs] for routine use”); HUMAN GENOME EDITING, *supra* note 12, at

superior to earlier gene therapies relying upon recombinant DNA, researchers continued to seek more efficient means of editing genes, which they found through use of CRISPR-Cas9.

CRISPRs were first described by Japanese researchers studying the *E. coli* genome in 1987,<sup>33</sup> though the acronym itself was not coined until 2002.<sup>34</sup> The term refers to sequences of the A, C, G, and T nucleases of some segments of DNA that repeat and are the same backward and forward—palindromes.<sup>35</sup> These palindromic repeats can act as a guide for identifying and locating specific sequences for modification within a given organism’s DNA. Building on years of experimentation, researchers can now create “guide RNA” with any combinations of nucleotides and thereby hone in on any segment of an organism’s DNA, palindromic or not, “like a genetic GPS.”<sup>36</sup>

But reaching target nucleotides is just the first step. What makes CRISPR so potentially transformative is how effectively it works in conjunction with its associated proteins, most often Cas9 (CRISPR associated protein 9, formerly known as Csn1). Cas9 proteins have the uncanny ability to grasp DNA and slice it with a precision far exceeding earlier techniques such as ZFNs and TALENs.<sup>37</sup> Bringing these constituent parts together, the CRISPR-Cas9 complex provides both unprecedented accuracy in targeting undesirable DNA and previously unrealized precision in editing it. Moreover, it is also both more efficient<sup>38</sup> and faster<sup>39</sup> than other modern gene editing tools, while at the same time being comparatively inexpensive—a CRISPR-Cas9 DNA molecule can now be purchased online from any number of providers for \$65 or less.<sup>40</sup> The most prominent modern techniques of gene editing and their origins now having been described, the following Subpart discusses successful applications of modern gene editing to illustrate how they have begun to transform modern biology, with an eye toward establishing how it might inform prenatal genetic counseling in future years.

### B. Existing Applications

Despite its novelty, gene editing through use of ZFNs, TALENs, and CRISPR has already eliminated or modified targeted genes across a number of species.

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47-48 (observing that “the protein engineering required to design site-specific versions of TALENs and, even more so, of ZFNs, remains technically challenging, time-consuming, and expensive”); NUFFIELD REVIEW, *supra* note 11, at 8.

33. Doudna & Charpentier, *supra* note 32.

34. Zoe Corbyn, *Biology’s Big Hit*, 528 NATURE 7581, Suppl., S4, S5 (2015).

35. Amy Maxmen, *The Genesis Engine*, WIRED, Aug. 2015, at 58.

36. *Id.* at 61.

37. *Id.* (“Compared to TALENs and zinc-finger nucleases [ZFNs], this was like trading rusty scissors for a computer-controlled laser cutter.”)

38. NUFFIELD REVIEW, *supra* note 11, at 9

39. Corbyn, *supra* note 34, at S5.

40. Anna Petherick, *Preface to Genome Editing*, 528 NATURE 7581, Suppl., S1 (2015).



These successful interventions have arisen with a rapidity that would have been impossible through use of the most prevalent predecessor techniques of gene editing, which employed relatively imprecise and expensive recombinant DNA technologies. This Subpart provides illustrative examples of successful modern gene editing in three areas—agriculture, animals, and human beings—in order to show just how transformative these modern techniques have already proven to be and to lay the foundation for a discussion of some of their emerging potential applications.

### 1. Agriculture

In the realm of agriculture, selective breeding of crops exhibiting desirable traits has long been commonplace, and today almost no crop that is commonly eaten is biologically “natural,” that is, unaltered by human intervention.<sup>41</sup> That said, traditional methods of selective breeding of crops to produce desired biological characteristics must be distinguished from the genetic engineering of crops, which generally requires direct, specific gene modification.<sup>42</sup> In recent years, there have been a number of breakthroughs in this latter category, in which specific genes have been successfully targeted and edited.<sup>43</sup>

CRISPR-Cas9 gene editing has been used on a number of crops, including wheat, rice, sweet orange, sorghum, and liverwort.<sup>44</sup> With respect to plants, genome editing is most often employed in attempts to increase pest resistance or drought tolerance, enhance health or nutritional benefit, or improve appearance (in order to reduce waste).<sup>45</sup> Scientists have already successfully employed gene editing to produce wheat that is resistant to powdery mildew<sup>46</sup> and rice that is resistant to bacterial blight,<sup>47</sup> improve the quality of staples such as potatoes<sup>48</sup> and soybean oil,<sup>49</sup> alter the appearance of apples in order to make them more appetizing,<sup>50</sup> and modify tomato genes to produce higher yielding plants that are

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41. See NUFFIELD REVIEW, *supra* note 11, at 56.

42. See *id.* at 57.

43. *Id.* at 57-58.

44. Jim Kozubek, MODERN PROMETHEUS: EDITING THE HUMAN GENOME WITH CRISPR-CAS9 326 (2016).

45. NUFFIELD REVIEW, *supra* note 11, at 60-61.

46. Yanping Wang et al., Simultaneous Editing of Three Homoeoalleles in Hexaploid Bread Wheat Confers Heritable Resistance to Powdery Mildew, 32 NATURE BIOTECHNOLOGY 947 (2014).

47. Junhui Zhou et al., Gene Targeting by the TAL Effector Pthxo2 Reveals Cryptic Resistance Gene for Bacterial Blight of Rice, 82 THE PLANT J. 632 (2015).

48. Benjamin M. Clasen et al., *Improving Cold Storage and Processing Traits in Potato through Targeted Gene Knockout*, 14 PLANT BIOTECHNOLOGY J. 169 (2016) (discussing a genetic enhancement to improve the taste of potatoes that have been kept in cold storage).

49. William Haun et al., Improved Soybean Oil Quality by Targeted Mutagenesis of the Fatty Acid Desaturase 2 Gene Family, 12 PLANT BIOTECHNOLOGY J. 934 (2014).

50. Chikano Nishitani, Efficient Genome Editing in Apple Using a CRISPR/Cas9 System, 6 SCI. REP. 31481 (2016).

less likely to drop their fruits to the ground, thereby making mechanical harvesting more efficient.<sup>51</sup>

## 2. Animals

The precise editing of animal genomes has also advanced by leaps and bounds in recent years thanks to modern techniques of editing genes. Researchers have sought to insert genetic modifications in animals both to test the potency and effectiveness of modern gene editing techniques, to assist in understanding basic biological processes, and to aid in the development of treatments for human diseases. There have already been significant successes in each of these areas.

In the past five years, genome editing allowing for targeted genetic engineering has been displayed in zebrafish,<sup>52</sup> fruit flies,<sup>53</sup> roundworms,<sup>54</sup> frogs,<sup>55</sup> and salamanders.<sup>56</sup> Modern gene editing techniques have also facilitated the generation of mice,<sup>57</sup> rats,<sup>58</sup> pigs,<sup>59</sup> and monkeys<sup>60</sup> better suited to studies seeking to understand human diseases. As Jennifer A. Doudna and Emmanuelle Charpentier, co-pioneers of CRISPR-Cas9, have noted, this technology “is already having a major impact on functional genomic experiments” in a number

51. See Heidi Ledford, *Fixing the Tomato: CRISPR Edits Correct Plant-Breeding Snafu*, 545 NATURE 394 (2017); Megan Molteni, *CRISPR May Cure All Genetic Disease—One Day*, WIRED (June 7, 2017, 5:03 PM), <https://www.wired.com/2017/06/crispr-may-cure-genetic-disease-one-day> [<http://perma.cc/2E8Q-2F8C>].

52. See, e.g., Nannan Chang et al., *Genome Editing with RNA-Guided Cas9 Nuclease in Zebrafish Embryos*, 23 CELL RES. 465 (2013); Woong Y. Hwang et al., *Efficient Genome Editing in Zebrafish Using a CRISPR-Cas System*, 31 NATURE BIOTECHNOLOGY 227 (2013).

53. See, e.g., Andrew R. Bassett et al., *Highly Efficient Targeted Mutagenesis of Drosophila with the CRISPR/Cas9 System*, 4 CELL REP. 220 (2013); Scott J. Gratz et al., *Genome Engineering of Drosophila with the CRISPR RNA-Guided Cas9 Nuclease*, 194 GENETICS 1029 (2013).

54. See, e.g., Ari E. Friedland et al., *Heritable Genome Editing in C. Elegans via a CRISPR-Cas9 System*, 10 NATURE METHODS 741 (2013).

55. See, e.g., Ira L. Blitz et al., *Biallelic Genome Modification in F<sub>0</sub> Xenopus Tropicalis Embryos Using the CRISPR/Cas System*, 51 GENESIS 827 (2013); Takuya Nakayama et al., *Simple and Efficient CRISPR/Cas0-Mediated Targeted Mutagenesis in Xenopus Tropicalis*, 51 GENESIS 835 (2013).

56. See, e.g., G. Parker Flowers et al., *Highly Efficient Targeted Mutagenesis in Axolotl Using Cas9 RNA-Guided Nuclease*, 141 DEV. 2165 (2014).

57. See, e.g., Albert W. Cheng et al., *Multiplexed Activation of Endogenous Genes by CRISPR-on, an RNA-Guided Transcriptional Activator System*, 23 CELL RES. 1163 (2013); Haoyi Wang et al., *One-Step Generation of Mice Carrying Mutations in Multiple Genes by CRISPR/Cas-Mediated Genome Engineering*, 153 CELL 910 (2013); Hui Wang et al., *One-Step Generation of Mice Carrying Reporter and Conditional Alleles by CRISPR/Cas-Mediated Genome Engineering*, 154 CELL 1370 (2013).

