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Alexandra L. Foulkes

Takahiro Soda

Martilias Farrell

Paola Giusti-Rodríguez

Gabriel Lázaro-Muñoz

LEGAL AND ETHICAL IMPLICATIONS OF CRISPR APPLICATIONS IN PSYCHIATRY*

ALEXANDRA L. FOULKES,** TAKAHIRO SODA,*** MARTILIAS FARRELL,**** PAOLA GIUSTI-RODRÍGUEZ,***** GABRIEL LÁZARO-MUÑOZ******

Gene-environment interactions play a key role in how psychiatric disorders manifest and develop. Psychiatric genetics researchers are making progress in identifying genomic correlates of many disorders. And recently, the field of genetics has given rise to a technology that many claim will revolutionize the biological sciences and propel the field into a transformative phase: the powerful gene-editing tool known as CRISPR-Cas9. This Article illustrates which psychiatric conditions are likely to make attractive targets for CRISPR as the technology evolves and CRISPR therapies become viable tools to manage or prevent disorders in a clinical setting. We examine the potential scientific and clinical challenges of applying CRISPR in the mental health context, along with the regulatory, ethical, and legal issues that might arise as a consequence of these applications.

** Law Clerk to the Honorable Timothy D. DeGiusti, Federal District Court Judge for the Western District of Oklahoma. J.D., University of Houston Law Center. M.S. Neuroscience, University College London.

*** Child & Adolescent Psychiatry Fellow, University of North Carolina Hospitals. M.D., Harvard Medical School. Ph.D. Brain and Cognitive Sciences, Massachusetts Institute of Technology.

**** Research Assistant Professor, University of North Carolina at Chapel Hill, Department of Genetics. Ph.D. Pharmacology, University of North Carolina.

***** Research Assistant Professor, University of North Carolina at Chapel Hill, Department of Genetics. Ph.D. Cell and Developmental Biology, Harvard University.

****** Assistant Professor, Baylor College of Medicine, Center for Medical Ethics and Health Policy. Ph.D. Neuroscience, New York University. J.D., University of Pennsylvania School of Law. MBE (Bioethics), University of Pennsylvania Perelman School of Medicine.

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INTRODUCTION

Treating psychiatric disorders with the drugs and therapies developed to date has proved challenging. Psychotropic medications often aren't effective for patients,[1] who in turn have a hard time committing to rigorous and slow-acting treatment regimens.[2] But in addition to being notoriously hard to treat, psychiatric disorders are also well known for being highly heritable.[3] As such, a number of recent large-scale genetic studies have focused their efforts on psychiatric disorders,[4] and this innovative research has begun to unravel the science behind important genes and causal pathways.[5] Breakthroughs in genetics have made room for a potentially superior treatment option: the future application of gene-editing technologies for addressing the symptoms of psychiatric disorders.[6]

Ever since the elegant discovery of the double helix in 1953,[7] scientists have looked for ways to manipulate and design DNA.[8] As a consequence, gene-editing tools have actually been around for some time.[9] Yet it wasn't until the advent of "a simple, inexpensive, and

1. *See* Anita Kablinger, *Treatment Resistance: Challenges and Solutions*, PSYCHIATRIC TIMES (Sept. 1, 2007), http://www.psychiatrictimes.com/articles/treatment-resistance-challenges-and-solutions [https://perma.cc/R6NZ-UJXR].

2. *See, e.g.*, Annette Zygmunt et al., *Interventions to Improve Medication Adherence in Schizophrenia*, 159 AM. J. PSYCHIATRY 1653, 1653 (2002) ("Rates of medication nonadherence among outpatients with schizophrenia have been found to approach 50% during the first year after hospital discharge. The actual rate of nonadherence may be even higher . . . ." (footnotes omitted)).

3. Michael J. Gandal et al., *The Road to Precision Psychiatry: Translating Genetics into Disease Mechanisms*, 19 NATURE NEUROSCIENCE 1397, 1397 (2016).

4. *See id.* (discussing "more recent, large-scale genome-wide studies" of psychiatric diseases).

5. *Id.*

6. *See* Tom Ulrich, *Gene Sifting for Gene Snipping: GWAS as a Source of Gene Editing Targets*, VECTOR (Oct. 29, 2015), https://vector.childrenshospital.org/2015/10/gwas-as-a-source-of-gene-editing-targets/ [http://perma.cc/CT8P-GTF2]; *see also* Roni Dengler, *Major Mental Illnesses Unexpectedly Share Brain Gene Activity, Raising Hope for Better Diagnostics and Therapies*, SCIENCE (Feb. 8, 2018, 2:00 PM), https://www.sciencemag.org/news/2018/02/major-mental-illnesses-unexpectedly-share-brain-gene-activity-raising-hope-better [https://perma.cc/EJ8D-D484].

7. *See generally* J. D. Watson & F. H. C. Crick, *Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid*, 171 NATURE 737 (1953) (describing the authors' discovery of the structure of DNA).

8. *See* Brian Colwell, *Biotechnology Timeline: Humans Have Manipulated Genes Since the 'Dawn of Civilization,'* GENETIC LITERACY PROJECT (July 18, 2017), https://geneticliteracyproject.org/2017/07/18/biotechnology-timeline-humans-manipulating-genes-since-dawn-civilization/ [http://perma.cc/NJ43-9XHM].

9. *See* Jennifer A. Doudna & Emmanuelle Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*, 346 SCIENCE, no. 1258096, Nov. 28, 2014, at 1, 1, 2 fig.1.

remarkably effective genome engineering method"—known as CRISPR-Cas9 ("CRISPR")[10]—that biology was propelled into a transformative phase: CRISPR triggered a revolution.[11]

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats[12] and works like a pair of molecular scissors.[13] Scientists can direct CRISPR to a specific spot along an individual's DNA and have the molecular scissors make cuts in the gene sequence.[14] Therapeutically relevant changes can then be inserted.[15] As clinical trials using CRISPR systems to target specific conditions are slated to start around the world, a debate has sparked on the legal and ethical implications of CRISPR technology.[16] Certainly, a prudent look to the potential niches in psychiatry where CRISPR systems may prove useful requires giving some attention to the legal and ethical issues that might arise. This is particularly so given the incendiary past of the American legal discourse on the intersection of psychiatric disorders and genetic modification.[17]

This Article argues that while applications of CRISPR in psychiatry may not be imminent, these applications are no longer improbable hypotheticals. And where applications in psychiatry may well exist in the near future, there are important legal and ethical concerns that warrant careful consideration. This Article will proceed in three parts. Part I serves as an overview of CRISPR technologies,

10. David Baltimore et al., *A Prudent Path Forward for Genomic Engineering and Germline Gene Modification*, 348 SCIENCE 36, 36 (2015). Although the terms CRISPR-Cas9 and CRISPR are used interchangeably, CRISPR-Cas9 is a system that incorporates "CRISPR," which are the repeat sequences frequently observed in single-celled organisms. *See Questions and Answers About CRISPR*, BROAD INST., https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/questions-and-answers-about-crispr [https://perma.cc/LM4S-MG92].

11. *See* Doudna & Charpentier, *supra* note 9, at 1.

12. DAVID P. CLARK & NANETTE J. PAZDERNIK, MOLECULAR BIOLOGY 573 (2d ed. 2013).

13. *See* Andrea Ramirez, *Editing the Book of Life with Molecular Scissors*, NIH: NAT'L HUM. GENOME RES. INST. (Apr. 3, 2013), https://www.genome.gov/27553432/editing-the-book-of-life-with-molecular-scissors/ [http://perma.cc/R2HJ-5R77]. The Cas9 in CRISPR-Cas9 refers to certain genes that are associated with important repeated sequences, known as *Cas* genes. *Cas* genes, including *Cas9* genes, produce the nuclease scissor proteins that scientists have used to design genome-editing tools that cut into human DNA. This is explained in more detail below. *See infra* Section I.A.

14. *See* Ramirez, *supra* note 13.

15. *See id.*

16. *See, e.g.*, E. Rodriguez, *Ethical Issues in Genome Editing Using CRISPR/Cas9 System*, 7 J. CLINICAL RES. & BIOETHICS, no. 1000266, Mar. 24, 2016, at 1, 2–3.

17. For example, in *Buck v. Bell*, 274 U.S. 200 (1927), Justice Holmes concluded with the unfortunate remark: "Three generations of imbeciles are enough." *Id.* at 207. For a short description of the facts and holding of *Buck*, see *infra* note 150.

skimming the surface of the relevant science, placing CRISPR systems in their historical context, and evaluating regulatory frameworks currently in place. Part II focuses on CRISPR and its potential uses in psychiatry, identifying where the technology might be most immediately applied. Part III addresses the legal, ethical, and policy challenges that arise from the application of CRISPR in a psychiatric context.

I. CRISPR TECHNOLOGIES: AN OVERVIEW

A. A Brief Introduction to the Science

DNA serves as a blueprint for all of an organism's characteristics and traits after birth: it is the instructions—a set of plans—for building a body.[18] A chain of DNA is made up of building blocks, small molecules called nucleotides.[19] These nucleotides string together to form different sequences that code for certain messages, and these different message sequences are referred to as genes.[20] The sum total of an individual's DNA—the collection of all of a person's genes—is referred to as a genome.[21] Scientists have been modifying organisms' genomes for some time, and recently these technologies have become highly effective.[22]

To understand gene-editing technologies, it's helpful to have a grasp on how scientists cut and repair DNA. Nuclease is a protein[23]

18. RICHARD DAWKINS, THE SELFISH GENE 23 (1976). Although a simple way to understand DNA, if taken literally this analogy is not precise. Genes alone do not serve as a blueprint, but rather the genetic blueprint has downstream effects, such as the interactions between different genes, that ultimately dictate how a body develops. *See* Bora Zivkovic, *BIO101—From Genes to Traits: How Genotype Affects Phenotype*, SCI. AM.: BLOG AROUND THE CLOCK (Sept. 17, 2011), https://blogs.scientificamerican.com/a-blog-around-the-clock/bio101-from-genes-to-traits-how-genotype-affects-phenotype [http://perma.cc/8CN4-4FRH].

19. DAWKINS, *supra* note 18, at 23. There are only four different nucleotides that make up DNA: Adenine, Thymine, Cytosine, and Guanine. *See id.* For an accessible explanation of the building blocks of DNA, see Bozeman Science, *What Is DNA?*, YOUTUBE (Dec. 7, 2011), https://www.youtube.com/watch?v=q6PP-C4udkA [http://perma.cc/Q8JF-4H5N].

20. *See DNA, Genes and Chromosomes*, U. LEICESTER, https://www2.le.ac.uk/projects/vgec/highereducation/topics/dna-genes-chromosomes [https://perma.cc/7YPE-B5CE].

21. *What Is a Genome?*, NIH: GENETICS HOME REFERENCE, https://ghr.nlm.nih.gov/primer/hgp/genome [http://perma.cc/B5PJ-54R5] (last updated Apr. 30, 2019).

22. *See* Baltimore et al., *supra* note 10, at 36.

23. All proteins are the product of gene sequences. For a quick and accessible explanation of protein synthesis, see Yourgenome, *From DNA to Protein—3D*, YOUTUBE (Jan. 7, 2015), https://www.youtube.com/watch?v=gG7uCskUOrA [http://perma.cc/5QY6-T3GQ].

that functions like the equivalent of molecular scissors.[24] Scientists can direct nuclease scissors to an exact spot among the billions of nucleotides making up a DNA sequence, and the nuclease will cut out a part of the DNA chain.[25] This cut can be repaired by either allowing the loose ends to join back together or by having the CRISPR system insert a new designer DNA segment to replace the piece cut out by the nuclease.[26]

Thanks to advances in DNA sequencing and genome-wide association studies ("GWAS"),[27] scientists now have more information about which DNA segments influence the development of disease.[28] The information gathered by GWAS can be applied through CRISPR technologies. As previously noted, CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats.[29] These repeats are distinct sequences of nucleotides, frequently observed in the DNA of single-celled organisms like bacteria.[30] Certain genes are associated with these repeated sequences, and these genes are known as *Cas* genes.[31] *Cas* genes, including the *Cas9* gene, produce the nuclease scissor proteins ("Cas proteins") that scientists use to design genome-editing tools that cut into human DNA.[32]

The Cas protein is one of two main components making up an engineered CRISPR system.[33] The second is known as a guide RNA. A guide RNA is a short synthetic RNA sequence that includes a

24. *See* Ramirez, *supra* note 13.

25. *Id.* We have simplified the description of the process so as to make it more accessible to a broader audience. The science behind CRISPR's mechanisms is much more complicated, and the excision language we have employed is far too cursory to adequately convey the nuances involved. Most of the time, CRISPR nucleases either make a double-stranded break or a nick in one strand. An excision needs two breaks, and even then, the excision really isn't a result of the molecular scissors: it's the DNA repair machinery deleting the intervening DNA. For a detailed explanation of CRISPR mechanisms as currently understood, see generally Samuel H. Sternberg & Jennifer A. Doudna, *Expanding the Biologist's Toolkit with CRISPR-Cas9*, 58 MOLECULAR CELL 568 (2015).

26. Ramirez, *supra* note 13.

27. In GWAS, scientists look at the genomes of a large number of afflicted individuals and find small variations that occur repeatedly in the genes of these individuals but don't appear in the genomes of nonafflicted individuals. *See Genome-Wide Association Studies Fact Sheet*, NIH: NAT'L HUM. GENOME RES. INST. (Aug. 27, 2015), https://www.genome.gov/20019523/ [http://perma.cc/DQ5J-ABG5].

28. *See* Baltimore et al., *supra* note 10, at 36.

29. CLARK & PAZDERNIK, *supra* note 12, at 573.

30. *Id.*

31. Philippe Horvath & Rodolphe Barrangou, *CRISPR/Cas, the Immune System of Bacteria and Archaea*, 327 SCIENCE 167, 167 (2010).

32. *See id.*

33. *CRISPR Guide*, ADDGENE, https://www.addgene.org/crispr/guide/ [http://perma.cc/X6A6-93AL].

sequence necessary for Cas-binding—a scaffold sequence—and a user-defined sequence that directs the CRISPR system to its genomic target.[34] This means one can change the genomic target of the Cas protein by simply changing the guide RNA's protein sequence.

Although CRISPR is the most effective and accessible method of genetic engineering available today, CRISPR was not the first gene-editing tool developed.[35] Other technologies targeting similar goals have been around for several decades.[36] Yet CRISPR is being championed as a technique that promises to revolutionize medicine where previous attempts have failed.[37] Technologies such as zinc finger nucleases ("ZFNs"), Transcription Activator-Like Effector Nucleases ("TALENs"), and mega-nucleases have seen some success.[38] But these technologies have yet to alter the landscape of modern medicine in the way CRISPR proponents have promised.[39]

B. CRISPR's Precursors: Previous Attempts at Achieving the Same Functionality

Gene-editing tools that predate CRISPR all share the same mechanism of action—they are all nucleases that create breaks at specific locations in DNA.[40] The most important characteristic of a nuclease, as it relates to medical gene editing, is the programmability of the molecular scissors[41]—that is, the relative ease with which scientists can design and produce a molecular scissor that will cut the

34. *Id.* "RNA is one of the three major biological macromolecules that are essential for all known forms of life (along with DNA and proteins)." *What Is RNA?*, RNA SOC'Y, https://www.rnasociety.org/about/what-is-rna/ [http://perma.cc/6FYH-YHP6].

35. *See* Doudna & Charpentier, *supra* note 9, at 1. In essence, "gene editing" connotes the use of a tool that can alter or even correct DNA and has effectively come to succeed the term "genetic engineering." John J. Mulvihill et al., *Ethical Issues of CRISPR Technology and Gene Editing Through the Lens of Solidarity*, 122 BRIT. MED. BULL. 17, 18 (2017).

36. *See* Doudna & Charpentier, *supra* note 9, at 1.

37. *See, e.g.*, Jacob S. Sherkow, *CRISPR, Patents, and Public Health*, 90 YALE J. BIOLOGY & MED. 667, 667 (2017) ("CRISPR has the potential to revolutionize medicine.").

38. *See* Doudna & Charpentier, *supra* note 9, at 1.

39. *See id.*

40. *See* Rasmus O. Bak, Natalia Gomez-Ospina & Matthew H. Porteus, *Gene Editing on Center Stage*, 34 TRENDS GENETICS 600, 600 (2018).

41. *See* Tuhin Kumar Guha, Alvan Wai & Georg Hausner, *Programmable Genome Editing Tools and Their Regulation for Efficient Genome Engineering*, 15 COMPUTATIONAL & STRUCTURAL BIOTECHNOLOGY J. 146, 147 (2017) (addressing the importance of programmability, given that "[o]ne crucial concern when applying these genetic editing tools is the potential of cleavage at non-targeted sites," which "can be lethal or generate undesirable mutations").

DNA at the desired location.[42] To place the utility of CRISPR in some context, two of CRISPR's precursors are described here in detail: ZFNs and TALENs.

ZFNs are one of the earliest popularized attempts at site-specific nuclease targeting.[43] Researchers combine the scissor component found in one protein, nonspecific *Fok*I endonuclease domain,[44] and the DNA-targeting component of another protein, a zinc finger protein, to create programmable DNA scissors.[45] Zinc fingers get their name from a particular sequence of amino acids. When these amino acids come together with a zinc ion, they can bind to a specific sequence of DNA three basepairs long.[46] To target a longer DNA segment, scientists put more zinc fingers together. For example, targeting eighteen basepairs of DNA would require six zinc fingers.

In order to target any particular DNA sequence, researchers had to develop a zinc finger for each of the sixty-four possible DNA basepair triplets.[47] Because of these complexities and others, creation of ZFN constructs has proven difficult.[48] Despite the associated challenges, ZFNs are some of the oldest and most studied designer nucleases available and are the focus of recent clinical trials.[49]

TALENs use the same architecture as ZFNs. With TALENs, the scissor component is fused with a different type of DNA-binding component: the transcription activator-like effector ("TALE").[50] These DNA-binding elements are different from zinc fingers in that their DNA-binding domains each recognize a single basepair of

42. *See id.*; *see also* Srinivasan Chandrasegaran & Jeff Smith, *Chimeric Restriction Enzymes: What Is Next?*, 380 BIOLOGICAL CHEMISTRY 841, 847 (1999) ("Many of the difficulties associated with gene therapy are likely to be overcome if one could insert the corrected version of the mutation at the precise location of the genetic defect within the genome . . . . Current gene therapy vectors lack the requisite sequence specificity necessary for the targeted correction of the defective site within the genome.").

43. *See* James Gallagher, *First Gene-Editing in Human Body Attempt*, BBC NEWS (Nov. 16, 2017), https://www.bbc.com/news/health-42009929 [http://perma.cc/C34W-P93G] (discussing the first attempt at gene editing in human cells, which was done using ZFNs).

44. *See* Chandrasegaran & Smith, *supra* note 42, at 843.

45. *Id.* at 844.

46. *Id.* at 843 ("[E]ach finger interacts with a base pair triplet within the DNA substrates.").

47. *See id.*

48. *See* Doudna & Charpentier, *supra* note 9, at 1.

49. *See, e.g.*, *Ascending Dose Study of Genome Editing by Zinc Finger Nuclease Therapeutic SB-FIX in Subjects with Severe Hemophilia B*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT02695160 [http://perma.cc/CK2K-PTXX] (last updated Feb. 12, 2019).

50. Michelle Christian et al., *Targeting DNA Double-Strand Breaks with TAL Effector Nucleases*, 186 GENETICS 757, 757 (2010).

DNA,[51] as opposed to the zinc fingers' three basepairs. Thus, it is simpler to design a TALEN that recognizes a specific eighteen-basepair sequence of DNA. Due to the nature of each DNA-binding element, however, TALENs are difficult to build using available molecular biology techniques—a technical hurdle that has stifled TALEN adoption.[52]

In contrast, the CRISPR system provides a high degree of DNA sequence specificity and programmability.[53] The relative ease of design and production of the CRISPR components is the primary feature that separates this system from its precursors and has caused a renewed interest and enthusiasm in medical gene editing.

C. The Legal and Ethical Legacy of Previous Attempts and Their Implications

Because CRISPR is not the first attempt at gene editing, at first blush, it seems as though many of the ethical issues raised by CRISPR are equivalent to those that surfaced several decades ago.[54] Given the previous attempts at achieving therapeutic outcomes by means of gene editing, a vast body of literature exists addressing important legal and ethical issues that arise in the context of genetic modification.[55] As such, a framework of general principles governing the rules for human gene editing already exists. This framework is worth considering as a foundation to any dialogue on the ethical implications of new gene-editing technologies.[56]

Early gene-therapy clinical research resulted in serious adverse events.[57] But it wasn't until the death of Jesse Gelsinger, a young

51. *See id.*

52. *See* Thomas Gaj, Charles A. Gersbach & Carlos F. Barbas III, *ZFN, TALEN, and CRISPR/Cas-Based Methods for Genome Engineering*, 31 TRENDS BIOTECHNOLOGY 397, 399 (2013).

53. *See id.* at 402.

54. *See, e.g.*, Mulvihill et al., *supra* note 35, at 17–18 ("We see no new ethical issues, compared with gene therapy and genetic engineering in general, apart from the explosive rate of findings.").

55. *See* Eric T. Juengst, *Crowdsourcing the Moral Limits of Human Gene Editing?*, HASTINGS CTR. REP., May–June 2017, at 15, 15 ("On the whole, [the Committee on Human Gene Editing's] report [authored in response to the success of CRISPR/Cas9 systems] builds reassuringly on what has come before and underscores that there are precedents, arguments, and well-accepted general principles to turn to in framing the 'rules' for human gene editing.").

56. *See id.* ("[T]he report also provides a great primer on the science and regulatory landscape of gene editing, and it reviews some of the key points from the debates over human germ-line and enhancement interventions to date.").

57. *See* Theodore Friedmann, *Principles for Human Gene Therapy Studies*, 287 SCIENCE 2163, 2163 (2000). Most notable is the death of eighteen-year-old Jesse Gelsinger

patient enrolled in a gene-therapy clinical trial, that a great number of these adverse events became public.[58] Important, though not unique to gene editing, is the fact that preclinical data cannot reveal all possible adverse outcomes. And so, as with any highly experimental treatment involving severely ill patients, human trials yield unexpected and unintended results.[59] The need for a more thorough understanding of the science and effects of the applications of gene editing in humans was criticized as a limitation of early technologies.[60] It remains a concern of the scientific community in the face of CRISPR's clinical applications.

It is critical that safety information regarding new technologies is made readily available.[61] As early mishaps in gene-therapy clinical trials have taught us, the lack of public awareness of safety problems impairs not only the ability of researchers to inform subjects of potential risks but also their ability to design safe studies. That is, when clinical research sites fail to report adverse events, other research sites cannot adjust their protocols and informed consent

who had been diagnosed with ornithine transcarbamylase deficiency. *Id.* Gelsinger is thought to have died as a result of an experimental gene-therapy clinical trial. *Id.* For a poignant account of Gelsinger's death, see generally Paul L. Gelsinger, *Uninformed Consent: The Case of Jesse Gelsinger*, *in* LAW AND ETHICS IN BIOMEDICAL RESEARCH: REGULATION, CONFLICT OF INTEREST, AND LIABILITY 12 (Trudo Lemmens & Duff R. Waring eds., 2006).

58. LORI B. ANDREWS, MAXWELL J. MEHLMAN & MARK A. ROTHSTEIN, GENETICS: ETHICS, LAW AND POLICY 405–06 (2002). Due to a long-standing Food and Drug Administration ("FDA") policy stating that adverse events are considered trade secrets and thereby need not be disclosed to the public, the adverse events that had been reported to the FDA were never disclosed. *Id.*; *see also* 21 C.F.R. §§ 601.50–.51 (2018). *But see id.* § 601.50(c) (stating that "[n]otwithstanding the provisions of § 601.51, the [FDA] shall disclose upon request to an individual on whom an investigational biological product has been used a copy of any adverse reaction report relating to such use"). And since the NIH did have a policy to make public adverse events reported to the agency, investigators failed to report their findings. ANDREWS ET AL., *supra*, at 406. Only thirty-nine serious adverse events had been reported to the NIH before Gelsinger's death. *Id.* Six hundred ninety-one reports streamed in afterward. *Id.*

59. *See id.* It is also important to note that scientists' depth of understanding of the pharmacokinetics and mechanisms for gene-editing technologies does not match the understanding that usually accompanies a potential new drug. *Id.* That is, scientists usually know a lot more about a new pharmacological agent up for FDA approval than they know about the mechanisms at play when gene-editing technologies are applied. There is also the possibility that modifications intended to target somatic cells may have unintended effects on the germline, which poses implications for how to manage enrolling patients of reproductive age into clinical trials. *See* Nancy M.P. King, *Accident & Desire: Inadvertent Germline Effects in Clinical Research*, HASTINGS CTR. REP., Mar.–Apr. 2003, at 23, 23.

60. *See generally* Friedmann, *supra* note 57 (discussing the lessons learned from adverse gene therapy studies and "reexamin[ing] the principles that constitute the foundation of clinical research in gene therapy").

61. *See* ANDREWS ET AL., *supra* note 58, at 406.

procedures based on the new information and may overlook important patterns in their patients' reported side effects. Likewise, patients cannot have a full understanding of the risks and benefits the research entails.[62] To safeguard against information deficiencies, commentators have proposed optimizing informed consent procedures to protect patient interests.[63] Additionally, they have suggested that the monitoring of clinical trials needs improvement.[64]

To be sure, previous attempts at genetic modification have generally underdelivered on lofty promises of profound benefits.[65] CRISPR technology, however, may finally find its way into the successful clinical applications that eluded all others. CRISPR is different: it's cheaper, easier to use, and developing at a much faster pace than its technological predecessors.[66] Also, its mechanism promises results that sound highly desirable: a simple process that can precisely target and cut out an undesirable mutation, replace it with a "normal" DNA sequence, and then zip the repaired DNA back up again.[67] But the assumption that CRISPR can be used therapeutically oversimplifies and understates the complexities of translating basic scientific research into a clinical setting. As before, part of the ethical challenge accompanying the introduction of CRISPR technologies into a clinical setting is divorcing hype from reality.[68]

We begin by identifying those areas of psychiatry in which CRISPR may find more immediate application and go on to address the legal and ethical implications unique to the applications of

62. *See id.* Incidentally, the FDA proposed a regulation that would have amended the biological licensing application and provided for the public disclosure of investigational new drug safety reports. *See* Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation, 66 Fed. Reg. 4688, 4688 (proposed Jan. 18, 2001). But the FDA eventually withdrew the proposed rule. *See* Withdrawal of Two Proposed Rules, 81 Fed. Reg. 79,400, 79,400 (Nov. 14, 2016) (withdrawing the proposed regulation because the FDA believed the concerns were outdated).