58. See, e.g., Xinli Hu et al., *Heritable Gene-Targeting with gRNA/Cas9 in Rats*, 23 CELL RES. 1322 (2013) (Letter to the Editor); Yuanwu Ma et al., *Heritable Multiplex Genetic Engineering in Rats Using CRISPR/Cas9*, 9 PLOS ONE e89413 (2014).

59. Kristin M. Whitworth, *Use of the CRISPR/Cas System To Produce Genetically Engineered Pigs from Inn Vitro-Derived Oocytes and Embryos*, 91 BIOLOGY OF REPROD. 1 (2014).

60. See, e.g., Yuyu Niu et al., *Generation of Gene-Modified Cynomolgus Monkey via Cas9/RNA Mediated Gene Targeting in One-Cell Embryos*, 156 CELL 836 (2014).

of animal model systems that will “advance the field of experimental biology in ways not imagined even a few years ago.”<sup>61</sup> The coming years will produce many more examples of successful genome editing in animals, many of which will relate to the ultimate objective of treating human diseases through genetic intervention.

### 3. *Humans*

With respect to human health, modern gene editing techniques have actual and potential applications in three areas: improving understanding of health and diseases; treating diseases; and avoiding diseases through early genetic interventions.<sup>62</sup> In terms of improving understanding, modern gene editing techniques have reduced the cost and increased the speed of research in order to widen the possible areas of genetic research and have made possible the relatively easy genetic manipulation of previously hard to modify cells and organisms.<sup>63</sup> CRISPR-Cas9 in particular has proven extraordinarily efficient at targeting and cutting DNA, “such that [in many experiments] no off-target cutting is detectable across the whole genome that is sequenced.”<sup>64</sup>

The precision of modern gene editing has already laid the foundation for rapid advances in treating and avoiding genetic diseases. In relation to the former, researchers have used CRISPR-Cas9 to target and disrupt viral genomes that affect humans directly.<sup>65</sup> The other modern techniques—TALENs and ZFNs—have also been successful in this regard. Taken together, modern gene editing techniques have to date proven effective in targeting and producing improved outcomes relating to the HIV virus,<sup>66</sup> Hepatitis B,<sup>67</sup> and leukemia.<sup>68</sup>

The use of modern gene editing techniques to avoid genetic diseases *ex ante*—rather than treat them after diagnosis—has also shown promise. Though there are currently no proven genetic modifications that have allowed human embryos to avoid diseases, the techniques that have been developed and employed with respect to laboratory animals such as mice and monkeys have begun to be

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61. Doudna & Charpentier, *supra* note 33, at 1258096-6.

62. See generally NUFFIELD REVIEW, *supra* note 11, at 34-53 (reviewing the implications of genome editing for human health).

63. *Id.* at 35.

64. *Id.* at 36; see also Benjamin P. Kleinstiver et al., High-fidelity CRISPR-Cas9 Nucleases with No Detectable Genome-wide Off-target Effects, 529 NATURE 490 (2015); Ian M. Slaymaker et al., Rationally Engineered Cas9 Nucleases with Improved Specificity, 351 SCIENCE 84 (2015).

65. NUFFIELD REVIEW, *supra* note 11, at 40.

66. See Michael Eisenstein, *Closing the Door on HIV*, 528 NATURE 7581 Suppl. S8 (2015) (describing the use of ZFNs to snip out a portion of the gene responsible for allowing HIV to enter immune cells in order to improve resistance and eliminate susceptibility to HIV).

67. See Vyas Ramanan et al., *CRISPR/Cas9 Cleavage of Viral DNA Efficiently Suppresses Hepatitis B Virus*, 5 SCI. REP. 10833 (2015) (describing the use of CRISPR-Cas9 as a means of suppressing viral genes and possibly curing patients).

68. NUFFIELD REVIEW, *supra* note 11, at 41 (describing a patient having acute lymphoblastic leukemia who was successfully treated through use of TALENs to edit T-cells).

explored in humans<sup>69</sup> and applied to human embryos in at least three cases.<sup>70</sup> Despite the lack of concrete proof of disease avoidance through use of modern gene editing techniques, there is reason to believe that modern gene editing will one day soon serve as an efficient means of avoiding genetic diseases and treating them in novel ways. The potential applications of modern gene editing in humans, as well as their applications in other areas, are explored in the following Subpart.

### C. Potential Applications

Modern gene editing techniques have opened the door to an unprecedented array of contributions across all areas of biology, and the proven successes of CRISPR-Cas9, ZFNs, and TALENs noted above are just the beginning. Though potential *human* genetic interventions are most relevant to the arguments set forth in this Article, it is first worth noting some of the ways modern gene editing might revolutionize other areas of biology in the coming years. The following Subpart describes some of the ways that modern gene editing is likely to impact agriculture, animals, and the natural environment.

#### 1. Agriculture, Animals, and the Natural Environment

With respect to plants, as noted above, modern genetic interventions will continue to focus on increasing pest resistance and drought tolerance, enhancing health or nutritional benefits, and improving appearance of crops so as to reduce food waste. Given the projected expansion of the human population from 7.3 billion in 2017 to 9.7 billion by 2050,<sup>71</sup> coupled with the increased risks to worldwide crop productivity brought about by climate change,<sup>72</sup> the need to produce improved crops could not be more pressing. The good news is that modern gene editing is already well on its way to improving crop yields and efficiency. Examples of potential applications of modern gene editing to plants abound, and include current experiments on soybeans, corn, rice, and wheat

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69. *Id.* at 45

70. See Connor, *supra* note 2 (describing Professor Mitalipov's experiment to genetically modify a human embryo); Xiangjin Kang et al., *Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas-mediated Genome Editing*, 33 J. ASSISTED REPROD. & GENETICS 581 (2016) (attempting to evaluate the use of CRISPR/Cas-9 to introduce genetic modifications in human embryos); Puding Liang et al., *CRISPR/Cas9-mediated Gene Editing in Human Trippronuclear Zygotes*, 6 PROTEIN & CELL 363 (2015) (describing a relatively unsuccessful effort to edit genes in human embryos with CRISPR-Cas9).

71. United Nations Population Div., of the Dep't of Economic and Social Affairs, *World Population Prospects: The 2015 Revision 2*, at 1 (2015), [https://esa.un.org/unpd/wpp/publications/files/key\\_findings\\_wpp\\_2015.pdf](https://esa.un.org/unpd/wpp/publications/files/key_findings_wpp_2015.pdf) [<https://perma.cc/EYD9-EPGE>].

72. See John R. Porter et al., *Food Security and Food Production Systems*, in CLIMATE CHANGE 2014: IMPACTS, ADAPTATION, AND VULNERABILITY 485-533, [http://www.ipcc.ch/pdf/assessment-report/ar5/wg2/WGIIAR5-Chap7\\_FINAL.pdf](http://www.ipcc.ch/pdf/assessment-report/ar5/wg2/WGIIAR5-Chap7_FINAL.pdf) [<https://perma.cc/F2EY-RW8P>]. (describing the risks to crops in some regions brought about by climate change and how farmers are beginning to adapt).

endeavoring to bring more efficient, CRISPR-bred seeds to market in as little as five years.<sup>73</sup> Modern gene editing has also shown the potential to increase substantially the yield of both tomatoes and cassava, a subsistence crop in sub-Saharan Africa and Latin America, facilitate the precise engineering of photosynthesis, and manipulate both the weight of crop seeds and the number of seeds produced by a given plant in order to increase efficiency.<sup>74</sup>

The potential of modern gene editing in animals is also significant, and current research in this area tends to focus in two areas: “increased fecundity and more efficient conversion of inputs into outputs.”<sup>75</sup> Research relating to increased fecundity has been mostly devoted to food animals, such as chickens and cattle. With respect to the former, scientists are currently seeking to perfect the process of producing chickens that produce only female (that is, egg-laying) offspring; with respect to the latter, there are current efforts to produce only male beef cattle offspring, which convert feed to muscle more efficiently than females.<sup>76</sup> In terms of efficiency (rather than fecundity), scientists are currently endeavoring to perfect gene editing methods to create pigs that grow more plentiful with relatively less food, cattle that grow disproportionately large muscles, and cashmere goats that grow longer hair for use in the production of sweaters and other luxury goods.<sup>77</sup>

Other ongoing experiments attempt to promote the health and welfare of food animals. These include experiments seeking to produce hornless (“polled”) cattle less likely to harm one another when kept in close proximity<sup>78</sup> and the engineering of certain breeds of pigs to increase their resistance to the African swine fever virus.<sup>79</sup> While none of the above advances in the genetic engineering of livestock have resulted in widespread applications in increasing fecundity, increased efficiency in converting inputs into outputs, or improved animal health and welfare, each has shown promise and is indicative of the impact that modern gene editing in livestock is likely to have in the coming years.

Finally, though the potential impact of modern gene editing on the natural environment and ecology is perhaps less direct and intuitive than any of the specific potential genetic interventions described above, current research has laid the foundation for widespread change in the near future. Researchers are currently working on a number of efforts that have the potential to significantly

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73. See David Talbot, *CRISPR Offers an Easy, Exact Way To Alter Genes To Create Traits Such as Disease Resistance and Drought Tolerance*, MIT TECH. REV. (MARCH/APRIL 2016), <https://www.technologyreview.com/s/600765/10-breakthrough-technologies-2016-precise-gene-editing-in-plants> [<https://perma.cc/G64S-P6AD>].