63. *See, e.g.*, Friedmann, *supra* note 57, at 2163, 2165; *see also* Gail E. Henderson et al., *Therapeutic Misconception in Early Phase Gene Transfer Trials*, 62 SOC. SCI. & MED. 239, 250–52 (2006) (proposing a novel method to manage the expectations of patients enrolling in early phase clinical trials and calling for investigators to describe the potential benefits of these trials realistically to patients who viewed them as their last hope).

64. Friedmann, *supra* note 57, at 2165. One of the most egregious findings of the FDA's investigations of early gene therapy trials was the fact that the investigators had serious and undisclosed conflicts of interest. *See* ANDREWS ET AL., *supra* note 58, at 405. They owned stock in the biotechnology company trying to monetize the gene therapy. *Id.*

65. *See* Juengst, *supra* note 55, at 15.

66. Evita V. Grant, *FDA Regulation of Clinical Applications of CRISPR-CAS Gene-Editing Technology*, 71 FOOD & DRUG L.J. 608, 632 (2016).

67. *See supra* Section I.A.

68. Mulvihill et al., *supra* note 35, at 19.

CRISPR in psychiatry.[69] Certainly, clinical applications of CRISPR technology for psychiatric disorders are ultimately distant goals.[70] After all, even if scientists are successful at modifying every gene potentially associated with a psychiatric disorder, the intervention's potential effects are still unknown. For example, even if genomes could be successfully edited to express the relevant proteins in nonpathogenic form, the impact of having lived years with pathogenic variants could have long-term downstream effects on the brain that limit the effectiveness of CRISPR interventions for reducing psychiatric symptoms.[71] Nevertheless, engaging in dialogue on the potential ethical and legal issues that might arise as these applications approach clinical realization is essential for preparing the scientific community to responsibly engage in the execution of CRISPR applications. This is especially true in the field of psychiatry, given the egregious history that exists at the intersection of psychiatry and the law.[72]

D. Regulating CRISPR: The Current Framework's Structure and Consequences

The enthusiasm for CRISPR and its possible applications are accompanied by questions as to how and to what extent the testing of CRISPR systems in humans should be regulated.[73] The Food and Drug Administration ("FDA"), housed within the Department of Health and Human Services ("DHHS"), is tasked with regulating technologies relating to drugs and biological products in accordance

69. *See infra* Section II.B, Part III.

70. *See infra* Part II.

71. *See infra* notes 163–64 and accompanying text.

72. *See infra* Section III.B.2.

73. Robert M. Califf & Ritu Nalubola, FDA, *FDA's Science-Based Approach to Genome Edited Products*, FDA VOICE (Jan. 18, 2017), https://perma.cc/X936-U9JJ, *reprinted in* Robert M. Califf & Ritu Nalubola, *FDA's Science-Based Approach to Genome Edited Products*, CHECK ORPHAN (Jan. 19, 2017), http://www.checkorphan.org/news/fda2019s-science-based-approach-to-genome-edited-products [https://perma.cc/C7H3-QDG7]; *see also* Preetika Rana, Amy Dockser Marcus & Wenxin Fan, *China, Unhampered by Rules, Races Ahead in Gene-Editing Trials*, WALL ST. J. (Jan. 21, 2018, 2:19 PM), https://www.wsj.com/articles/china-unhampered-by-rules-races-ahead-in-gene-editing-trials-1516562360 [https://perma.cc/WZ4S-GQ3Q (dark archive)]. Clinical trials using CRISPR technologies are already underway in China, where the regulation and oversight of clinical trials is different than the oversight in the United States. *See* Rana et al., *supra*. Chinese clinicians stated that the potential benefit of CRISPR technologies outweigh the benefit of more rigorous regulations: "Dr. Wu says he sees saving patients' lives as paramount. He began by testing [CRISPR] on three patients and has modified genes of more than a dozen. He says he is planning other trials with lung-cancer and pancreatic-cancer patients." *Id.*

with the Federal Food, Drug, and Cosmetic Act of 1938,[74] the Public Health Service Act of 1944,[75] and their subsequent amendments.[76] As with previous gene-editing tools, the FDA treats CRISPR in accordance with its 1998 guidance on human somatic cell therapy and gene therapy.[77] Gene-therapy products, including CRISPR systems, are currently regulated under the existing framework for biological products.[78] This means that CRISPR interventions have to undergo testing via clinical trials before obtaining FDA approval for clinical use.[79]

Once a CRISPR compound is developed and information about its potential toxic effects is gathered via animal research, the sponsor of the CRISPR compound must submit an Investigational New Drug

74. Federal Food, Drug, and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301–399(f) (2012)).

75. Public Health Service Act, ch. 373, 58 Stat. 682 (1944) (codified as amended at 42 U.S.C. §§ 201–300mm-61 (2012)); *see also* Statement of Policy for Regulating Biotechnology Products, 49 Fed. Reg. 50,878, 50,878 (Dec. 31, 1984) ("The administrative review of products using biotechnology is based on the intended use of each product on a case-by-case basis."). The proposed FDA regulation providing for the public disclosure of Investigational New Drug ("IND") safety reports for gene-therapy studies "marked the first time that the FDA proposed to adopt formal regulations specifically dealing with gene therapy" as separate from biotechnology more generally. ANDREWS ET AL., *supra* note 58, at 406.

76. Important for our purposes, FDA oversight covers public and private institutions. As Grant noted in her piece:

> This is especially important with respect to CRISPR-Cas technology, which is easy to use, widely available, and inexpensive. Private institutions such as fertility clinics, are capable of using it without reliance on federal funding. Hence, federal legislation may be ineffective if it prohibits only funding of specific research activities. FDA authority over private institutions allow[s] it to regulate the private sector in situations in which federal legislative prohibitions do not explicitly address.

See Grant, *supra* note 66, at 632.

77. *See generally* CTR. FOR BIOLOGICS EVALUATION & RESEARCH, FDA, GUIDANCE FOR INDUSTRY: GUIDANCE FOR HUMAN SOMATIC CELL THERAPY AND GENE THERAPY (1998), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm081670.pdf [https://perma.cc/M4W3-9VGH] (intending to "provide manufacturers with current information regarding regulatory concerns for production, quality control testing, and administration of recombinant vectors for gene therapy; and of preclinical testing of both cellular therapies and vectors"). The guidance defines a gene therapy as "a medical intervention based on modification of the genetic material of living cells. Cells may be modified *ex vivo* for subsequent administration to humans, or may be altered *in vivo* by gene therapy given directly to the subject." *Id.* at 3.

78. *Id.* at 4 ("IND applications for somatic cell and gene therapies should follow the same format and contain the same sections as IND's for any investigational biological product, as described in 21 CFR 312.23.").

79. *See id.* at 23.

("IND") application to the FDA.[80] An IND application includes information about the results of initial testing, the compound's composition and manufacturing, and a plan for how the sponsor intends to test the effects of the CRISPR compound on humans.[81]

As described above, the guide RNA is one of the two main components of an engineered CRISPR system.[82] The guide RNA component of the CRISPR system directs the system to its genomic target. Because a particular guide RNA is needed for a CRISPR system to reach a particular target, each system is theoretically useful for a very limited purpose. As such, FDA approval is sought—not for a generic CRISPR treatment applicable to all CRISPR systems, regardless of which guide RNA they contain, but rather for a discrete and specific CRISPR system.[83]

After the FDA determines that the proposed study will not place human subjects under unreasonable risk of harm, the CRISPR system must go through three stages of clinical trials.[84] First, the CRISPR

80. *See The Drug Development Process, Step 3: Clinical Research*, FDA (Jan. 4, 2018), https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm [https://perma.cc/36XJ-TKLC].

81. *See id.*

82. *See supra* notes 33–34 and accompanying text.

83. *See The Drug Development Process, Step 3: Clinical Research*, *supra* note 80. The fact that CRISPR systems composed of different guide RNAs have to be approved by the FDA independently has important consequences for potential off-label uses. Historically, the FDA has lacked the authority to regulate the practice of medicine. *See, e.g.*, Chaney v. Heckler, 718 F.2d 1174, 1179 (D.C. Cir. 1983) (noting that the legislative history of the Federal Food, Drug, and Cosmetic Act reflects congressional intent to prohibit the FDA from regulating the practice of medicine), *rev'd on other grounds*, 470 U.S. 821 (1985); David A. Kessler, *The Regulation of Investigational Drugs*, 320 NEW ENG. J. MED. 281, 285 (1989). The agency itself accepted this view. *See* Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) ("[I]t is clear that Congress did not intend the [FDA] to regulate or interfere with the practice of medicine . . . ."). It's the agency's lack of authority over the practice of medicine that allows physicians to prescribe drugs for uses that the agency has not approved without violating federal law. *See* Kessler, *supra*, at 285. For example, the FDA approved ketamine for the treatment of pain in the early 1970s. *See* Gigen Mammoser, *Ketamine Is Creating a New Wave of Drugs to Treat Depression*, HEALTHLINE (June 13, 2018), https://www.healthline.com/health-news/ketamine-creating-wave-of-drugs-to-treat-depression#1 [https://perma.cc/JQ5S-AM7Z]. But it wasn't until the year 2000 that ketamine's efficacy as an antidepressant was discovered. *Id.* Once early reports of ketamine's efficacy in treating depression surfaced, doctors began prescribing ketamine infusions to patients off-label. *Id.* This was before the FDA approved the drug for use as an antidepressant and, consequently, before clinical trials were able to uncover important safety and efficacy data. *Id.* Given that a CRISPR system containing a particular guide RNA is designed for a very specific target, off-label uses would be severely limited.

84. *See What Are the Types of Clinical Research?* (Jan. 4, 2018), FDA, https://www.fda.gov/ForPatients/ClinicalTrials/Types/default.htm [https://perma.cc/V8PY-

system must undergo Phase I trials. Phase I trials are conducted on healthy human volunteers.[85] During Phase II trials, investigators collect data on whether the CRISPR system actually works as intended.[86] Those enrolled in Phase II trials have been diagnosed with the condition the CRISPR system intends to treat.[87] Finally, large-scale Phase III studies are conducted. During these trials, between 300 and 3000 subjects diagnosed with the target condition are enrolled to gather more robust data on safety and effectiveness.[88] Only after all of those hurdles are successfully cleared will a CRISPR system obtain FDA approval for use in a clinical setting.

Previous attempts at developing clinical applications for gene-editing technologies drew critiques of the schemes implemented to regulate the drug approval process.[89] Commentators, reflecting on the early rounds of clinical trials researching gene-editing therapies, noted that the monitoring of clinical trials needs improvement—namely, more public disclosure and close collaboration between public regulatory agencies and specialized advisory boards.[90] These and other concerns remain valid in the face of upcoming CRISPR clinical trials.[91]

E48A] (noting that there are four phases of FDA trials but explaining that phase IV trials are "[p]ost-marketing studies, which are conducted *after* a treatment is approved for use by the FDA" (emphasis added)).

85. *See The Drug Development Process, Step 3: Clinical Research*, *supra* note 80. The number of people enrolled in phase I trials varies but usually falls between twenty and one hundred subjects. *Id.* The goal of this phase is to understand the most frequent side effects and the system's kinetics. *Id.*

86. *Id.* Phase II trials are placebo controlled, meaning some people who enter the trial receive treatment with the CRISPR system while others do not. Safety and short-term side effects are also evaluated. *See, e.g.*, *A Phase 2, Randomized, Placebo-Controlled, Multicenter Study to Investigate the Efficacy and Safety of Apremilast (CC-10004) for Treatment of Subjects with Active Ulcerative Colitis*, CROHN'S & COLITIS FOUND., http://www.crohnscolitisfoundation.org/research/participate-in-research/find-studies-and-clinical-trials/pda-study/Apremilast/a-phase-2-randomized-1.html [https://perma.cc/T77C-GWZM].

87. *The Drug Development Process, Step 3: Clinical Research*, *supra* note 80.

88. *Id.*; *see also* Eva Andermann et al., *Psychiatric and Cognitive Adverse Events: A Pooled Analysis of Three Phase III Trials of Adjunctive Eslicarbazepine Acetate for Partial-Onset Seizures*, 82 EPILEPSY & BEHAV. 119, 121 (2018) (illustrating that the number of patients enrolled into phase III trials is often in the hundreds).

89. *See* Friedmann, *supra* note 57, at 2165.

90. *Id.*; *see also* Grant, *supra* note 66, at 617 ("[The] FDA was slow to answer the call for regulation of . . . gene therapy.").

91. Recently, the FDA paused a CRISPR clinical trial slated to start in the United States and asked for more information to be included on the sponsor's IND application. *See* Rich Haridy, *FDA Hits Pause on One of the First US Human Clinical Trials to Use CRISPR*, NEW ATLAS (May 31, 2018), https://newatlas.com/us-crispr-human-trial-hold-fda/54862/ [https://perma.cc/8N4W-S3E9].

II. THE STATUS OF CRISPR FOR TREATING OR PREVENTING PSYCHIATRIC CONDITIONS

Concededly, none of the clinical trials applying CRISPR technologies slated to start in either the United States or abroad involve applications to psychiatric disorders. While advances in neuroscience over the past few decades have been tremendous, the field itself is still rather young. And clinical translations of neuroscience research into psychiatry have proven challenging.[92] CRISPR, however, offers unique insights into the underlying biology of psychiatric disorders and may have an important and imminent role to play in developing therapies for a particular subset of psychiatric conditions.

A. Review of Current Research in CRISPR Clinical Applications

As of today, CRISPR systems have been successfully used to induce genetic modifications in a number of different species, including rats,[93] mice,[94] pigs,[95] nonhuman primates,[96] and human cell lines.[97] But beyond CRISPR's successful modification of genes, experiments have recently confirmed that CRISPR technology can actually be used in the treatment of inherited diseases. CRISPR-induced modifications now have a targeted purpose and are used to achieve desired results. For example, CRISPR has successfully reintroduced normally functioning genes into the genome of a live animal, leading to the improvement of muscle function.[98] Similarly, CRISPR has been used to enhance liver function and induce changes

92. *See* John Horgan, *The Brain: The Final Frontier of Science*, GLOBE & MAIL (Mar. 29, 2018), https://www.theglobeandmail.com/technology/science/the-brain-the-final-frontier-of-science/article1038205/ [https://perma.cc/72DG-TEND].

93. *See* Benjamin Bakondi et al., In Vivo *CRISPR/Cas9 Gene Editing Corrects Retinal Dystrophy in the S334ter-3 Rat Model of Autosomal Dominant Retinitis Pigmentosa*, 24 MOLECULAR THERAPY 556, 556 (2016).

94. *See* Simona Valletta et al., ASXL1 *Mutation Correction by CRISPR/Cas9 Restores Gene Function in Leukemia Cells and Increases Survival in Mouse Xenografts*, 6 ONCOTARGET 44,061, 44,062 (2015).

95. *See* Luhan Yang et al., *Genome-Wide Inactivation of Porcine Endogenous Retroviruses (PERVs)*, 350 SCIENCE 1101, 1101 (2015).

96. *See* Zhuchi Tu et al., *Promoting Cas9 Degradation Reduces Mosaic Mutations in Non-Human Primate Embryos*, 7 SCI. REP., no. 42081, Feb. 3, 2017, at 1, 1.

97. *See generally* Zhao Zhang et al., *CRISPR/Cas9 Genome-Editing System in Human Stem Cells: Current Status and Future Prospects*, 9 MOLECULAR THERAPY: NUCLEIC ACIDS 230, 230 (2017) (highlighting "the basic biology and application of the CRISPR/Cas9 system in current human stem cell research").

98. Rodolphe Barrangou & Jennifer A. Doudna, *Applications of CRISPR Technologies in Research and Beyond*, 34 NATURE BIOTECHNOLOGY 933, 937 (2016).

in cholesterol metabolism in mice.[99] Further, CRISPR has also successfully corrected genetic mutations and achieved functional restoration of simple genetic conditions in animal models.[100]

In humans, a recently proposed clinical trial is looking to test the efficacy of a CRISPR system in cancer patients.[101] The researchers will edit the immune cells of the participants.[102] Scientists in China have successfully edited genes in human embryos, replacing a thalassemia-causing gene with its corrected form and achieving desired results.[103] U.S.-based companies have launched clinical trials for the application of CRISPR technologies to treat the β-thalassemia blood disorder.[104] Together, these applications suggest that CRISPR might be used successfully to correct human diseases arising from single-gene mutations, where the target is clear and the causal underpinnings of the disease are well understood.

Particularly in the context of psychiatry and neuropsychiatric diseases, CRISPR systems have been used to study the roles of different proteins in directing neurodevelopment so as to better understand the function of pathways that regulate genes and their expression.[105] Studies using CRISPR on genes implicated in Autism Spectrum Disorder ("ASD") have successfully induced changes in the size and morphology of mouse neurons.[106] And a study using CRISPR

99. *Id.*

100. *See generally* Nataša Savić & Gerald Schwank, *Advances in Therapeutic CRISPR/Cas-9 Genome Editing*, 168 TRANSLATIONAL RES. 15 (2016) (collecting examples of successful CRISPR applications in restoring function).

101. *See* Françoise Baylis & Marcus McLeod, *First-in-Human Phase 1 CRISPR Gene Editing Cancer Trials: Are We Ready?*, 17 CURRENT GENE THERAPY 309, 309 (2017).

102. *See id.* at 310.

103. *See* Ewen Callaway, *Embryo-Editing Research Gathers Momentum*, 532 NATURE 289, 290 (2016) (discussing Puping Liang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes*, 6 PROTEIN & CELL 363, 363 (2015)). Thalassemia is "an inherited blood disorder characterized by the presence of less hemoglobin and fewer red blood cells in your body than normal." *Thalassemia*, MAYO CLINIC (Nov. 2, 2016), https://www.mayoclinic.org/diseases-conditions/thalassemia/symptoms-causes/syc-20354995 [https://perma.cc/39ZX-X7ZK].

104. *A Safety and Efficacy Study Evaluating CTX001 in Subjects with Transfusion-Dependent β-Thalassemia*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT03655678 [https://perma.cc/S9DJ-9GJX] (last updated Feb. 4, 2019).

105. *See, e.g.*, Elizabeth A. Alcamo et al., *Satb2 Regulates Callosal Projection Neuron Identity in the Developing Cerebral Cortex*, 57 NEURON 364, 364 (2008).

106. *See, e.g.*, Eric Deneault et al., *Complete Disruption of Autism-Susceptibility Genes by Gene Editing Predominantly Reduces Functional Connectivity of Isogenic Human Neurons*, 11 STEM CELL REP. 1211, 1211 (2018) ("[P]resent[ing] a CRISPR gene editing strategy to insert a protein tag and premature termination sites creating an induced pluripotent stem cell (iPSC) knockout resource for functional studies of ten ASD-relevant genes . . . ."); Michael R. Williams et al., *A Retroviral CRISPR-Cas9 System for Cellular Autism-Associated Phenotype Discovery in Developing Neurons*, 6 SCI. REP., no. 25611,

to knock out genetic variants repeatedly associated with schizophrenia has helped scientists understand the impact of disease-relevant mutations.[107] Fragile X syndrome—thought to be the most common form of inherited intellectual disability—is caused by a known repeat in a specific gene.[108] This repeat causes certain changes to the genome.[109] Using CRISPR, scientists have deleted the nucleotide repeat known to cause Fragile X.[110] The deletion reversed some of the known harmful downstream consequences of the repeat sequence.[111]

B. CRISPR in Psychiatry: More Immediate Practical Applications

The state of the science reveals areas where CRISPR might find more immediate practical application. As noted above, preclinical findings of studies involving CRISPR systems suggest that the technology might be successfully used to correct human diseases arising from single-gene mutations, known as monogenic diseases.[112] There are certain conditions with psychiatric manifestations that are known to have monogenic causes and genetically defined symptoms.

The *Diagnostic and Statistical Manual of Mental Disorders* ("DSM-5")—the definitive manual used by psychiatrists and other mental health experts for the diagnosis and treatment of psychiatric disorders—devotes an entire section to neurocognitive disorders ("NCDs").[113] Most NCDs have an adult onset.[114] For many, there is a

May 10, 2016, at 1, 1 (concluding that the implementation of a CRISPR system is an efficient system for an Autism-associated phenotype discovery in wild-type animals).

107. *See* Matthew D. Rannals et al., *Psychiatric Risk Gene Transcription Factor 4 Regulates Intrinsic Excitability of Prefrontal Neurons via Repression of* SCN10a *and* KCNQ1, 90 NEURON 43, 43, 45 (2016).

108. X. Shawn Liu et al., *Rescue of Fragile X Syndrome Neurons by DNA Methylation Editing of the* FMR1 *Gene*, 172 CELL 979, 979 (2018).

109. *See id.* One of the changes that occurs is DNA methylation. Methylation is the process by which genes are turned "on" and "off." *See* Cath Ennis, *Epigenetics 101: A Beginner's Guide to Explaining Everything*, GUARDIAN (Apr. 25, 2014), https://www.theguardian.com/science/occams-corner/2014/apr/25/epigenetics-beginners-guide-to-everything [https://perma.cc/RF4F-ZVGG]. When genes are on, they produce proteins. *Id.*

110. *See* Chul-Yong Park et al., *Reversion of* FMR1 *Methylation and Silencing by Editing the Triplet Repeats in Fragile X iPSC-Derived Neurons*, 13 CELL REP. 234, 234 (2016).

111. *See id.*

112. *See supra* notes 93–104 and accompanying text.

113. *See* AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS 591–644 (5th ed. 2013) [hereinafter DSM-5]. "The NCDs are unique among DSM-5 categories in that these are syndromes for which the underlying pathology, and frequently the etiology as well, can potentially be determined. The various underlying

variation of the disorder that is inherited and for which a causative genetic mutation has been identified.[115]

One such example is noted above. Fragile X presents in humans when a single gene, known as the *FMR1* gene, shuts down. When a gene shuts down, it stops producing proteins.[116] In one study, scientists successfully applied CRISPR systems to remove the tags on the *FMR1* gene that are responsible for keeping the gene shut off.[117] As a result, the genes began producing proteins normally again, and once the edited cells were transferred into mice, the cells continued to produce proteins normally for a subsequent three months.[118] These results were astounding: the test achieved almost full restoration of normal protein expression levels of the *FMR1* gene.[119] This means that scientists may, in the not-so-distant future, be able to engineer a lasting solution for Fragile X syndrome.

Similar to Fragile X, Huntington's disease is also caused by a single, identifiable genetic mutation.[120] In cells from both animal models and humans, CRISPR was able to deactivate Huntington's defective gene with remarkable efficiency.[121] Clinical testing on Huntington's could be expected to start as early as five years from now.[122]

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disease entities have all been the subject of extensive research, clinical experience, and expert consensus on diagnostic criteria." *Id.* at 591.

114. *Major Neurocognitive Disorder in Adults*, MINDYRA, http://www.mindyra.com/solutions/adults/majorneurocognitivedisorder [https://perma.cc/LXH5-GVCG].

115. Some of the disorders that fall within this category are as follows: NCD due to Alzheimer's disease, NCD due to Parkinson's disease, NCD with Lewy Bodies, Frontotemporal NCD, and NCD due to Huntington's disease. DSM-5, *supra* note 113, at 591. For Huntington's disease in particular, the diagnosis is made by genetic confirmation of the causative genetic mutation. *Huntington Disease*, NIH: NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCI. (July 8, 2015), https://rarediseases.info.nih.gov/diseases/6677/huntington-disease/cases/18858 [https://perma.cc/E9RF-GLLF].

116. *See Fragile X Syndrome*, NIH: GENETICS HOME REFERENCE, https://ghr.nlm.nih.gov/condition/fragile-x-syndrome#genes [https://perma.cc/5L8R-APG5] (last updated Apr. 30, 2019).

117. *See* Liu et al., *supra* note 108, at 979.

118. *Id.* at 984–85.

119. *See id.* at 979.

120. Alex Mas Monteys et al., *CRISPR/Cas9 Editing of the Mutant Huntingtin Allele In Vitro and In Vivo*, 25 MOLECULAR THERAPY 12, 12 (2017).

121. *See id.* at 19–20. Increasing scientific evidence supports eliminating the distinction between psychiatric and neurological disorders. *See* P. D. White, H. Rickards & A. Z. J. Zeman, *Time to End the Distinction Between Mental and Neurological Illnesses*, 344 BRIT. MED. J., no. e3454, May 24, 2012, at 1,1.

122. Michael Eisenstein, *CRISPR Takes on Huntington's Disease*, NATURE (May 30, 2018), https://www.nature.com/articles/d41586-018-05177-y#ref-CR1 [https://perma.cc/4T47-YVVW].

CRISPR might also be more immediately applied to mitochondrial disorders with psychiatric phenotypes, such as Niemann-Pick disease. Niemann-Pick is a rare and life-threatening condition—frequently diagnosed in children during their elementary school years—in which cholesterol and other lipids are not properly metabolized within the cell.[123] The disease is sometimes referred to as "childhood Alzheimer's"[124] and has a known genetic cause.[125] There are currently no viable treatments or cures for Niemann-Pick,[126] but the disorder has been identified as one that might be among the first treated with CRISPR technologies.[127]

Wilson's disease is another particularly interesting target. This genetic disorder often presents with neuropsychiatric symptoms, but it primarily involves the liver.[128] Given that psychiatric symptoms can be these patients' chief complaint, a true diagnosis often eludes clinicians for some time.[129] It's the mutation of a single gene, *ATP7B*, that leads to Wilson's disease.[130] And the possibility of delivering gene therapy to the liver is much more tractable at this time than interventions targeting the brain directly.[131]

123. *Niemann Pick Disease Type C*, NAT'L ORG. FOR RARE DISORDERS, https://rarediseases.org/rare-diseases/niemann-pick-disease-type-c/ [http://perma.cc/B8W7-CW36].

124. Univ. of Pa., *Effective Treatment for Niemann Pick Type C Identified*, SCIENCEDAILY (Feb. 25, 2015), https://www.sciencedaily.com/releases/2015/02/150225151752.htm [http://perma.cc/T37F-U4MA].