74. Armin Scheben & David Edwards, *Genome Editors Take on Crops*, 355 SCIENCE 1122, 1122-23 (2017).

75. NUFFIELD REVIEW, *supra* note 11, at 64.

76. Sara Reardon, *The CRISPR Zoo*, 531 NATURE 160, 162 (2016).

77. NUFFIELD REVIEW, *supra* note 11, at 64; see also Xiaolong Wang et al., *Generation of Gene-modified Goats Targeting MSTN and FGF5 via Zygote Injection of CRISPR/Cas9 System*, 5 SCI. REP. 13878.

78. Reardon, *supra* note 76, at 162-63.

79. NUFFIELD REVIEW, *supra* note 11, at 64.

alter the natural environment, both locally and worldwide.

At the micro level, researchers at Harvard have already begun work to reintroduce extinct woolly mammoths through use of CRISPR genome editing in elephant cells. They believe that cloning attempts of woolly mammoths can begin in 2018, and that the first new mammoth will be born two years after the successful implantation of a fused elephant-mammoth embryo in a living Asian elephant.<sup>80</sup> There are similar efforts to reintroduce the passenger pigeon, which was driven to extinction by overhunting in the late nineteenth century,<sup>81</sup> and the health hen.<sup>82</sup>

More broadly, there has been a recent breakthrough in using gene editing technology to commercialize algae-based biofuels by increasing their lipid production, thereby supplementing the global supply of petroleum-based fuels<sup>83</sup> and potentially reducing significantly the need to drill and lowering carbon levels in the atmosphere.<sup>84</sup> There are also ongoing experiments seeking to eradicate populations of non-native predators in certain environments. For example, Predator Free New Zealand, a public-private partnership, seeks to target and eradicate non-native predators such as rats, weasels, and possums through use of modern gene editing.<sup>85</sup> Though it should go without saying, eradicating these non-native species would result in significant environmental changes, foreseeable or otherwise.

Most significantly, so called “gene drives” have the greatest potential to alter the environment and basic ecology of certain regions, or even the planet, through use of modern gene editing. A gene drive is a method of accelerating the propagation of a trait throughout a population by ensuring that targeted genetic elements spread at a rate faster than that of normal inheritance.<sup>86</sup> Whereas during normal inheritance there is generally a 50% chance that offspring will inherit a given gene on one chromosome, gene drive systems cut the partner chromosome in such a way that offspring inherit the target gene nearly all of the time.<sup>87</sup> This

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80. *Woolly Mammoth Revival*, REVIVE & RESTORE <http://reviverestore.org/projects/woolly-mammoth> [<https://perma.cc/9FT8-VMN3>] (describing the benefits of bringing back the woolly mammoth and a possible method of doing so); see also NUFFIELD REVIEW, *supra* note 11, at 79 (noting efforts to bring back the woolly mammoth, passenger pigeon, and health hen).

81. Reardon, *supra* note 76, at 162.

82. NUFFIELD REVIEW, *supra* note 11, at 79.

83. See Imad Ajjawi et al., *Lipid Production in Nannochloropsis Gaditana is Doubled by Decreasing Expression of a Single Transcriptional Regulator*, 35 NATURE BIOTECHNOLOGY 647 (2017) (describing the process of increasing lipid levels in certain algae, thereby increasing their potential as a source of combustible energy).

84. See Nick Stockton, *Fattened, Genetically Engineered Algae Might Fuel the Future*, WIRED, (June 19, 2017), <https://www.wired.com/story/synthetic-genomics-genetically-engineered-algae-might-fuel-the-future> [<https://perma.cc/QQC9-B8ZR>] (describing the Ajjawi study and noting its potential).

85. NUFFIELD REVIEW, *supra* note 11, at 78-79.

86. *Id.* at 79.

87. Claire Ainsworth, *A New Breed of Edits*, 528 NATURE 7581 Suppl. S15, S16 (2015).

manner of modifying inheritance allows scientists to enable a desirable genetic variant “to spread through a population even though it does not provide a selective advantage to the organism.”<sup>88</sup>

While gene drives could be useful in controlling plant pathogens and reversing pesticide and herbicide resistance, the most advanced and promising applications target populations of wild insects that transmit tropical diseases.<sup>89</sup> The eventual goal is to release synthetic gene drives to control mosquito populations or limit their ability to transmit Zika, dengue fever, yellow fever, and malaria.<sup>90</sup> Advances in CRISPR-Cas9 have accelerated the likelihood of success in this area,<sup>91</sup> and one study employing this method of gene editing succeeded in driving a targeted mutation into 97% of offspring in just two generations.<sup>92</sup>

## 2. Humans

As noted above,<sup>93</sup> potential applications of modern gene editing to humans can be roughly divided into three categories: improving understanding of health and disease,<sup>94</sup> treating disease,<sup>95</sup> and avoiding disease.<sup>96</sup> Treating and avoiding disease are the categories of most interest here, for should a significant number of diseases become treatable or avoidable, particularly in the near future, genetic counselors will face an array of novel and challenging questions as to how best to counsel their patients.

Several potential applications of gene editing to treat human disease are currently in the preclinical or clinical research stage.<sup>97</sup> These include treatments

88. NUFFIELD REVIEW, *supra* note 11, at 80.

89. *Id.* at 80.

90. *Id.* at 81.

91. *Id.*

92. See Valentino M. Gantz & Ethan Bier, The Mutagenic Chain Reaction: A Method for Converting Heterozygous to Homozygous Mutations, 348 SCIENCE 442, 443 (2015).

93. See *supra* note 62 and accompanying text.

94. See NUFFIELD REVIEW, *supra* note 11, at 35 (“Genome editing techniques can be used to generate cell lines with specific characteristics to provide disease models and investigate underlying pathology, as well as to screen potential medicines by evaluating their toxicity before they are considered for trials in animals and use in human subjects. . . . [G]enome editing can be used to develop cells whose genetic background is identical (isogenic) to that of the disease model. Editing isogenic genomes introduces a change so that the cell line differs only in respect to that specific change. This gives greater certainty about the effect of the precise, known difference between the disease variant and the control.”).

95. See *id.* at 40-43 (explaining that gene editing treatments of disease include modifying the genome of the disease directly, improving the performance of white blood cells to attack disease more effectively, and editing select genes to repair mutations that lead to disease).

96. See *id.* at 45-48. Avoiding genetic disease here refers to efforts “to deliver the editing machinery into a single-cell embryo (zygote), shortly after fertilisation or to edit the gametes (sperm or egg) prior to or during fertilisation.” *Id.* at 45. Though to date there have been no successful modifications of human embryos, research in this area has already begun, and the “techniques that would make this possible have been developed and used in many organisms, including mice and monkeys. . . .” *Id.*

97. See HUMAN GENOME EDITING, *supra* note 12, at 70-71

for sickle-cell disease, HIV, hemophilia B, and Duchenne's muscular dystrophy, as well as enhancements in cancer immunotherapy.<sup>98</sup> Research is also underway to repair genetic mutations that can result in cystic fibrosis and Becker muscular dystrophy through use of CRISPR-Cas9.<sup>99</sup> Further down the road, there is the potential to treat single-gene neurological disorders such as Angelman syndrome, Huntington's disease, and Prader-Willi syndrome.<sup>100</sup> But all of this is just the beginning. As scientific techniques and knowledge improve, the types of cells that can be isolated, modified, and transplanted will grow, and there will be a corresponding increase in the range of possible applications of genome editing to cure disease.<sup>101</sup>

Avoiding human diseases at the embryonic stage or sooner is also well on its way. Though there are currently no reported successful attempts, such interventions are likely to emerge in the coming years as advances in genome sequencing identify a larger number of genetic variants that are or may be associated with increased risk of disease.<sup>102</sup> To the extent that the identification of these variants emerges in tandem with developments in personalized genomic medicine,<sup>103</sup> there will be significant pressure to apply these medical tools to embryos.<sup>104</sup>

Already we know of an estimated 10,000 conditions that are inherited through a single gene.<sup>105</sup> Should this number grow considerably in future years, as is expected, so too will the number of possible genetic interventions at the embryonic stage or sooner. Though genetic modification of human embryos is currently forbidden or illegal in many jurisdictions, the techniques that would make it possible already exist and have been employed in animals as sophisticated as mice and monkeys.<sup>106</sup> And as noted above,<sup>107</sup> in addition to Professor Mitalipov's results published in August of 2017, there have been at least two studies in China in which scientists have attempted to manipulate human embryos genetically to avoid disease.

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98. See, e.g., Virginia Gewin, *Expanding Possibilities*, 528 NATURE S10 (2015) at S10 (noting the particular promise of modern gene editing for treating blood and bone marrow maladies, including HIV and sickle-cell disease); Eisenstein, *supra* note 66, at S8-S9 (describing successful efforts to treat HIV through gene editing).

99. NUFFIELD REVIEW, *supra* note 11, at 41-42.

100. Gewin, *supra* note 98, at S11.

101. See HUMAN GENOME EDITING, *supra* note 12, at 72.

102. NUFFIELD REVIEW, *supra* note 11, at 46.

103. Personalized genomic medicine is already here. See, e.g., Megan Molteni, *Fast, Precise Cancer Care is Coming to a Hospital Near You*, Wired (June 26, 2017, 7:00 AM), <https://www.wired.com/story/fast-precise-cancer-care-is-coming-to-a-hospital-near-you> [<http://perma.cc/N2JV-AQMM>] (noting the FDA's recent approval of a genetic-sequencing-based test "that can tell you how different drugs will work for you, based on the genetic makeup of your tumor").