125. Mary Gearing, *Treating Muscular Dystrophy with CRISPR Gene Editing*, ADDGENE BLOG (Jan. 26, 2016, 10:30 AM), https://blog.addgene.org/treating-muscular-dystrophy-with-crispr-gene-editing [http://perma.cc/688P-NB5U].

126. *See* Erica Peacock, *Gene Therapy: Bringing Hope to the Rare Disease Community*, RARE DISEASE REV. (Mar. 12, 2018), https://www.rarediseasereview.org/publications/2018/3/12/gene-therapy-bringing-hope-to-the-rare-disease-community [http://perma.cc/7QDM-SZNK].

127. *See* Gearing, *supra* note 125.

128. *Wilson Disease*, NIH: NAT'L INST. DIABETES & DIGESTIVE & KIDNEY DISEASES, https://www.niddk.nih.gov/health-information/liver-disease/wilson-disease [http://perma.cc/48QS-FZ3Z].

129. GEORGE J. BREWER, WILSON'S DISEASE: A CLINICIAN'S GUIDE TO RECOGNITION, DIAGNOSIS, AND MANAGEMENT 4 (2001).

130. *Id.* at 139.

131. As noted above, it is important to keep in mind that, although a single gene may be involved in the etiology of these conditions, there may be multiple causative mutations within that single gene.

C. *Likelihood of CRISPR Applications to Polygenic Psychiatric Disorders*

With technology as it currently stands, targeting psychiatric disorders caused by multiple genes—polygenic conditions[132]—is a distant reality. To be sure, recent preclinical studies have managed to enhance CRISPR's target specificity and use certain CRISPR systems containing multiple guide RNAs to target many genes at once—a task known as multiplexing.[133] But because of the complicated and largely unknown genetic architecture of polygenic psychiatric disorders, along with the effects of complex epigenetic processes for which we still can't account, CRISPR clinical applications in this area aren't likely an imminent reality. Even if CRISPR were shown to be efficacious in a clinical setting, the editing targets for most psychiatric disorders—certainly all polygenic psychiatric disorders—are not yet clear.

One reason for this complexity is the lack of understanding about the role of noncoding, gene-regulatory regions in neuropsychiatric disease. The coding region of a gene contains the instructions for the production of proteins. Coding regions make up about one percent of all DNA.[134] Noncoding regions make up the other ninety-nine percent and, until very recently, were referred to as "junk DNA." Noncoding regions were thought to have no purpose at all.[135] Consequently, much of the research in genetics has been focused on DNA's coding regions.[136] As it turns out, however, this focus may have been misguided, as noncoding regions play a more important role in polygenic disorders than was previously believed. For instance, one article identified 108 loci associated with schizophrenia, and a great many happened to occur in noncoding regions.[137] Accordingly, though

132. *What Are Complex or Multifactorial Disorders?*, NIH: GENETICS HOME REFERENCE, https://ghr.nlm.nih.gov/primer/mutationsanddisorders/complexdisorders [https://perma.cc/5SBD-BDSA] (last updated Apr. 30, 2019).

133. Mary Gearing, *CRISPR 101: Multiplex Expression of gRNAs*, ADDGENE BLOG (Jan. 28, 2016, 10:50 AM), https://blog.addgene.org/crispr-101-multiplex-expression-of-grnas [http://perma.cc/5CWM-MD5N].

134. Jonathan Henninger, *The 99 Percent . . . of the Human Genome*, HARV. U.: SCI. NEWS (Oct. 1, 2012), http://sitn.hms.harvard.edu/flash/2012/issue127a/ [http://perma.cc/7VQ3-RXR7].

135. Stephen S. Hall, *Hidden Treasures in Junk DNA*, SCI. AM. (Oct. 1, 2012), https://www.scientificamerican.com/article/hidden-treasures-in-junk-dna/ [http://perma.cc/3WUN-8E6S].

136. *Id.*

137. Schizophrenia Working Grp. of the Psychiatric Genomics Consortium, *Biological Insights from 108 Schizophrenia-Associated Loci*, 511 NATURE 421, 421–22 (2014) ("Of the 108 loci, 75% include protein-coding genes . . . .").

noncoding regions are now garnering more attention, further investigation is still needed to fully understand their role in neuropsychiatric diseases.

Among polygenic psychiatric disorders, the genetics of schizophrenia are best understood. This is, in part, due to the fact that the heritability of schizophrenia has been estimated to be as high as eighty-seven percent.[138] After decades of research, it has been determined that genes play a very important role in the development of schizophrenia. Scientists have successfully located multiple alterations in the genomic DNA of neurons and discovered that they are, in fact, likely responsible for causing the disorder.[139] Yet obstacles such as CRISPR's inability to cross the blood-brain barrier, lack of definite targets, genetic overlap between schizophrenia and other psychiatric conditions, and lack of knowledge about the efficacy and long-term safety of CRISPR systems mean there is a long way to go before CRISPR technologies can be translated into a clinical cure for schizophrenia.[140]

Another obstacle to applying CRISPR for the treatment of psychiatric disorders concerns neurodevelopmental disorders. Take, for example, intellectual developmental disorder ("IDD") and ASD. Sequencing efforts of IDD cases have been successful. Studies have now identified a genetic cause for up to forty percent of severe IDD cases.[141] But for many of the genetically defined IDD cases, most of the deleterious effects of the identified pathogenic genomic variants may have already taken place by the time of diagnosis.[142] This is the case even though the diagnosis can take place as early as in utero.[143] It is not apparent that changing a pathogenic variant after birth would correct the associated behaviors and phenotype.

Nonetheless, it is possible that repair by CRISPR may improve some aspects of psychiatric symptomatology. After all, current

138. *See* Alastair G. Cardno et al., *Heritability Estimates for Psychotic Disorders: The Maudsley Twin Psychosis Series*, 56 ARCHIVES GEN. PSYCHIATRY 162, 162 (1999). This means the closer the familial relationship, the higher the risk for developing schizophrenia.

139. Stephan Ripke et al., *Genome-Wide Association Analysis Identifies 13 New Risk Loci for Schizophrenia*, 45 NATURE GENETICS 1150, 1150 (2013).

140. Chuanjun Zhuo et al., *Genomic Editing of Non-Coding RNA Genes with CRISPR/Cas9 Ushers in a Potential Novel Approach to Study and Treat Schizophrenia*, 10 FRONTIERS MOLECULAR NEUROSCIENCE, no. 28, Feb. 3, 2017, at 1, 6–7.

141. Simone M. Karam et al., *Genetic Causes of Intellectual Disability in a Birth Cohort: A Population-Based Study*, 167A AM. J. MED. GENETICS 1204, 1211 (2015).

142. *Id.* at 1207.

143. *See* Regie Lyn P. Santos-Cortez et al., *Novel Candidate Genes and Variants Underlying Autosomal Recessive Neurodevelopmental Disorders with Intellectual Disability*, 137 HUM. GENETICS 735, 744 (2018).

psychopharmacologic treatments available today, which target behaviors, do not directly address underlying structural abnormalities.[144]

A final important consideration is the fact that many of the identified causative variants are exceedingly rare. That is, though a particular gene may have clear associations with IDD, there are often numerous variants within that gene that led to each particular individual's case of IDD.[145] Targeting and identifying each and every one of those possible pathogenic variants within the single gene presents another daunting challenge.

Certainly, CRISPR techniques hold much promise as important tools in helping us understand the biology underlying neuropsychiatric disorders. CRISPR is illuminating pathways beyond the reach of older technologies.[146] Its translation into the clinical setting, however, would necessarily depend upon its ability to reveal the biological mechanisms responsible for psychiatric conditions.

For the time being, therefore, the brain remains a daunting target. Given its cellular and structural complexity, relative inaccessibility, irreplaceable function, and minimal regenerative capacity, neuropsychiatric conditions will not likely serve as CRISPR's initial testing grounds. But CRISPR technology is developing quickly, and clinical applications in the future—for certain disorders—are no longer improbable hypotheticals.[147] Before these become a reality, scientists and clinicians need a better understanding of the technology and its unintended effects.[148] Likewise, many have called for discourse on the ethical issues implicated by CRISPR applications.[149]

144. Laura Weiss Roberts & Shaili Jain, *Ethical Issues in Psychopharmacology*, PSYCHIATRIC TIMES (May 7, 2011), http://www.psychiatrictimes.com/geriatric-psychiatry/ethical-issues-psychopharmacology [http://perma.cc/S9MD-7CTT].

145. *See generally* Jay W. Ellison, Jill A. Rosenfeld & Lisa G. Shaffer, *Genetic Basis of Intellectual Disability*, 64 ANN. REV. MED. 441 (2013) (discussing how the proliferation of microarray analysis has led scientists to the conclusion that there is "extensive genetic heterogeneity" for intellectual disability).

146. For example, scientists are developing reliable animal models and investigating the role of long noncoding RNA functions and higher-order chromatin structures. Prashanth Rajarajan et al., *Spatial Genome Organization and Cognition*, 17 NATURE REVIEWS: NEUROSCIENCE 681, 688 (2016).

147. *See id.* at 685.

148. *See, e.g.*, Zhuo et al., *supra* note 140, at 6–7.

149. *Id.*

III. LEGAL AND ETHICAL CHALLENGES OF CRISPR IN THE CONTEXT OF PSYCHIATRIC ILLNESS

The use of CRISPR technologies in psychiatric populations must conscientiously regard the dubious past of American law on the intersection of psychiatric disorders and genetics. The legal and ethical issues that arise as CRISPR technologies become available have, to some extent, all been seen before. After all, the goal of gene therapy could be characterized as removing genetic defects from the population. And what is the genetic cleansing of a human population if not the issue addressed by the incendiary Supreme Court decision in *Buck v. Bell*?[150] Careful thought will be particularly important within the delicate context of psychiatry given this subgroup's.[151]

A. Vulnerability of Patients Likely to Enlist in CRISPR Research in Psychiatry

Attempts to define vulnerability within the medical community have been criticized by some for being wildly inconsistent and for producing definitions that are entirely too broad.[152] As we have noted above, the medical community typically includes those diagnosed with mental illness within the vulnerable population label.[153] For research purposes, however, patients diagnosed with psychiatric disorders historically have not been labeled as vulnerable, and those enrolled in clinical trials for psychiatric disorders are therefore not always

150. 274 U.S. 200 (1927). In this case, the United States Supreme Court reviewed the constitutionality of Virginia's Sterilization Act, under the authority of which the State proposed to have Carrie Buck sterilized. *Id.* at 205–06. Officials of the Virginia Colony asserted that Carrie and her mother shared the hereditary traits of feeblemindedness and sexual promiscuity. *Id.* The Court voted 8-1 to allow Buck's sterilization and, by extension, the sterilization of any other American in similar circumstances. *See id.* at 207. Justice Holmes, writing for the majority, concluded with the unfortunate remark: "Three generations of imbeciles are enough." *Id.*

151. In the domain of health care, vulnerable populations include those with chronic mental conditions such as schizophrenia, bipolar disorder, and major depression. As we will address later, this designation does not extend into the domain of clinical research. *See* Samia A. Hurst, *Vulnerability in Research and Health Care; Describing the Elephant in the Room?*, 22 BIOETHICS 191, 192 (2008). The vulnerable-population label denotes a reference to a disadvantaged subsegment of people. *Id.* at 191–92. The term for our purposes implies that these subgroups require utmost care, given that their freedom and capability to protect themselves from intended or inherent risks is abbreviated, be it from an impairment of freewill or an inability to make informed choices. *See id.*

152. *See* Philip T. Yanos, Barbara S. Stanley & Carolyn S. Greene, *Research Risk for Persons with Psychiatric Disorders: A Decisional Framework to Meet the Ethical Challenge*, 60 PSYCHIATRIC SERVICES 374, 375 (2009).

153. *See supra* note 151.

afforded additional safeguards.[154] In the sections that follow, we'll consider whether subjects enrolled in CRISPR clinical trials should be labeled as a vulnerable population for research purposes. In so doing, we describe the likely characteristics shared by these patients and turn to both examples of capacity[155] and power-based vulnerabilities[156] affecting these subjects.

1. The Population Most Likely to Undergo CRISPR Clinical Trials Is Treatment Resistant

Despite the vast amounts of resources invested into the exploration of their genetic architecture, there are still no biomarkers that allow for conclusive diagnoses of major psychiatric disorders.[157] In a sense, much of clinical practice in psychiatry still relies on self-reports, observations, and trial-and-error treatment selection.[158] That is, biologically heterogeneous conditions in psychiatry are often treated generally, since treatments that are most likely to help a particular individual cannot be identified.[159]

To be sure—and as Section II.A illustrates—the explosion of research in genetics, particularly in the field of psychiatry, has produced some fruitful information.[160] Psychiatric disorders' high rates of heritability have become more apparent than ever before.[161] Simultaneously, these studies reveal that, for most disorders, there is a complex genetic architecture that provides multiple potential targets for CRISPR interventions. Though most of the genes identified are only responsible in very small part for the overall risk of developing a disorder,[162] as noted above, there are variants that seem

154. *See, e.g.*, 45 C.F.R. § 46.107 (2018) (not including those diagnosed with psychiatric disorders in its list of vulnerable populations).