104. See NUFFIELD REVIEW, *supra* note 11, at 46.

105. *Id.* at 45.

106. *Id.*

107. See *supra* note 70 and accompanying text.



In short, the broad category of gene therapy is in the midst of a radical reinvention. Although the timetable for specific applications of gene editing to treat or avoid human disease is unknowable and reliant upon scientific and regulatory advances that are difficult to predict, what is clear is that there will be many precise and potentially life-saving interventions coming to market in the near future. The following Part explains how the very novelty of these interventions will challenge prenatal genetic counseling, a field that already is much maligned and has been subject to regulation at both the state and federal level.

### III. HOW MODERN GENE EDITING WILL CHALLENGE PRENATAL GENETIC COUNSELING

This Part focuses on a specific period during pregnancy: when a woman learns that the fetus she is carrying will be born with a genetic disorder, or perhaps not be born at all.<sup>108</sup> During this difficult period, she must make several significant medical decisions in short order, and she often does so with the assistance of a genetic counselor. This Part provides an overview of prenatal genetic counseling and discusses some of the challenges it currently faces. It does so in order to situate this field in relation to the emergence of modern gene editing as a means of treating prenatally diagnosed medical conditions. As will be shown below, prenatal genetic counseling is badly in need of reform, and its current shortcomings will become even more pronounced in the coming years due to the ongoing emergence of novel and transformative gene therapies.

#### A. *A Primer on Prenatal Genetic Counseling*

Prenatal genetic counseling of women carrying genetically anomalous fetuses inevitably must confront a number of vexing ethical concerns.<sup>109</sup> A pregnant woman learning of a fetal abnormality must, at a time of extraordinary stress and anxiety, develop enough of an understanding of the potential challenges she, her child, and her family will be forced to endure in order to make an informed decision about whether to bring her pregnancy to term.<sup>110</sup> As applications of

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108. Expectant mothers learn of potential fetal abnormalities in a number of ways. See Asbury, *supra* note 14, at 299-302. Serum screening, the most common method of identifying potential fetal abnormalities, is a “test of the mother’s blood that usually takes place between the eleventh and thirteenth weeks of pregnancy,” but can take place at various times during the first or second trimester of pregnancy. *Id.* at 300 (citation omitted). Where serum screening identifies an elevated risk of a fetal abnormality, “pregnant women most often undergo a more invasive test for confirmation: chorionic villus sampling (CVS) of the placenta during the first trimester or amniocentesis (extraction of amniotic fluid through a needle inserted into the mother’s abdomen) in the second.” *Id.*

109. This Subpart borrows its framework and parts of its substance from an earlier article. See Asbury, *supra* note 14, at 295-98.

110. To be sure, personal attitudes toward abortion play a significant role in the difficulty of this decision. For mothers who would choose to bring their fetus to term under any circum-

modern gene editing continue to expand, she will soon have to consider a third option—whether to attempt to edit out a fetal genetic abnormality, either in utero or soon after birth. It is at this juncture of decision-making that prenatal genetic counseling plays the crucial role of assisting expectant mothers in making sense of their numerous options and deciding how to proceed.

Though the core aspiration of modern genetic counseling is “nondirectiveness”—providing unbiased genetic information rather than guiding expectant mothers to proceed or abort their pregnancy<sup>111</sup>—numerous studies have shown that real-life practice diverges significantly from this objective.<sup>112</sup> Expectant mothers who undergo genetic counseling frequently feel that they receive incomplete or one-sided information that stresses the negative aspects of genetic findings rather than the unknown or positive aspects.<sup>113</sup> In this way genetic counselors are all too often anything but nondirective, and critiques acknowledging the elusiveness of nondirectiveness have emerged from both within and outside of the field.<sup>114</sup>

The failure of genetic counseling to provide nondirective advice to expectant mothers has not gone unnoticed by legislators. In 2008, Congress passed the Prenatally and Postnatally Diagnosed Conditions Awareness Act (PPDCAA),<sup>115</sup> aimed at providing expectant mothers with “accurate information in order to

stance, a genetic abnormality serves only as a basis for learning more about their fetus’s condition and preparing to raise a child with special needs. For those who would consider having an abortion under some circumstances, however, the choice can be extraordinarily difficult.

111. See, e.g., Patricia L. Devers et al., *Noninvasive Prenatal Testing/Noninvasive Prenatal Diagnosis: The Position of the National Society of Genetic Counselors*, 22 J. GENETIC COUNSELING 291, 292 (2013) (citing Position Statement: Reproductive Freedom, NAT’L SOC’Y OF GENETIC COUNSELORS (June 1, 2010), <https://www.nsgc.org/p/bl/et/blogaid=35> [<https://perma.cc/FW3U-FC36>]) (“NSGC firmly believes that reproductive decisions should be made in the context of unbiased and comprehensive information, free from discrimination or coercion . . .”).

112. See Asbury, *supra* note 14, at 302-07. The following Subpart discusses these studies and the nature of genetic counseling in practice more generally.

113. See, e.g., Anne C. Madeo et al., *The Relationship Between the Genetic Counseling Profession and the Disability Community: A Commentary*, 155 AM. J. MED. GENETICS PART A 1777, 1779 (2011) (describing a Down syndrome study finding that while 95% of genetic counselors discussed its underlying biomedical aspects, just 26% described its many well-documented and positive “social aspects of life” and finding that among the genetic counseling encounters analyzed, “86% mentioned pregnancy termination, 37% continuation of pregnancy and 13% adoption”) (citing E. Farrelly et al., *Genetic Counselors and Prenatal Testing: Where is the Discussion About Disability?*, 19 J. GENETIC COUNSELING 671, 671 (2010)); Christy D. Roberts et al., *The Role of Genetic Counseling in the Elective Termination of Pregnancies Involving Fetuses with Disabilities*, 36 J. SPECIAL EDUC. 48, 53 (2002) (finding that 87% of women in their cohort “indicated that genetic counseling did not give them information about future-quality-of-life issues for a child with a disability” and 82.6% “indicated that the genetic counselor did not provide them with both positive and negative aspects of giving birth to a child with a disability”).

114. See, e.g., Madeo et al., *supra* note 113, at 1777-80 (discussing some of the tensions between the attitudes and practices of genetic counselors and the perspectives of disability and advocacy communities).

115. Prenatally and Postnatally Diagnosed Conditions Awareness Act, Pub. L. No. 110-374, § 2(1)-(3), 122 Stat. 4051, 4051 (2008).

allow them to make informed decisions about raising children with genetic disorders . . .”<sup>116</sup> Since then, due in large part to underfunding of the PPDCAA,<sup>117</sup> eighteen states from across the political spectrum have passed like-minded legislation,<sup>118</sup> seven of which have done so within the past three years.<sup>119</sup> While there are key differences between each state’s and the federal government’s legislation with respect to matters such as covered diagnoses, services provided, and manner of disseminating information,<sup>120</sup> in each case, legislatures felt compelled to provide additional information in response to the failures of prenatal genetic counseling. The following Subpart explains why nondirectiveness has proven particularly challenging in this area, and hence why so many states and the federal government have chosen to intervene.

### B. Nondirectiveness in Prenatal Genetic Counseling Remains Elusive

Be it by licensed genetic counselors or otherwise,<sup>121</sup> prenatal genetic counseling plays a crucial role in complicated pregnancies.<sup>122</sup> Upon detection of a fetal anomaly, counselors are tasked with helping women decide whether to terminate the pregnancy, treat the fetus in utero,<sup>123</sup> or manage the pregnancy and

116. Asbury, *supra* note 14, at 313 (citations omitted).

117. *See id.* at 314.

118. *See id.* at 314-15. These states include “liberal strongholds Massachusetts and Maryland, traditional swing states Pennsylvania, Ohio, Florida, and Virginia, and deeply conservative Kentucky, Kansas, and Louisiana.” *Id.* at 315. The other two having such laws on the books prior to 2015 are Delaware and Missouri. *Id.*

119. *See* 410 ILL. COMP. STAT. ANN. 511/15 (West 2015); IND. CODE ANN. § 16-35-9.2-3 (West 2015); ME. REV. STAT. ANN. tit. 22, § 1642 (2015); NEB. REV. STAT. ANN. § 71-4103 (West 2015); N.J. STAT. ANN. § 26:2-195 (West 2015); TEX. HEALTH & SAFETY CODE ANN. § 161.653 (West 2015); WASH. REV. CODE ANN. § 18.71A.110 (West 2016).

120. *See* Asbury, *supra* note 14, at 314-19 (comparing and contrasting the existing state legislation in this area).

121. Access to counselors who are members of the National Society of Genetic Counselors (NSGC) varies considerably, as they tend to be concentrated in certain large cities. *See* Kathryn Schleckser, Note, *Physician Participation in Direct-to-Consumer Genetic Testing: Pragmatism or Paternalism?*, 26 HARV. J.L. & TECH. 695, 725-26 (2013) (describing the high concentration of NSGC-member genetic counselors in urban areas such as New York, Philadelphia, and San Francisco and their relative dearth in and around cities such as New Orleans, Boise, and Fargo). Moreover, a recent search on the web page of the American Board of Genetic Counseling, the field’s accrediting body, found that there are just eleven certified genetic counselors in Idaho (ten of whom are in Boise), five in Mississippi, one in Wyoming, and zero in West Virginia. *See Find a Counselor*, AM. BD. OF GENETIC COUNSELING, INC., [https://customer.abgc.net/abgc/ABGCwcm/Find\\_Counselor/ABGCwcm/Contact\\_Management/FindCounselor.aspx?hkey=94273207-1a6e-4c6d-ac24-0c6b3793c8cd](https://customer.abgc.net/abgc/ABGCwcm/Find_Counselor/ABGCwcm/Contact_Management/FindCounselor.aspx?hkey=94273207-1a6e-4c6d-ac24-0c6b3793c8cd) [<https://perma.cc/H53M-LYJA>].