155. Capacity-based vulnerability is the vulnerability that arises as a consequence of subjects having an impaired capacity to provide fully informed consent. *See* Yanos et al., *supra* note 152, at 375.

156. Power-based vulnerability is vulnerability due to a population being generally more susceptible to social influence and the commands of authority figures. *Id.*

157. Daniel Moreno-De-Luca, Michael E. Ross & David A. Ross, *Leveraging the Power of Genetics to Bring Precision Medicine to Psychiatry: Too Little of a Good Thing?*, 83 BIOLOGICAL PSYCHIATRY e45, e45 (2018).

158. *See* JAMES H. LAKE, TEXTBOOK OF INTEGRATIVE MENTAL HEALTH CARE 18 (2007).

159. *See* Moreno-De-Luca et al., *supra* note 157, at e45.

160. *See id.*

161. *See id.*; *see also* Gandal et al., *supra* note 3, at 1397. Most notably, the genetic contribution to the condition of schizophrenia has been placed at seventy-nine percent. Rikke Hilker et al., *Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register*, 83 BIOLOGICAL PSYCHIATRY 492, 495 (2018).

162. *See* Moreno-De-Luca et al., *supra* note 157, at e45.

more promising. That said, for a majority of conditions, there is still a great deal left to learn.

Even if a psychiatric disorder presented with clear symptoms and had a clear genetic target the prospect of CRISPR intervention poses dilemmas. First, there are likely biological consequences to living with a pathogenic variant for years,[163] and it's likely that these consequences cannot be immediately accounted for by simply replacing the affected gene sequence with a new one. Second, we are only beginning to understand the genetic architecture of psychiatric disorders, as well as the epigenetic components of psychiatric symptomatology.[164] Targeting genes that are believed to be responsible for disorders may not have the intended therapeutic effect because the intervention does not address the epigenetics involved in the etiology of the condition.

Against this background, it becomes clear that treatments applying CRISPR systems should be thought of as highly experimental.[165] And because it intends to change one of the most fundamental aspects of our biology, CRISPR should be understood as highly invasive. Clinical trials looking to apply invasive and experimental technologies to psychiatric populations provide ample precedent for a description of the groups usually recruited for enrollment. For example, Electroconvulsive Therapy ("ECT") trials are usually conducted on patient populations that are considered treatment resistant: patients who have tried numerous interventions to no avail.[166] ECT is considered highly invasive for a number of

163. A pathogenic variant can be thought of as a "faulty gene."

164. *See* Rachel Yehuda et al., *Holocaust Exposure Induced Intergenerational Effects on* FKBP5 *Methylation*, 80 BIOLOGICAL PSYCHIATRY 372, 379 (2016).

165. *See* David Crow, *CRISPR Gene Editing Ready for Testing in Humans*, FIN. TIMES (Mar. 5, 2018), https://www.ft.com/content/d6a773a0-cece-11e7-947e-f1ea5435bcc7 [http://perma.cc/2VUT-834X] ("The field is in its infancy and progress in any new area of science is never smooth.").

166. *See* Nancy Kerner & Joan Prudic, *Current Electroconvulsive Therapy Practice and Research in the Geriatric Population*, 4 NEUROPSYCHIATRY 33, 34 (2014) ("[ECT] is utilized worldwide for various severe and treatment-resistant psychiatric disorders."); Eric L. Ross, Kara Zivin & Daniel F. Maixner, *Cost-Effectiveness of Electroconvulsive Therapy vs Pharmacotherapy/Psychotherapy for Treatment-Resistant Depression in the United States*, 75 JAMA PSYCHIATRY 713, 714 (2018) ("Although ECT can be a first-line treatment for depression with life-threatening psychotic or suicidal features, it is most often used in the United States for depression that has failed to respond to pharmacotherapy and/or psychotherapy."); *What Is Electroconvulsive Therapy (ECT)?*, AM. PSYCHIATRIC ASS'N, https://www.psychiatry.org/patients-families/ect [http://perma.cc/FF7H-6S85] ("Electroconvulsive therapy (ECT) is a medical treatment most commonly used in patients with severe major depression or bipolar disorder that has not responded to other treatments."). The definition of "treatment resistance" in

reasons, primarily the need for general anesthesia during the therapy's administration.[167] Similarly, experimental trials in psychiatry involving the use of ketamine, scopolamine, and other psychedelics target treatment-resistant patients.[168] The same is true of trials involving invasive deep brain stimulation procedures.[169] Invasive and innovative interventions are usually reserved for those patients who either have not responded to numerous treatments over a long period of time and have been continuously affected by the symptoms they deem undesirable[170] or those who have been unable to tolerate the side effects of traditional psychotropic medications.

Arguably, intervention with gene-editing technologies is more invasive than intervention with ECT, ketamine, and the other highly invasive treatments discussed above. Unlike currently available interventions, treatment with CRISPR for psychiatric disorders would likely entail direct exposure of biologics to the brain, lead to permanent change in the patient's genetic blueprint, and require

psychiatry varies and is usually defined in the context of the disorder diagnosed. For example, treatment-resistant depression "typically refers to the occurrence of an inadequate response following adequate antidepressant therapy among patients suffering from unipolar depressive disorders." Maurizio Fava, *Diagnosis and Definition of Treatment-Resistant Depression*, 53 BIOLOGICAL PSYCHIATRY 649, 649 (2003). In the context of schizophrenia, treatment resistance—also known as treatment refractoriness—has been "defined as continuing psychotic symptoms with substantial functional disability and/or behavioral deviances that persist in well-diagnosed persons with schizophrenia despite reasonable and customary pharmacological and psychosocial treatment that has been provided continuously for an adequate time period." Hans D. Brenner et al., *Defining Treatment Refractoriness in Schizophrenia*, 16 SCHIZOPHRENIA BULL. 551, 552–53 (1990); *see also* Norman Sussman, *Introduction: Treatment Resistance in Psychiatry*, PSYCHIATRIC TIMES (Nov. 27, 2017), https://www.psychiatrictimes.com/special-reports/introduction-treatment-resistance-psychiatry [https://perma.cc/2DZB-2GHZ].

167. *See What Is Electroconvulsive Therapy (ECT)?*, *supra* note 166.

168. *See, e.g.*, James W. Murrough et al., *Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial*, 170 AM. J. PSYCHIATRY 1134, 1135 (2013); Chun Yang & Kenji Hashimoto, Letter to the Editor, *Combination of Nitrous Oxide with Isoflurane or Scopolamine for Treatment-Resistant Major Depression*, 13 CLINICAL PSYCHOPHARMACOLOGY & NEUROSCIENCE 118, 118 (2015); *see also* Carlos Zarate et al., *New Paradigms for Treatment-Resistant Depression*, 1292 ANNALS N.Y. ACAD. SCI. 21, 25 (2013).

169. *See* Paul E. Holtzheimer & Helen S. Mayberg, *Deep Brain Stimulation for Psychiatric Disorders*, 34 ANN. REV. NEUROSCIENCE 289, 290 (2011).

170. Although a precise definition of treatment resistance is hard to come by and often varies depending on the particular psychiatric disorder at issue, some have characterized treatment resistance as "patients who experience persistent psychiatric symptoms with impaired functioning despite one or more adequate treatment trials." L. Fredrik Jarskog, Book Review, 171 AM. J. PSYCHIATRY 374, 374 (2014) (reviewing CHARLES B. NEMEROFF, MANAGEMENT OF TREATMENT-RESISTANT MAJOR PSYCHIATRIC DISORDERS (2012)); *see also supra* note 166.

genetic sequencing prior to CRISPR's application.[171] Therefore, it is reasonable to assume that, if and when the technology is developed, the same population of treatment-resistant patients would make for the best candidates for CRISPR clinical trials in psychiatry. To be sure, if gene-editing technology trials of the past are any indication, those who enroll in these research studies will be treatment resistant and may be willing to consider riskier interventions to address their symptoms.[172]

2. Risk-Benefit Analysis for Testing CRISPR in Treatment-Resistant Populations

The target of treatment for patients with psychiatric disorders is "to restore a state of psychological wellness and high functioning."[173] In deciding how to reach this goal, physicians must conduct a risk-benefit analysis for prescribing psychotropic medications or alternative therapies. As this analysis relates to any patient diagnosed with a psychiatric disorder, the balancing is particularly complex.[174] Lackluster therapeutic and diagnostic precision, psychosocial factors, common comorbidities, and the high importance given to the subjective experiences of patients complicate the prescribing physicians' decisionmaking processes.[175] For a favorable risk-benefit ratio to exist, biological, psychological, and social factors must align.[176] The already delicate balance changes when a patient diagnosed with a psychiatric disorder experiences treatment resistance.

Treatment-resistant patients typically feel debilitated for a long period of time,[177] experience feelings of hopelessness and

171. The privacy implications of gathering genetic-sequencing information from patients prior to treatment are discussed *infra* Section III.A.3.

172. *See* Friedmann, *supra* note 57, at 2163–65. In the alternative, as noted in Section II.B, trials will target monogenic diseases for which there is no cure. Just like treatment-resistant patients, the patients affected by the monogenic disorders that have no viable treatment alternatives are most likely to be targeted by CRISPR in the near future. Both groups face parallel ethical dilemmas as a result. This discussion, therefore, will proceed by considering the implications of clinical research in a treatment-resistant population.

173. Maurizio Fava & Katharine G. Davidson, *Definition and Epidemiology of Treatment-Resistant Depression*, 19 PSYCHIATRIC CLINICS N. AM. 179, 179 (1996).

174. Swapnil Gupta & John Daniel Cahill, *A Prescription for "Deprescribing" in Psychiatry*, 67 PSYCHIATRIC SERVICES 904, 904 (2016).

175. *Id.*

176. *Id.*

177. *See* Jarskog, *supra* note 170, at 375 ("Most [psychiatric] disorders do not have formally defined treatment-resistant subtypes, but the prevalence of persistent and debilitating symptoms is a ubiquitous problem.").

helplessness,[178] and may be at risk of suicide.[179] Therefore, treatment-resistant patients—along with their treating physicians—are generally more willing to take risks to find a solution.[180] Accordingly, institutional review boards and other regulatory bodies are more likely to allow invasive interventions if the population being treated is treatment-resistant and/or has few or no alternative options. After all, the risk of not acting might outweigh any risks that an invasive intervention like CRISPR might pose.[181] Ultimately, however, clinicians and researchers should understand the characteristics and symptoms of treatment-resistant patients as having the effect of altering not only the risk-benefit analysis for available treatment options but also the power differential between patients, clinicians, and researchers. As a particularly affected subgroup of a population already stigmatized and underserved,[182] treatment-resistant individuals should be considered at high risk for power-based vulnerability and coercion.

3. Treatment-Resistant Patients with Psychiatric Conditions Are Highly Stigmatized

To some extent, the severity or presentation of treatment-resistant conditions is intertwined[183] with the stigma faced by all individuals diagnosed with psychiatric disorders.[184] Issues of power-based vulnerability also arise if one considers the consequences of stigma attached to mental health issues. A clinician or researcher who

178. *See, e.g.*, Murrough et al., *supra* note 168, at 1134 ("The primary outcome was change in depression severity . . . as assessed by the Montgomery-Åsberg Depression Rating Scale."); *see also* Stuart A. Montgomery & Marie Åsberg, *A New Depression Scale Designed to be Sensitive to Change*, 134 BRIT. J. PSYCHIATRY 382, 388 (1979) (measuring, among other things, whether subjects experienced "feeling[s] of being beyond help and without hope").

179. *See* Isidoor O. Bergfeld et al., *Treatment-Resistant Depression and Suicidality*, 235 J. AFFECTIVE DISORDERS 362, 362 (2018).

180. *See, e.g.*, Celia B. Fisher et al., *Ethical Issues in Including Suicidal Individuals in Clinical Research*, IRB: ETHICS & HUM. RES., Sept.–Oct. 2002, at 9, 9–13.

181. *See* Bergfeld et al., *supra* note 179, at 362 (discussing the high rates of suicide attempts amongst treatment-resistant populations).

182. *See* Yanos et al., *supra* note 152, at 374.

183. Elise Stobbe, *Resistance to Seeking Treatment for Mental Illness—How Others Can Help*, BRAINBLOGGER (May 27, 2006), http://brainblogger.com/2006/05/27/anti-stigmatization-resistance-to-seeking-treatment-for-mental-illness-how-others-can-help/ [http://perma.cc/82GT-9H48] ("More than any other reason, stigma, or fear of the consequences of being labeled 'mentally ill', prevents a person—who realizes he or she may need help—from reaching out for that help.").

184. *See* Cody Brannan, Alexandra L. Foulkes & Gabriel Lázaro-Muñoz, *Preventing Discrimination Based on Psychiatric Risk Biomarkers*, 180B AM. J. MED. GENETICS 159, 162 (2019).

possesses the information regarding a patient's mental health has the power to misuse and mishandle the information and thereby has the power to potentially subject her patient to the stigma associated with the information's improper publication. And so, to better understand the vulnerability of the population likely to be among the first to undergo CRISPR treatments in psychiatry, a good understanding of the evidence of mental health stigma and its implications is indispensable.

Generally, stigma encompasses different elements of stereotyping, segregation, status loss, and discrimination.[185] Numerous studies have established that mental health stigma is highly prevalent.[186] Negative attitudes toward patients of psychiatry aren't limited to the general lay population. Rather, negative attitudes are often widespread among clinicians themselves.[187] Stigma often leads to discriminatory actions. For example, there is evidence that patients diagnosed with psychiatric conditions are being paid lower wages than their undiagnosed counterparts.[188] Those diagnosed with psychiatric conditions also generally have lower chances of obtaining and keeping employment and receive subpar insurance benefits.[189] Further, those stigmatized often report being aware of the fact that society undervalues them and actively experience routine unfair treatment and avoidance by other people.[190] It has also been suggested that those suffering from treatment-resistant conditions experience more severe stigma than other patients diagnosed with psychiatric conditions.

Known stigma against those with treatment-resistant psychiatric disorders raises related concerns about privacy,[191] especially in light of the fact that CRISPR interventions would likely require collecting

185. *Id.* (quoting Bruce G. Link & Jo C. Phelan, *Conceptualizing Stigma*, 27 ANN. REV. SOC. 363, 367 (2001)).

186. *See, e.g.*, Matthias C. Angermeyer & Herbert Matschinger, *The Stereotype of Schizophrenia and Its Impact on Discrimination Against People with Schizophrenia: Results from a Representative Survey in Germany*, 30 SCHIZOPHRENIA BULL. 1049, 1049 (2004); Yoko Baba et al., *Stigma Toward Psychosis and Its Formulation Process: Prejudice and Discrimination Against Early Stages of Schizophrenia*, 73 COMPREHENSIVE PSYCHIATRY 181, 181 (2017); Patrick W. Corrigan, Fred E. Markowitz & Amy C. Watson, *Structural Levels of Mental Illness Stigma and Discrimination*, 30 SCHIZOPHRENIA BULL. 481, 481–89 (2004).

187. Brannan et al., *supra* note 184, at 4.

188. *Id.*

189. *Id.*

190. *Id.*

191. *See* Laura Plantinga et al., *Disclosure, Confidentiality, and Families: Experiences and Attitudes of Those with Genetic Versus Nongenetic Medical Conditions*, 119C AM. J. MED. GENETICS 51, 51–52 (2003).

participants' genetic information. Studies reveal significant public concerns about genetic privacy.[192] Interestingly, people express greater concern about protecting the privacy of their mental health records than the privacy of their genetic information.[193] Patients finding themselves involved in an intervention requiring both the disclosure of genetic information and mental health history should be considered especially vulnerable. In an effort to reduce further exposure to potentially hazardous stigma and its consequences, clinicians and researchers should take particular care to protect this population from improper disclosure and misuse of medical information, all while operating within a system that gives more protection to medical information in general.[194] Scientists should likewise be aware of the fact that having genetic and mental health information at their disposal changes the power balance between themselves and the research subject.

4. Vulnerabilities Surrounding Decisionmaking Capacity

Along with power-based vulnerabilities, patients first enrolled into CRISPR clinical trials in psychiatry may likely encounter vulnerabilities stemming from issues of informed consent. The decision to undergo a treatment using CRISPR is something that must be driven by the individual's desire to eliminate certain symptoms and the consequences of these symptoms from the patient's life. That is, as opposed to targeting a specific genetic profile generally.[195] But what happens if—in the midst of complicated power dynamics and unwieldy risk assessments—the patient's decisionmaking capacity is impaired? To what extent may treatment-resistant populations be so affected by their cognitive impairments that they become unable to give meaningful informed consent? Available research tells us that the answer to these questions is far from clear. Nonetheless, there are reasons for ascribing safeguards to informed consent procedures involving treatment-resistant psychiatric

192. *Id.* at 52.

193. *See id.* at 55 tbl.III, 58. In a study involving 600 individuals—100 from each of six disease groups—at a major medical center, individuals were asked whether specific privacy protections should be in place for certain medical conditions. In relevant part, 68.6% responded that abortion history should be protected, 60.1% were concerned about mental health history, 54.0% about HIV/AIDS status, 46.5% about genetic test results, and 44.4% about drug and alcohol history. *Id.* at 55 tbl.III.

194. *See* LORI B. ANDREWS, FUTURE PERFECT: CONFRONTING DECISIONS ABOUT GENETICS 140–42 (2001); Brannan et al., *supra* note 184, at 4–5.

195. Otherwise, these interventions would start treading dangerously close to the eugenics movements of the past. *See infra* Section III.B.2.

populations, especially for invasive and experimental interventions such as those involving CRISPR systems.

While there is no bright-line rule for determining when an individual has decisionmaking capacity to consent to treatment or research interventions, several studies have documented the degree to which persons with psychiatric disorders are able to do so.[196] Two notable conclusions can be drawn from this data. First, a majority of patients diagnosed with psychiatric disorders—particularly schizophrenia—have the decisionmaking capacity to provide informed consent.[197] Second, researchers found that it is typical for a person diagnosed with a psychiatric disorder to have an understanding of the research that is subpar to the understanding of persons without psychiatric disorders.[198] The recruitment source for the study and whether the protocol calls for inpatient or outpatient treatment impacts the proportion of participants who demonstrated capacity to provide informed consent.[199] For example, a trial with long-term inpatients concluded that sixty-seven percent of persons with schizophrenia performed inadequately on tests of decisional impairment.[200] But others found that only twenty percent to thirty percent of persons with schizophrenia from predominantly outpatient samples showed evidence of decisional impairment.[201]

These findings suggest that although diminished capacity is an important consideration in regard to persons who have psychiatric disorders, it nevertheless is not universal or even typical. And therefore, it may be best to consider this vulnerability as likely to fluctuate with mental state. Determining how to gauge and act on the

196. *See* Laura B. Dunn, *Capacity to Consent to Research in Schizophrenia: The Expanding Evidence Base*, 24 BEHAV. SCI. & L. 431, 432, 435–36 (2006).

197. *See id.* at 436–37, 440. We refer to trials on patients diagnosed with schizophrenia because phenotypes associated with the disorder are typically more likely to affect decisionmaking capacity than with other common psychiatric conditions. For example, trials have found that more than ninety percent of participants with major depression demonstrated full consent comprehension. Paul S. Appelbaum et al., *Competence of Depressed Patients for Consent to Research*, 156 AM. J. PSYCHIATRY 1380, 1382 (1999).

198. *See* Dunn, *supra* note 196, at 441.

199. *Compare* William T. Carpenter et al., *Decisional Capacity for Informed Consent in Schizophrenia Research*, 57 ARCHIVES GEN. PSYCHIATRY 533, 533 (2000) (both inpatient and outpatient), *with* Jeffery A. Kovnick et al., *Competence to Consent to Research Among Long-Stay Inpatients with Chronic Schizophrenia*, 54 PSYCHIATRIC SERVICES 1247, 1247 (2003) (inpatient only), *and* Barton W. Palmer et al., *Assessment of Capacity to Consent to Research Among Older Persons with Schizophrenia, Alzheimer Disease, or Diabetes Mellitus*, 62 ARCHIVES GEN. PSYCHIATRY 726, 726 (2005) (outpatient only).

200. *See* Kovnick et al., *supra* note 199, at 1250.

201. *See* Palmer et al., *supra* note 199, at 729–30.

likelihood of this vulnerability being present is an ethical issue CRISPR researchers will have to resolve.

5. Regulatory Treatment of Patients with Psychiatric Disorders as a Vulnerable Population

Notwithstanding both the power-based and consent-based vulnerabilities we have identified above, there are currently no consistent federal or state regulations instituting prudent safeguards. Under the current guidelines from the DHHS, there are no special procedures guiding research involving persons diagnosed with psychiatric disorders of any severity.

Regulations governing human subject research in the United States—when said research is either funded by or committed to the oversight of any of fifteen federal departments—are detailed in what is known as the Common Rule.[202] The Common Rule is meant to codify the following principles, inter alia, and put them into practice: (1) respect for the autonomous decisionmaking of those capable of providing it and (2) providing protection for persons with diminished autonomy.[203] As such, the Common Rule seeks to ensure voluntary participation in research through informed consent.[204] In 2011, for the first time in a long time, DHHS set out to revise the Common Rule.[205] These revisions followed a call to the research committee, prompted by DHHS, for "information and comments about whether guidance or additional regulations are needed" for research involving people who have impaired decisionmaking capacity, such as people who have psychiatric disorders.[206] A final rule was adopted in June 2018 and

202. U.S. Dep't of Health & Human Servs., *Federal Policy for the Protection of Human Subjects ('Common Rule')*, OFF. FOR HUM. RES. PROTECTIONS, https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html [https://perma.cc/NP4Y-GHHQ].

203. *See* NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH 4–5 [hereinafter THE BELMONT REPORT], https://videocast.nih.gov/pdf/ohrp_belmont_report.pdf [https://perma.cc/7F5X-54FG].

204. *See* 45 C.F.R. § 46.116(b)(8) (2018); THE BELMONT REPORT, *supra* note 203, at 10 ("[T]he consent process can be analyzed as containing three elements: information, comprehension and voluntariness.").

205. *See* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512, 44,512 (July 26, 2011).

206. Request for Information and Comments on Research that Involves Adult Individuals with Impaired Decision-Making Capacity, 72 Fed. Reg. 50,966, 50,966 (Sept. 5, 2007).

took effect in January 2019.[207] The final rule does not explicitly include those diagnosed with psychiatric disorders as a vulnerable population.[208] Rather, the new Common Rule uses the phrase "individuals with impaired decision-making capacity" to replace the phrase "mentally disabled persons."[209] So, while DHHS's guidebook for institutional review boards excludes mention of those diagnosed with psychiatric disorders from its instructions on procedures for research involving special classes of human subjects, it is possible these new regulations would encourage a different approach.[210] Guidance from states on what to do when decisionmaking abilities are insufficient so as to require additional safeguards is sparse and inconsistent.[211] At times these guidelines are altogether absent.[212]

Some institutional review boards already apply different standards to studies involving persons with psychiatric disorders.[213] And, outside of the research context, the medical community has included patients diagnosed with psychiatric conditions under the label of "vulnerable population."[214] Given the likely profile of patients to be first exposed to CRISPR research in psychiatry, safeguards for ensuring the protection of patients' best interests should be firmly in place as a means of mitigating this population's potential vulnerabilities. Again, the critiques of previous trials involving gene-editing technologies provide important insight. Critics of early trials explicitly called for an improvement to the way

207. Federal Policy for the Protection of Human Subjects: Six Month Delay of the General Compliance Date of Revisions While Allowing the Use of Three Burden-Reducing Provisions During the Delay Period, 83 Fed. Reg. 28,497, 28,497 (June 19, 2018); Federal Policy for the Protection of Human Subjects: Delay of the Revisions to the Federal Policy for the Protection of Human Subjects, 83 Fed. Reg. 2885, 2886 (Jan. 22, 2018).

208. *See generally* Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7264 (Jan. 19, 2017) (codified in scattered Titles of the C.F.R.) (explaining that vulnerable populations include "children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons").

209. *See id.* at 7204.

210. *See generally* U.S. Dept. of Health & Human Servs., *Chapter VI: Special Classes of Subjects*, INSTITUTIONAL REV. BOARD GUIDEBOOK (1993), http://wayback.archive-it.org/org-745/20150930182815/http://www.hhs.gov/ohrp/archive/irb/irb_chapter6.htm [https://perma.cc/LEM2-T7H6] (providing IRBs with additional guidance for managing research involving special classes of vulnerable subjects).

211. *See* Erin S. DeMartino et al., *Who Decides When a Patient Can't? Statutes on Alternate Decision Makers*, 376 NEW ENG. J. MED. 1478, 1481 (2017).

212. *Id.* at 1480 fig.1.

213. *See* Yanos et al., *supra* note 152, at 374.

214. *See* LU ANN ADAY, AT RISK IN AMERICA: THE HEALTH AND HEALTH CARE NEEDS OF VULNERABLE POPULATIONS IN THE UNITED STATES 15 (1993).

clinicians obtain informed consent.[215] The informed consent process, critics claimed, needs to be made as thorough as possible to safeguard the population of patients seeking gene-editing treatments.[216] In this context, these safeguards must also include clear guidelines regarding who can serve as an appropriate surrogate decisionmaker when potential participants have insufficient decisionmaking capacity.

In response to the lessons from history, regulatory bodies should aim for clarity and uniformity in their rules. But absent government action, the research community should nevertheless seek to take all steps necessary to protect treatment-resistant patients who are highly stigmatized and may lack decisionmaking capacity. These steps should include the introduction of safeguards into informed consent procedures and surrogate decisionmaking.

B. General Ethical and Policy Issues Raised by CRISPR Applications in Psychiatry

1. Extinction

Despite CRISPR's therapeutic potential, technical issues surrounding CRISPR systems raise ethical concerns, chief among them being the potential for off-target effects.[217] Off-target effects can be thought of as unintended mutations that result from the CRISPR intervention.[218] Ethical concerns are especially poignant where the off-target effects involve the unintended mutation of the germline, meaning these unintended changes become heritable in humans.[219]

In theory, the CRISPR alterations discussed in this Article would take place on somatic cells. A somatic cell modification is limited to the progeny of the original cell that developed the mutation and is not passable from parent to child.[220] In contrast, a germline mutation is a mutation to the cells from which eggs and sperm are derived and through which genetic changes can be passed to the next generation.[221] Thus, unlike genome editing of human germline cells, genome editing of human somatic cells aims to repair or eliminate

215. *See supra* Section I.C.