122. This Subpart borrows its framework and parts of its substance from an earlier article. *See* Asbury, *supra* note 14, at 302-07.

123. Fetal surgery has become increasingly common for the treatment of conditions such as myelomeningocele (a form of spina bifida), congenital fetal lung malformations, twin-twin transfusion syndrome, congenital diaphragmatic hernias, sacrococcygeal teratoma (a tumor that grows on the fetus’s tailbone). *See* Kathryn M. Maselli & Andrea Badillo, *Advances in Fetal*

delivery with an eye toward future medical interventions and raising a child with a potential disability.<sup>124</sup> Unlike obstetricians and other health care professionals—who are often minimally trained and inadequately prepared to counsel patients in this manner (though they often do)<sup>125</sup>—licensed genetic counselors are generally required to undergo two years of masters-level training designed to enable them to inform and counsel patients navigating their way through the numerous medical, ethical, and psychological issues at play in this realm.<sup>126</sup>

In accordance with prevailing norms of nondirectiveness, genetic counselors and others providing prenatal genetic counseling endeavor to avoid or downplay the social and political implications of the information they provide. They instead emphasize their technical competence<sup>127</sup> in an effort to maintain the objective and scientific character of their communications. Genetic counselors generally provide patients with raw data and risk factors to address their questions and concerns, followed by an individual and family health history where the information given to the counselor is “normatively organized by the counselor’s medical protocols.”<sup>128</sup> In this regard, counselors play a dual role, acting as both information-giver and counselor.<sup>129</sup>

Beyond these basic parameters, however, the manner in which genetic counseling plays out in practice varies considerably, as counseling must in each instance be tailored to a wide range of patient backgrounds and needs.<sup>130</sup> The combination of the counselor’s dual role and the cultural, religious, racial, intellectual, and economic diversity of the patient population produces a matrix of possibilities that renders it impossible to develop a single, generally-applicable set of best practices for administering counseling in a manner that is truly nondirective.

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*Surgery*, 4 ANN. TRANSL. MED. 394, 394 (2016). As will be discussed in the following Part, modern gene editing will allow for treatments at the embryonic stage—that is, before becoming a fetus.

124. Rachel Rebouché and Karen Rothenberg, *Mixed Messages: The Intersection of Prenatal Genetic Testing and Abortion*, 55 HOW. L.J. 983, 990 (2012); see also TROY DUSTER, BACKDOOR TO EUGENICS 69 (2d ed. 2003) (“The counselor primarily provides information, elaborates options, answers complicated genetic questions, explains risk figures and probabilities, and offers a measure of emotional support and understanding. The counselor, according to ideology, does not hint, cajole or try to influence in a direction that is against the indications of the counselee.”).

125. See Rebouché & Rothenberg, *supra* note 124, at 990.

126. See RAYNA RAPP, TESTING WOMEN, TESTING THE FETUS: THE SOCIAL IMPACT OF AMNIOCENTESIS IN AMERICA 56-57 (Routledge 1999).

127. DUSTER, *supra* note 124, at 79.

128. RAPP, *supra* note 126, at 63; see also *id.* at 64-68 (providing a generalized discussion of how prenatal genetic counseling sessions take place in practice).

129. DUSTER, *supra* note 124, at 83.

130. *Id.* at 172 (“On the one hand, each counseling session is a unique configuration of personal experience, of familial and peer pressures . . . of religious and spiritual beliefs . . . of connections of specific histories to the genetic disease . . . and, of course, the social and cultural meanings attached to each [disorder].”).

It should therefore come as no surprise that few parents experiencing prenatal genetic counseling find it to be neutral.<sup>131</sup> Despite counselors' intent and nondirective aspirations, "neutrality is virtually impossible" because "social values and priorities . . . are embedded in medical institutions and frameworks" and "insistence on impartiality can ultimately frustrate patients, some of whom want to receive expert advice from genetic practitioners."<sup>132</sup> The result has been that despite—or perhaps because of—due consideration of the individual needs and background of each patient, "most clients seeking genetic counseling in conjunction with predictive testing will be given directive counseling."<sup>133</sup>

Though direct recommendations to maintain or terminate the pregnancy are forbidden,<sup>134</sup> genetic counselors manage to steer their patients in a number of ways. When asked repeatedly, "What do you think I should do?"—an inquiry occurring on average over five times during each counseling session<sup>135</sup>—it becomes increasingly difficult for counselors to side-step the question and emphasize that it is the patient's personal decision.<sup>136</sup> Instead, counselors may "selectively reinforce" a patient's perceived inclination or general attitude,<sup>137</sup> "choose not to disclose certain information," or "suggest what [he or] she considers the 'most appropriate' course of action for the patient under the circumstances."<sup>138</sup>

This is not to fault genetic counselors entirely, for the circumstances under which prenatal genetic counseling must take place render true nondirectiveness all but impossible. Given the sheer volume of information that genetic counselors could convey to an expectant mother in the limited time they have together, a counselor necessarily must be selective as to which information she presents. In this regard, it is inevitable that the counselor's assumptions about the potential personal, economic, and social impacts of the information she might disclose<sup>139</sup> inform both the information she selects to include in a consultation and how she frames it.<sup>140</sup>

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131. See, e.g., Barbara A. Bernhardt, *Empirical Evidence that Genetic Counseling Is Directive: Where Do We Go from Here?*, 60 AM. J. HUM. GENETICS 17, 19 (1997); Susan Michie et al., *Nondirectiveness in Genetic Counseling: An Empirical Study*, 60 AM. J. HUM. GENETICS 40 (1997).

132. Alexandra M. Stern, *Eugenic Nation: Faults and Frontiers of Better Breeding in Modern America* 213 (Univ. of Cal. Press 2005).

133. Bernhardt, *supra* note 131, at 18.

134. STERN, *supra* note 132, at 213.

135. Bernhardt, *supra* note 131, at 17.

136. See RAPP, *supra* note 126, at 96–100.

137. Bernhardt, *supra* note 131, at 17.

138. Alan J. Belsky, *Injury As A Matter of Law: Is This the Answer to the Wrongful Life Dilemma?*, 22 U. BALT. L. REV. 185, 220–221 n.196 (1993) ("The counselor may well justify nondisclosure of certain diagnoses on the assumption that the parents, upon receipt of such information, may decide 'unreasonably' to abort the fetus.").

139. See DUSTER, *supra* note 124, at 82–83.

140. Bernhardt, *supra* note 131, at 18 ("Genetic counselors always have the power to influence clients by choosing to discuss one aspect of a situation while ignoring or downplaying another."). As one article summarized, "cultural, socioeconomic, educational, and ethical factors

Nonetheless, this selective presentation of information—coupled with the failure of many counselees to understand the information they are presented<sup>141</sup>—constitutes at minimum a failure to deliver the accurate, helpful, and neutral information prenatal genetic counseling strives to provide. And given the inherent challenges of nondirectiveness in practice, it makes perfect sense that prenatal genetic counseling is often perceived as directive<sup>142</sup>—albeit to varying degrees. These existing challenges notwithstanding, nondirective prenatal genetic counseling will only become more difficult as novel gene editing techniques to treat or avoid disease begin to emerge in the coming years. The following Subpart explains why.

### C. *Modern Gene Editing Makes Nondirectiveness Even Harder*

Despite its faults, prenatal genetic counseling currently has the luxury of focusing on the binary question of whether it is in an expectant mother's best interest to abort or maintain a pregnancy characterized by a fetal anomaly. But the promise of modern gene editing makes it all but certain that there will soon be a realistic third possibility—attempting to edit the fetus's genetic code in order to treat the condition either before or after birth. This third option will make nondirective prenatal genetic counseling even more difficult for at least three reasons.

First, there will be simply more information that could be presented to the expectant mother to help her reach a decision. Under current practices, prenatal genetic counselors should, during a relatively brief encounter, do their best to explain a) the basics of the indicated abnormality; b) the statistical probability that the fetus actually has it;<sup>143</sup> c) the potential presentations of the abnormality;<sup>144</sup> d) the fetus's spectrum of potential life outcomes (which can be considerable);<sup>145</sup> and

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significantly affect the way counselors describe genetic disorders *and their possible outcomes*.” Mark A. Rothstein & Sharona Hoffman, *Genetic Testing, Genetic Medicine, and Managed Care*, 34 WAKE FOREST L. REV. 849, 862 (1999) (emphasis added).

141. Regardless of which information counselors choose to present, there remains a no less important concern that expectant mothers often fail to grasp the limited information they do receive due to its complexity. Some patients, despite politely feigning understanding during the counseling session, later report that they could not follow all the words and diagrams being used to explain genetics and the risk of disorders. See RAPP, *supra* note 126, at 113. One study found that as many as 30% of counselees could not recall crucial risk figures that counselors presented during consultation. See PETER D. TURNPENNY & SIAN ELLARD, *EMERY'S ELEMENTS OF MEDICAL GENETICS* 268 (14th ed. 2011).

142. TURNPENNY & ELLARD, *supra* note 141, at 268 (noting that of couples attending genetic counseling, “approximately 50% have been influenced to some extent”).

143. See Asbury, *supra* note 14, at 300 (providing the example that out of 1,000 pregnancies, as many as forty will be “screen positive” for Down syndrome during first or second trimester fetal serum screening, only one of which will actually have the condition).

144. See *id.* at 301 (“[T]he vast majority of diagnosed prenatal genetic conditions are multivariate, can develop unpredictably, and are not fully understood, even by geneticists who have devoted their lives to studying them.”)

145. See, e.g., DUSTER, *supra* note 124, at 53 (highlighting children with sickle-cell anemia as

e) the potential social and psychological risks of terminating or maintaining the pregnancy.<sup>146</sup> Next-generation counselors will have to cover all of the above, but will also face the additional challenge of explaining a) what gene editing is; b) the potential risks—known and unknown, for both mother and fetus—of undergoing any gene editing procedure; and c) the likelihood that gene editing will be successful in treating the fetus's condition. Because genetic counselors under current conditions already tend to provide selective, biased, and incomplete information<sup>147</sup>—and because the information provided is frequently misunderstood<sup>148</sup>—the introduction of a new set of variables that genetic counselors could possibly articulate during counseling will inevitably make it far more difficult to facilitate truly informed reproductive choices. This will in turn make prenatal genetic counseling even less nondirective.

Second, because modern gene editing techniques are so new and their applications are evolving so quickly, genetic counselors will soon face the additional challenge of deciding under what circumstances it is appropriate even to broach the subject. Take, for example, a woman whose fetus has been diagnosed with sickle-cell disease or cystic fibrosis. The counselor must of course explain to her the nature of the disease, potential life outcomes and other factors, as per the ordinary practices of prenatal genetic counseling. But how should this counselor handle the fact that there are currently studies indicating that the most common forms of these conditions will likely be treatable through gene editing in as little as a few years?<sup>149</sup> Does the counselor have an obligation to tell her patient about these studies? Or should she perhaps be forbidden from doing so, focusing instead on currently existing methods of treatment, such as termination or potentially less successful medical interventions that could result in her child's having a painful or perhaps abbreviated life?

These questions become more complicated upon consideration of the fact that gene editing breakthroughs are taking place throughout the world, and are

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an example of disparate outcomes—some live a full life with minor symptoms, while others experience excruciating pain and die at an early age).

146. ELIZABETH RING-CASSIDY & IAN GENTLES, *WOMEN'S HEALTH AFTER ABORTION: THE MEDICAL AND PSYCHOLOGICAL IMPACT* 167 (2002) ("For an informed choice to be truly available pregnant women and their partners need to be told about the possible impact of abortion on them and their other children, and they also need to have information about the care of children with special needs."); Asbury, *supra* note 14, at 329 ("In addition to describing the challenges of raising a child born with a potential disability, caregivers should also explain that grief, depression, and post-traumatic stress are distinct possibilities should they choose to terminate.")

147. See Part II.B, *supra*.

148. See *supra* note 141 and accompanying text.

149. See, e.g., Gerald Schwank et al., *Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients*, 13 *CELL STEM CELL* 653 (2013) (demonstrating the effectiveness of CRISPR-Cas9 in treating cystic fibrosis patients); Mark A. DeWitt et al., *Selection-free Genome Editing of the Sickle Mutation in Human Adult Hematopoietic Stem/Progenitor Cells*, 8 *SCI. TRANSL. MED.* 360ra134 (2016) (describing the modification of stem cells from sickle-cell patients through use of CRISPR-Cas9).

subject to an array of regulatory schemes.<sup>150</sup> Should a counselor inform her patient that a doctor in China or Russia has successfully edited out an abnormality that her fetus is carrying, even if the procedure has been performed only once or twice, and never in the United States? Should her decision in this regard turn on her assessment of whether the patient will have the ability and desire to travel to China or Russia? What about an abnormality that is in most instances manageable without a genetic intervention, such as Beckwith-Wiedemann Syndrome (BWS)? Should BWS become treatable through gene editing either before or after birth, would it be appropriate for a counselor to discuss TALENs or CRISPR-Cas9 in the ordinary course of genetic counseling despite their potential risks and even though BWS is not incompatible with a high quality of life? One could imagine numerous other examples, but what is most important to take away here is that deciding whether to mention the possibility of editing out a genetic abnormality will often prove exceedingly difficult for genetic counselors given the evolving gene editing landscape and, more importantly, can itself be directive.<sup>151</sup>

Third, CRISPR applications that are soon likely to emerge raise fundamental questions about the ongoing wisdom of nondirective prenatal genetic counseling. Consider the case of a woman carrying a fetus with a genetic abnormality that can be rectified through CRISPR-Cas9 gene editing, where the procedure is proven to work in both laboratory and clinical settings, with minimal risks.<sup>152</sup> In such a scenario, it might no longer behoove the counselor—and it might no longer benefit the patient—to offer objective, nondirective information, rather than indicating that a CRISPR-based intervention is in the best interest of the fetus and mother. But as things currently stand, principles of nondirectiveness require that such an intervention be included as part of a menu of options (including abortion) rather than suggested or urged, even though a low-risk fix would be the best

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150. See Motoko Araki & Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing Into In Vitro Fertilization*, 12 REPROD. BIO. & ENDOCRIN. 108 (2014) (categorizing various national approaches to human germline gene modification, from banned (legislatively or through guidelines), to restrictive, to ambiguous).

151. This can happen in one of two ways. By not telling an expectant mother that a genetic intervention might be available, the counselor is steering her away from this option, toward either terminating her pregnancy or bringing the fetus to term with the expectation that her child will carry the abnormality for life. In this regard, she is not making a fully informed choice, and accordingly her counseling has been directive. Discussing all possible genetic interventions without regard to their efficacy or advisability, on the other hand, can act to nudge expectant mothers toward undergoing the procedure to “fix” their fetus. See Bret D. Asbury, “Backdoor to Eugenics? The Risks of Prenatal Diagnosis for Poor, Black Women,” 23 DUKE J. GEN. L. & POL’Y 1, 16 (2015) (describing how patients, especially pregnant women, tend to accept uncritically whatever genetic screening and testing modalities are available to them, which suggests that patients being offered the chance to undergo a genetic intervention on their fetus would be most often inclined to accept). This too can constitute a form of directiveness.

152. Hemophilia B could soon provide one such example. See Yuting Guan et al., *CRISPR/Cas9-Mediated Somatic Correction of a Novel Coagulator Factor IX Gene Mutation Ameliorates Hemophilia in Mouse*, 8 EMBO MOL. MED. 477 (2016) (describing the successful treatment of Hemophilia B in mice through use of CRISPR-Cas9 and noting that this study suggests this technique is a “feasible therapeutic strategy for hemophilia B” in humans).



course of action for most women. In this way, the emergence of CRISPR interventions that are proven to be simple and safe will result in novel and salient challenges to the very practice of nondirectiveness.

These three complications arising out of the emergence of modern gene editing—a sharp increase in the volume of information that could be conveyed in counseling sessions, the ever-changing landscape of potential gene editing applications, and the eventual normalization of CRISPR as a simple, safe medical intervention—illustrate how the ability to edit fetal genomes will further undercut prenatal genetic counselors' ability to adhere to nondirectiveness. And though pro-information legislation in the mold of the PPDCAA continues to emerge from the states in response to the current shortcomings of genetic counseling,<sup>153</sup> such legislation has been silent across the board with respect to providing access to information specific to gene editing. The following Part offers a vision for how prenatal genetic counseling should function in a post-CRISPR world as it attempts to abide by its nondirective aspirations, while at the same time giving due consideration to the social and financial ramifications of whatever information counselors provide.

#### IV. PRENATAL GENETIC COUNSELING IN THE ERA OF GENETIC INTERVENTION

The dilemma that prenatal genetic counseling will soon face should by now be clear: the already difficult decision of how best to counsel pregnant women nondirectively will become all the more challenging in a world in which gene editing can address prenatally diagnosed conditions. This Part explores how prenatal genetic counseling should adapt to this emergent reality. It sets forth its prescriptions against the backdrop of three organizing questions: 1) under what circumstances should counselors discuss therapeutic gene editing; 2) what role should legislation play in ensuring that pregnant women be made aware of the possibility of a genetic intervention; and 3) to what extent might it be appropriate medically, ethically, and financially to promote and subsidize access to such interventions. The following Subparts address these questions in turn.

##### A. *When and How To Discuss Genetic Interventions*

Prenatal genetic counselors face quite a challenge when taking on a new patient. In a very short period of time, they must assess their patient's needs and capacities, as well as provide them with a great deal of information<sup>154</sup> that should be helpful, but in no way directive.<sup>155</sup> And though a counselor's primary

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153. See *supra* notes 118-119 and accompanying text (noting that eighteen states have passed pro-information legislation in the past decade, seven of which have done so in the past three years).

154. See *supra* notes 143-146 and accompanying text (describing five categories of information that should be conveyed in a genetic counseling session indicated by the elevated risk of a fetal abnormality).

155. See *supra* notes 111-114 and accompanying text (describing genetic counseling's non-

contribution derives from her experience and expertise, the most successful counseling sessions are characterized by robust two-way communication,<sup>156</sup> where the counselor does not just talk at her client, but also listens carefully and receptively. In its best form, counseling should be iterative and repeated over a period of time,<sup>157</sup> allowing for patients to follow up with any additional inquiries as frequently and for as long as they would like before determining how best to proceed.