216. *See supra* Section I.C.

217. Xiang Jin Kang et al., *Addressing Challenges in the Clinical Applications Associated with CRISPR/Cas9 Technology and Ethical Questions to Prevent Its Misuse*, 8 PROTEIN CELL 791, 792 (2017).

218. *Id.*

219. *See id.*

220. Kristine Krafts, *Germline vs. Somatic Mutations*, PATHOLOGY STUDENT (Aug. 22, 2013), http://www.pathologystudent.com/?p=8539 [https://perma.cc/75QD-EWL6].

221. *Id.*

pathogenic variants that cause disease only in that particular individual and not in his offspring.[222]

But perhaps the theoretically sharp distinction between germline modification and somatic cell editing is somewhat idealistic. After all, early gene-therapy trials often saw unintended consequences impacting the germlines of research subjects, and early on, the FDA called for extreme caution when enrolling fertile patients into gene therapy studies.[223] It is also possible that science may find a way to intentionally alter the germline to eradicate targeted conditions from future offspring. If this is in fact the case, CRISPR trials in psychiatry do have the potential to affect future generations. Scientists must consider the ethics of possibly eliminating genes associated with psychiatric conditions from future offspring's genetic profiles.

2. Legal History, Eugenics, and Psychiatry

Any discussion of extinction necessarily brings to mind the eugenics movement that flourished in America and elsewhere during the first part of the twentieth century and led to the implementation of a number of state statutes authorizing the sterilization of people affected by mental illness.[224] Eugenics was founded on two core ideas: (1) the presumed hereditary influence of mental illness and (2) that people with mental illness had more children than the average person.[225] It's important to remember that great thinkers of the time saw eugenics as a legitimate and important public health movement, endorsed by most scientists working in the field of human genetics.[226] Ultimately, the effects of the eugenics movement on those with psychiatric disorders reverberated throughout the world, as eugenics

222. Edward Lanphier et al., *Don't Edit the Human Germ Line*, NATURE (Mar. 12, 2015), http://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111 [https://perma.cc/G8WA-53KC] ("The premise is that corrective changes to a sufficient number of cells carrying the mutation—in which the genetic fixes would last the lifetimes of the modified cells and their progeny—could provide a 'one and done' curative treatment for patients.").

223. *See* Kang et al., *supra* note 217, at 792.

224. *See, e.g.*, Act of Apr. 4, 1967, ch. 138, sec. 1, § 35-36, 1967 N.C. Sess. Laws 194, 194 ("[T]he State of North Carolina . . . is hereby authorized and directed to have the necessary operation for asexualization or sterilization performed upon any mentally defective or feeble-minded inmate of patient thereof . . . ."), *repealed by* Act of Apr. 7, 2003, ch. 13, § 1, 2003 N.C. Sess. Laws 11, 11.

225. Philip R. Reilly, *Eugenics Ethics, Sterilization Laws*, *in* 1 ENCYCLOPEDIA OF ETHICAL, LEGAL, AND POLICY ISSUES IN BIOTECHNOLOGY 204, 205 (Thomas H. Murray & Maxwell J. Mehlman eds., 2000).

226. ALLEN BUCHANAN ET AL., FROM CHANCE TO CHOICE: GENETICS AND JUSTICE 27–28 (2000).

went on to form the core of Nazi doctrine.[227] An estimated 300,000 people were sterilized under Hitler's Germany.[228] Most of those targeted by sterilization laws were patients in mental health hospitals.[229] Additionally, throughout the United States, courts upheld the constitutionality of states' sterilization statutes, finding them "justified by the findings of biological science."[230]

But our legal system's egregious treatment of those with psychiatric conditions is not a thing of the past. Today, "[t]he incidence of human rights violations in mental health care across nations has been described as . . . an 'unresolved global crisis.'"[231] In the United States over the last four decades, failed public policy, targeted budget cuts, and economic crises have had a disproportionate impact on those with serious psychiatric disorders.[232] As a consequence, those with psychiatric disorders have been relegated to an effective underclass, leaving those with untreated conditions cycling through psychiatric hospitals, civil courts, criminal courts, the streets, and correctional institutions.[233]

Recently, the United States Supreme Court commented on a consequence of this subjugation in *Brown v. Plata*.[234] In the case, plaintiffs in two class actions alleged Eighth Amendment violations based on the mistreatment of those affected by psychiatric disorders in state correctional institutions.[235] In a poignant opinion, the Court—speaking through Justice Kennedy—ordered California to drastically reduce its prison population.[236] In doing so, Justice Kennedy noted that suffering and death had resulted from the shortcomings in mental health care and medical care for the mentally ill.[237] Ironically

227. *Id.* at 28.

228. *Forced Sterilizations*, JEWISH VIRTUAL LIBR., https://www.jewishvirtuallibrary.org/nazi-persecution-of-the-mentally-and-physically-disabled [https://perma.cc/6LWS-DAWX].

229. *Id.*

230. *See, e.g.*, Smith v. Command, 204 N.W. 140, 142 (Mich. 1925).

231. Sebastian Porsdam Mann, Valerie J. Bradley & Barbara J. Sahakian, *Human Rights-Based Approaches to Mental Health*, 18 HEALTH & HUM. RTS. J. 263, 263 (2016).

232. *See* ALISA ROTH, INSANE: AMERICA'S CRIMINAL TREATMENT OF MENTAL ILLNESS 3 (2018) ("People with mental illness are among the most disadvantaged members of our society, and when they end up in the criminal justice system, they tend to fare worse than others.").

233. *See id.* at 2.

234. 563 U.S. 493 (2011).

235. *Id.* at 499–500.

236. *Id.* at 504 ("A psychiatric expert reported observing an inmate who had been held in such a cage for nearly 24 hours, standing in a pool of his own urine, unresponsive and nearly catatonic. Prison officials explained they had 'no place to put him.'").

237. *Id.*

California's legislative response to the decree made no mention of inmates with psychiatric disorders.[238]

3. Diversity

Keeping in mind eugenics' shameful history, in contemplating the use of CRISPR to treat psychiatric disorders, it is important to stress that an optimal therapy would target the behavior an individual has deemed disruptive and detrimental to his or her quality of life, as opposed to a specific genetic profile. CRISPR gene-editing therapy for an affected adult individual would not aim to eradicate a specific trait entirely from a population. After all, the broader goal of genetic cleansing would tread dangerously close to discrimination: the distinction between diversity and disability is not always clear.[239]

With the completion of the Human Genome Project, scientists had at their disposal a "map [of] the human genetic terrain"—a standardized reference text.[240] The purpose of genome sequencing was to identify defective genes and correct genetic mistakes.[241] But the view of disability as a textual error—a "genetic other"—reinforces a negative construction of disabilities and undervalues genetic diversity.[242] People without disabilities consistently underestimate the life satisfaction of the disabled.[243] In fact, the difference in quality of life between the two groups is rather small, and a large proportion of people with serious disabilities describe their quality of life favorably.[244] People also tend to overestimate how health impacts happiness, giving health more weight than other factors, including

238. Anastasia Cooper, *The Ongoing Correctional Chaos in Criminalizing Mental Illness: The Realignment's Effects on California Jails*, 24 HASTINGS WOMEN'S L.J. 339, 341 (2013).

239. COMM. ON SCI., TECH., & LAW, NAT'L ACADS. OF SCIS., ENG'G, & MED., INTERNATIONAL SUMMIT ON HUMAN GENE EDITING: A GLOBAL DISCUSSION 4 (2015), https://www.nap.edu/read/21913/chapter/1 [https://perma.cc/X5SU-PHWP].

240. *See* James C. Wilson, *(Re)Writing the Genetic Body-Text: Disability, Textuality, and the Human Genome Project*, CULTURAL CRITIQUE, Winter 2002, at 23, 23.

241. *Id.* at 25.

242. *Id.* After all, this reference text is anything but diverse: it was derived from samples of European origin. *See id.* at 26 ("Without [the Human Genome Diversity] Project, science will characterize 'the' human genome, with its historical and medical implications, largely in terms of what is known from a small sample of people of European origin.").

243. *See* Erika Check Hayden, *Should You Edit Your Children's Genes?*, NATURE (Feb. 23, 2016), http://www.nature.com/news/should-you-edit-your-children-s-genes-1.19432 [https://perma.cc/754M-5LXM].

244. *See id.* ("One study found that half of people with serious disabilities ranked their quality of life as 'good' or 'excellent.'").

economic stability or social support.[245] Further, while in the United States psychiatric disorders are considered pathological and viewed as generally undesirable,[246] the sentiment is not ubiquitous.[247] Take for example the Belgian town of Geel, where strangers with mental illness have been embraced for centuries.[248] In Geel, those with psychiatric disorders are called guests or boarders, as opposed to patients.[249] Further, the attitudes of society shift over time as data is gathered and synthesized, and it is possible that what we consider a psychiatric disorder today may not be classified as such in the future. After all, homosexuality was once, in the not-so-distant past, categorized as a mental illness.[250]

The goal of eradicating a specific trait entirely from a population also sounds a lot like the resurfacing of the eugenics movement.[251] CRISPR technologies could be used to guide human evolution, which was ultimately how some thinkers of the day conceptualized early eugenics.[252] It is true that once the genetic composition that results in a phenotype is eradicated from within the individual's germline cells, he or she will no longer be capable of passing that trait onto his or her offspring.[253] For our purposes, however, the changes made in the DNA of an individuals' somatic cells would not be heritable.[254] Gene-editing therapies developed from the application of CRISPR

245. *Id.*

246. *See* Mary O'Hara, *How the West Won Mental Health Thinking*, GUARDIAN (Apr. 5, 2011), https://www.theguardian.com/society/2011/apr/05/west-foisting-mental-health-doctrines-world [https://perma.cc/F264-8YBJ].

247. *See, e.g.*, Angus Chen, *For Centuries, a Small Town Has Embraced Strangers with Mental Illness*, NPR (July 1, 2016, 3:00 AM), http://www.npr.org/sections/health-shots/2016/07/01/484083305/for-centuries-a-small-town-has-embraced-strangers-with-mental-illness [https://perma.cc/B8FQ-ZQ26].

248. *Id.* ("[T]he extraordinary phenomenon presented at Geel of 400 insane persons moving freely about in the midst of a population which tolerates them without fear and without emotion.").

249. *Id.*

250. *See* Neel Burton, *When Homosexuality Stopped Being a Mental Disorder*, PSYCHOL. TODAY (Sept. 18, 2015), https://www.psychologytoday.com/blog/hide-and-seek/201509/when-homosexuality-stopped-being-mental-disorder [https://perma.cc/EHN6-8H8X] ("Not until 1987 did homosexuality completely fall out of the DSM.").

251. Paul Enríquez, *Genome Editing and the Jurisprudence of Scientific Empiricism*, 19 VAND. J. ENT. & TECH. L. 603, 670 (2017).

252. *See* Nathaniel Comfort, *Can We Cure Genetic Diseases Without Slipping into Eugenics?*, NATION: BIOETHICS (July 16, 2015), https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into-eugenics/ [https://perma.cc/VS9M-JVMG].

253. *See* Tim Beck, *CRISPR: The Future of Medicine and Human Evolution*, IN-TRAINING (May 12, 2017), http://in-training.org/crispr-future-medicine-human-evolution-13534 [https://perma.cc/AX7A-3N2P].

254. *See* Krafts, *supra* note 220.

technologies are ultimately unlike the insidious negative eugenics movement of our past in that the individual is free to reproduce and continue on their unmodified genetic line.[255] The focus of gene-editing therapies, the individual's genetic code, is different from the focus of the eugenics movement—altering the composition of the population at large.[256] The former is focused on enhancing the well-being of an individual.[257] The latter was centered on the future of the human race at the individual's expense.[258]

CONCLUSION

Ample need exists for novel treatments in psychiatry, and CRISPR is an attractive candidate as a future solution. Most immediately, applications for treating monogenic diseases are likely. And because of the speed at which these technologies are evolving, coupled with the fact that CRISPR technologies are helping to further unravel the genetic architecture of more complicated diseases, additional applications in psychiatry are no longer highly improbable hypotheticals. The use of gene-editing technologies in the delicate realm of psychiatry, however, should take into consideration the harm in society's binary view of disability as abnormal. Science and medicine, after all, are not value-free.[259] And biomedical technologies participate in translating social agendas into technological ones.[260]

255. *Id.*

256. *See* Comfort, *supra* note 252 ("Eugenics is 'the self-direction of human evolution.'").

257. Matt Ridley, *Foreword* to DAVENPORT'S DREAM: 21ST CENTURY REFLECTIONS ON HEREDITY AND EUGENICS, at ix, xi (Jan A. Witkowski & John R. Inglis eds., 2008) ("One aims for individual happiness with no thought to the future of the human race; the other aims to improve the race at the expense of individual happiness.").

258. *Id.*

259. SANDRA HARDING, WHOSE SCIENCE? WHOSE KNOWLEDGE?: THINKING FROM WOMEN'S LIVES 37 (1991) ("[T]he technologies used to produce scientific information are not value-neutral. For example, the development of the telescope moved authority about the patterns of the heavens from the church to the secular world and supported the emerging importance of the authority of individual observation. Contemporary scientific technologies . . . shift values in the sciences in other ways.").

260. *See id.* at 37–38.