The reality, however, is that most counseling happens quickly, is largely one-sided, and provides little opportunity for follow-up questions or requests for clarification. Accordingly, rather than discuss what prenatal genetic counseling might look like in an ideal world,<sup>158</sup> this Subpart sets forth best practices for when and how prenatal genetic counselors should discuss gene editing under current norms and constraints. In this regard, there are two clear and important questions. First, given the constant growth in the number of genetic disorders that can or might soon be treatable through gene editing, under what circumstances is it appropriate for a genetic counselor to raise the possibility of a genetic intervention with her patient? Second, as the technology evolves and applications of therapeutic gene editing become more clearly established, should a genetic intervention ever be obligatory or routinely recommended, notwithstanding genetic counseling's nondirective aspirations?

With regard to the first question, the possible responses suggest a three-tiered taxonomy. To be sure, nondirectiveness and best practices suggest that hard and fast rules with respect to the contents of the counselor-patient conversation are to be discouraged, but in dealing with this novel question, some form of guidance seems appropriate. The first tier addresses scenarios in which the possibility of editing fetal genes to treat a prenatally diagnosed condition in humans is unproven or highly speculative. For example, there is current research in the discovery stage for treating Huntington's disease,<sup>159</sup> a fatal neurological disorder. Promising as this research might be, clinical applications for treating Huntington's disease genetically remain years away. In scenarios such as this one, where a genetic intervention is remote and might never come to fruition, medical professionals offering prenatal genetic counseling should not discuss gene editing, and should focus instead on the current binary of whether or not to terminate the pregnancy.

The second, middle scenario relates to genetic interventions that have been proven under some circumstances, but not necessarily in fetuses or embryos. HIV provides an illustrative example. Though no clinical trial using gene editing to

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directive aspirations and noting that it often fails in this regard).

156. Asbury, *supra* note 14, at 330.

157. See *id.*

158. For one vision of what this might look like, see *id.* at 327-33.

159. See, e.g., Hemi Malkki, *Selective Deactivation of Huntington Disease Mutant Allele by CRISPR-Cas9 Gene Editing*, 12 NATURE REVIEWS NEUROLOGY 614 (2016); see also HUMAN GENOME EDITING, *supra* note 12, at 71, 92-93 (noting that research on therapeutic gene editing in relation to treating Huntington's disease is in the discovery stage).

treat HIV has been completed,<sup>160</sup> there have been promising genetic treatments in adults.<sup>161</sup> It follows that when counseling a woman carrying a fetus with HIV, it is appropriate for a genetic counselor to refer to the possibility of a future genetic intervention as a means of treating the condition. She might well be unaware of the range of possible treatments for HIV, and in this regard a discussion of gene therapy fits well within the parameters of nondirective counseling that seeks to provide information rather than coerce.

The third scenario is the trickiest to conceptualize because its underlying scientific breakthroughs have yet to arrive. But it is not hard to imagine a world in which a particular fetal genetic intervention is both safe and effective, and likely in the best interest of most patients. Sickle-cell disease provides one such example because it is considered a straightforward target for CRISPR-Cas9,<sup>162</sup> there are already studies describing the successful modification of genes that cause sickle-cell disease,<sup>163</sup> and it is considered among the clearest examples of how gene editing can be applied to prevent or treat disease.<sup>164</sup> In the likely scenario that scientists are able to develop a safe and effective genetic treatment for sickle-cell disease, it would be irresponsible for a prenatal genetic counselor not to discuss it with a client whose fetus has this condition, and it should be beyond her discretion not to do so.<sup>165</sup> Obvious as this might sound, requiring genetic counselors to say or not say certain things while meeting with their clients is in tension with counselor autonomy and the aspiration of nondirectiveness. But as gene therapy moves from the fringes of human medicine to its mainstream, patients deserve to be made aware of instances where gene therapy can cure their fetus's disease.

This leads to the second important question, whether genetic interventions should ever be recommended, rather than merely described as an option (or not) during prenatal genetic counseling. Recommending gene therapy is clearly

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160. See HUMAN GENOME EDITING, *supra* note 12, at 70, 93.

161. See Eisenstein, *supra* note 66, at S8-S9 (describing successful efforts to treat HIV in humans through gene editing).

162. See Gewin, *supra* note 98, at S11.

163. See, e.g., DeWitt, *supra* note 149; Matthew C. Canver et al., BCL11A Enhancer Dissection by Cas9-Mediated in situ Saturating Mutagenesis, 527 Nature 192, 196 (2015) (“The work presented here offers a framework for therapeutic genome editing of the BCL11A enhancer for  $\beta$ -haemoglobin disorders” such as sickle-cell disease.).

164. HUMAN GENOME EDITING, *supra* note 12, at 69 (stating that sickle-cell disease is a “clear example[] of how genome editing might be applied to cure disease”).

165. The concern about the selective presentation of information as a means of providing directive counseling discussed in Part II.B is particularly salient with respect to new treatments, which are often expensive and require a special commitment from patients. Selective sharing of information based on assumptions about the patient has the potential to result in the nondisclosure of novel treatments such as gene therapy to poor women and women of color. See Asbury, *supra* note 151, at 15-18 (describing some of the challenges that medical professionals—be they doctors, nurses, or genetic counselors—face in connecting with nonwhite, less educated, and poor populations, particularly poor African Americans). This is one of many reasons it is worth mandating that all patients receive the same information about gene therapy as it becomes safe and effective in treating certain conditions, nondirective aspirations notwithstanding.

directive, and though clients ask their counselors for direct advice routinely,<sup>166</sup> the primary mission of prenatal genetic counseling is to empower women to make the best choice based on their needs and the most relevant information available, not to suggest how best to proceed. That said, it seems inevitable that we will soon reach the point at which practicing sound medicine will require that gene editing be a recommended treatment for at least some fetal abnormalities. Once there, though the ultimate decision whether to pursue gene editing will remain within the patient's sound discretion, the reality is that most women will abide by this recommendation.<sup>167</sup> This undoubtedly goes against the aim of nondirectiveness, and leads to the paradoxical conclusion that prenatal genetic counselors should be left out of discussing safe and effective gene therapies to treat prenatal genetic abnormalities (as opposed to gene therapies that are less proven). The alternatives would be either to abandon nondirectiveness in genetic counseling or to withhold direct recommendation of an intervention that is in the best interest of practically every patient.

In sum, genetic counselors should comfortably ignore gene editing interventions that are unproven or speculative (such as those relating to Huntington's disease) and exercise customary discretion in discussing potential genetic interventions in relation to conditions that have been successful in narrow circumstances (such as HIV). But with respect to conditions that are or will soon be routinely treatable through gene editing (such as sickle-cell disease), the decision whether or not to present gene therapy as a safe and prudent medical option should not rest within the discretion of genetic counselors. Instead, again assuming a high level of effectiveness, genetic interventions under these circumstances should be set forth as an attractive medical option by doctors or nurses unburdened by norms of nondirectiveness, rather than by prenatal genetic counselors encumbered by norms of neutrality.

### B. *Improving Legislation*

In addition to the above guidelines, legislation can also assist in ensuring that women carrying genetically anomalous fetuses receive gene editing information that might assist them in deciding whether to abort or proceed with their pregnancy. As noted above, eighteen states have passed some form of pro-information legislation, seven of which have done so in the past three years.<sup>168</sup>

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166. See *supra* note 135 and accompanying text.

167. Prenatal medicine is replete with examples of interventions that are ostensibly optional but become practically obligatory when indicated. See Asbury, *supra* note 151, at 16 (noting that "pregnant women offered various forms of prenatal testing or screening most often accept whatever modalities are offered, thinking that it is in the best interest of the fetus they are carrying.") The most prominent examples are chorionic villus sampling and amniocentesis. See Asbury, *supra* note 14, at 300 (noting that women learning of the possibility of a fetal abnormality most often undergo one of these forms of invasive testing despite the risk of miscarriage associated with each of them).

168. See *supra* notes 118-119 and accompanying text.

None of this legislation, however, mandates that women carrying genetically anomalous fetuses be made aware of the possibility of gene therapy in either the short- or long-term.

As CRISPR therapies having the potential to treat prenatally diagnosed conditions continue to evolve in the coming years, it is essential that states concerned about helping women make informed choices include possible genetic interventions among the information they provide. Despite the flurry of legislation in this area, no state currently ensures that this information be made available. This oversight can and should be addressed immediately.

Taking the legislation in Washington as an example, the necessary tweak is minor. Like several others, Washington's statute specifically addresses the provision of information to women who receive a prenatal or postnatal diagnosis of Down syndrome.<sup>169</sup> It requires that physicians providing such a diagnosis share with their patients certain information gathered under another statutory provision.<sup>170</sup> In addition to basic materials about Down syndrome and contact information for support services, the second statute requires that the resources made available to Washington women include information relating to "intellectual and functional development" of children born with Down syndrome and "therapy options."<sup>171</sup> Though depending on the medical team these "options" could well include gene therapy, given the novelty of CRISPR and other methods of modern gene editing, there is ambiguity as to whether they fall within

169. See WASH. REV. CODE ANN. § 18.71.250 (West 2016). Other states addressing their pro-information legislation specifically to Down syndrome include Ohio, Pennsylvania, Maryland, Delaware, Louisiana, and Massachusetts. See Asbury, *supra* note 14, at 316. More recently, Illinois, Maine, Nebraska, New Jersey, and Texas have also addressed pro-information legislation exclusively to Down syndrome. See 410 ILL. COMP. STAT. ANN. 511/15 (West 2015); ME. REV. STAT. ANN. tit. 22, § 1642 (2015); NEB. REV. STAT. ANN. § 71-4103 (West 2015); N.J. STAT. ANN. § 26:2-195 (West 2015); TEX. HEALTH & SAFETY CODE ANN. § 161.653 (West 2015).

170. See WASH. REV. CODE ANN. § 18.71.250 (West 2016).

171. See WASH. REV. CODE ANN. § 43.70.738 (West 2016). The statute provides in full:

- (1)(a) The department shall develop the following resources regarding Down syndrome:
- (i) Up-to-date, evidence-based, written information about Down syndrome and people born with Down syndrome that has been reviewed by medical experts and national Down syndrome organizations; and
  - (ii) Contact information regarding support services, including information hotlines specific to Down syndrome, resource centers or clearinghouses, national and local Down syndrome organizations, and other education and support programs.
- (b) The resources prepared by the department must:
- (i) Be culturally and linguistically appropriate for expectant parents receiving a positive prenatal diagnosis or for the parents of a child receiving a postnatal diagnosis of Down syndrome; and
  - (ii) Include: Physical, developmental, educational, and psychosocial outcomes; life expectancy; clinical course; and intellectual and functional development and therapy options.
- (2) The department shall make the information described in this section available to any person who renders prenatal care, postnatal care, or genetic counseling to expectant parents receiving a positive prenatal diagnosis or to the parents of a child receiving a postnatal diagnosis of Down syndrome.
- (3) For the purposes of this section, "Down syndrome" means a chromosomal condition that results in the presence of an extra whole or partial copy of chromosome 21.

Washington's legislative mandate. A simple revision of the language to read "therapy options, including any proven or emergent gene editing therapies" would ensure that Washington women receive the most current information available regarding the treatment of their fetus's genetic disorder.

### C. Ensuring Accessibility

The final question requiring consideration is to what extent it might be appropriate to subsidize access to genetic interventions to treat prenatally diagnosed conditions. This inquiry is distinct from the above questions relating to what information pregnant women should receive from their counselors or per statutory requirements, asking instead what support should be made available to women who would like to pursue gene therapy, but cannot afford it. Although reasonable people might disagree as to the level of support such women should receive, it is difficult to uncouple the putative right to be made aware of fetal gene therapy from the reality that some women will be unable to pursue it due to financial considerations. Indeed, it would be cruel to notify a pregnant woman that her fetus has a treatable genetic disorder (for example, sickle-cell disease), but because she cannot afford the five- or six-figure fee to treat it, her choices are either to terminate the pregnancy<sup>172</sup> or to bring the fetus to term knowing that it will have a painful life that could end prematurely.

Fortunately, providing support for prenatal genetic interventions can be justified both medically and financially, thereby sidestepping the ethical conundrum that arises from notifying a patient of a transformative therapy she cannot afford. Medically, a proven genetic intervention that treats or cures a condition is obviously desirable, so long as the gene editing is precise enough that it does not produce any off-target mutations. Part of what makes Mitalipov's breakthrough in August of 2017 so striking is that it reduced the error rate to a level previously thought to be impossible.<sup>173</sup> This level of precision suggests that there will soon be no medical reason to avoid treating disease through gene editing, and it will customarily be the best medical choice for nearly all patients.

Despite its relatively steep (though declining) cost,<sup>174</sup> gene editing can also be justified financially to the extent it is understood as a form of preventative care rather than a luxurious application of designer medicine. Long-term, it may well

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172. It bears repeating that such genetic terminations are associated with elevated rates of grief, depression, and post-traumatic stress. *See supra* note 15 and accompanying text.

173. *See* Connor, *supra* note 2 ("But Mitalipov and his colleagues are said to have convincingly shown that it is possible to avoid both mosaicism and 'off-target' effects, as the CRISPR errors are known.").

174. *See* David Warmflash, *Gene Therapy 2.0: Will CRISPR Make Expensive Treatment Available to All?*, GENETIC LITERACY PROJECT, (Aug 16, 2016), <https://www.geneticliteracyproject.org/2016/08/16/gene-therapy-2-0-will-crispr-make-expensive-treatment-accessible/> [perma.cc/PZ4J-SGYS] (noting that current gene therapy can cost as much as \$1,000,000, but the price of techniques such as CRISPR will be a fraction of that).

be cheaper to intervene in utero or soon after birth to treat or cure a disease in order to avoid a lifetime of medical costs. While it is unlikely given the current political climate that baseline coverage under the Affordable Care Act will be expanded to include gene editing to treat prenatally diagnosed conditions,<sup>175</sup> states retain the flexibility to set forth minimum levels of coverage as they deem fit.

There is already evidence that in the prenatal realm, the implementation of an elevated baseline of care can have a real and immediate impact. By way of example, California currently has perhaps the most robust genetic screening and testing program in the nation, covering not just ordinary blood tests and amniocentesis, but also more expensive interventions such as chorionic villus sampling and diagnostic ultrasound as well.<sup>176</sup> Due in large part to the breadth of California's coverage, roughly two out of three women there undergo some form of prenatal genetic screening, a rate far exceeding the national norm.<sup>177</sup> With strong, visionary leadership from statehouses throughout the country, gene therapy to treat fetal abnormalities can start down the path toward becoming an ordinary component of prenatal care, just as maternal checkups, amniocentesis, and, increasingly, newer methods of noninvasive prenatal diagnosis (which were once themselves considered too new, unproven, and expensive to be covered by insurance) are today.

As we move toward a world in which treating or curing disease through use of gene editing becomes increasingly common, one can only be wary of how this rapidly evolving landscape will translate to ordinary patients. This Part has attempted to show how prenatal genetic counseling can adapt to the emergent flood of treatment possibilities in a manner that pushes back against its propensity to shape choice directly and provides the information every woman carrying a genetically anomalous fetus deserves. While true nondirectiveness might remain ever elusive, states are increasingly reaching the conclusion that women learning of (at least some) fetal abnormalities should be made aware of certain basic information as they decide whether to abort or proceed with their pregnancy, separate and apart from what their genetic counselor chooses to tell them. That information, codified in state statutes across the country, should be clarified to include the possibility of genetic interventions where indicated. And as therapies

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175. "Maternity and newborn care" is one of the essential health benefits that all health insurance plans must provide under the Affordable Care Act. This has been construed to include "prenatal and postnatal care" in all 50 states. *See* Asbury, *supra* note 14, at 320-21. Though gene editing could reasonably be included as part of "newborn care" or "prenatal and postnatal care," this has not happened to date. The Affordable Care Act also contains a preventative care mandate that could also be construed so as to make coverage of genetic interventions to treat or cure prenatally diagnosed conditions a matter of right. *See id.* at 322-23. This too has yet to happen.

176. *See id.* at 325.

177. Henry T. Greely, *Get Ready for the Flood of Fetal Gene Screening*, 469 NATURE 289, 290 (2011) (noting that if women nationally opted for non-invasive prenatal genetic screening at the same rate as women in California, the United States would "move from conducting fewer than 100,000 fetal genetic tests a year to about 3 million").

continue to emerge, states should lead the way toward the normalization of gene therapy as a customary component of prenatal care. To be sure, all of the above turns on a great deal of speculation, but as the Mitalipov study shows, things are moving quickly. And it is better to be prepared for things to come than to maintain the status quo long after it makes sense to do so.

## V. CONCLUSION

Modern gene editing has altered the trajectory of biology, and its applications to plants, animals, the environment, and human beings continue to grow by the day. But with each scientific breakthrough, difficult questions emerge. This Article has set forth a vision for how the nascent ability to treat and cure fetal abnormalities through gene editing should inform prenatal genetic counseling of expectant mothers. Though this question remains theoretical for the time being, ZFNs, TALENs, and, most notably, CRISPR, have redefined the outer limits of what gene editing can achieve in just a few years. Despite being politically charged and subject to regulatory constraints, embryonic gene editing research will continue to move forward. As it does, the specter of the first genetically modified human being looms large—now a matter of when rather than if.

State and federal legislation intended to provide women carrying genetically anomalous fetuses with adequate information falls well short of addressing the needs of the next generation of mothers.<sup>178</sup> Genetic counseling, for its part, remains mired in debates surrounding nondirectiveness, even as all too often the information counselors provide is directive. As gene editing matures and begins to play more of a part in reproductive medicine, neither legislation nor genetic counseling shows much promise in delivering women the up-to-date, balanced, and helpful information they deserve. The hope of this Article is to help to turn the tide to ensure that reproductive choices after CRISPR are both fully informed and robustly supported each step of the way.

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178. As noted above, federal legislation has failed due to a lack of funding. *See supra* note 117 and accompanying text. State legislation has also failed for two reasons. First, though eighteen states have passed pro-information legislation, *see supra* notes 118-119, thirty-two states have not. Accordingly, women in most states must “rely on individual research and whatever information their health care providers deem appropriate in determining whether to proceed with their pregnancies.” Asbury, *supra* note 14, at 318. Second, among the eighteen states that do have pro-information legislation aimed at fetal abnormalities, a large majority (twelve) address their legislation exclusively to Down Syndrome. *Id.* at 316. *See supra* note 169. This means that there is no legislative requirement that up-to-date and potentially helpful information be shared with women carrying fetuses with any other abnormalities.