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Introduction: A Lawyer's Guide to CRISPR

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INTRODUCTION: A LAWYER'S GUIDE TO CRISPR*

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This Symposium on Legal, Ethical, and Policy Implications of New Gene-Editing Technologies was motivated by recent scientific developments in the field of gene editing. For years, genomic medicine has been hailed as the future of clinical treatment. The general premise is that doctors will use detailed information about a particular patient's DNA (and other "biomarkers") to custom-tailor diagnoses, advice, drug choices and doses, and other specifics of treatment.[1] President Obama's highly publicized Precision Medicine Initiative[2] (now rebranded—cryptically—as the "All of Us" Research Program)[3] illustrates both the hope and the hype.

Despite this hope and hype, genomic medicine has thus far had a limited effect on the day-to-day practice of medicine, and that effect has been most notable in cancer treatment (for example, the use of *BRCA* gene testing in treating breast cancer made famous by Angelina Jolie).[4] The limiting factors have included the facts that (1) genes tend to influence the probability of getting a disease but rarely "cause" a disease in a deterministic sense; (2) the relative influences of environment, lifestyle, and epigenetic factors (changes in DNA's

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1. *See generally* Alan Wong et al., *Multiplexed Barcoded CRISPR-Cas9 Screening Enabled by CombiGEM*, 113 PROC. NAT'L ACAD. SCI. 2544 (2016) (providing an overview of the ability to tailor diagnoses, drug choice, and treatment options through CRISPR-Cas9 screening of patients).

2. Press Release, Office of the Press Sec'y, White House, Fact Sheet: President Obama's Precision Medicine Initiative (Jan. 30, 2015), https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative [https://perma.cc/9U9H-8H7N].

3. *See All of Us Research Program*, ALL OF US, https://www.joinallofus.org/en [https://perma.cc/3HCR-2EJJ].

4. *See, e.g.*, Angelina Jolie, Opinion, *My Medical Choice*, N.Y. TIMES (May 14, 2013), https://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html [https://perma.cc/H8DP-LS3P].

immediate chemical environment in the body) on the ways genes are expressed are only beginning to be understood; and (3) for the rare cases of clear genetic-disease causation, treatment can only be symptomatic, since we have no "cures" at the genetic level.[5]

In fact, the holy grail of genomic medicine has always been the ability not just to identify dangerous gene mutations but to *fix* them: to go into a patient's cells and change a dangerous DNA sequence to a healthy one. There have been efforts to do "gene therapy" by using viruses and other vectors to add desired DNA into the patient's cells. There have been some limited successes[6] but also some catastrophic failures, most infamously the death of a teenage boy in Pennsylvania[7] and cases of leukemia-like side effects in France.[8] In hindsight, the problems were probably due to insufficient knowledge about the DNA-delivery mechanisms.[9]

Now a new "gene-editing" technology, called CRISPR (or CRISPR-Cas9), may have the potential to provide a safe and effective way to cut out mutated sequences of DNA and paste in normal variants. As is so often the case in science, it is actually a new application of old knowledge—in this case, about the immune systems of bacteria. There is a long way to go before CRISPR becomes part of patient care, but, for the first time, there seems to be a way to leapfrog the use of potentially risky vectors to deliver DNA into a patient's cells. The promise and potential value of the technology is reflected in the epic struggle underway over the foundational patent rights, featuring MIT and the Broad Institute on one side and the University of California-Berkeley and several European luminaries

5. Irwin Fridovich et al., *Human Genetic Disease: Management of Genetic Disease*, ENCYCLOPEÆDIA BRITANNICA, https://www.britannica.com/science/human-genetic-disease/Management-of-genetic-disease [https://perma.cc/GQ4Z-VJPS].

6. There is a rare eye disease (choroideremia), for example, where in a trial of "14 patients [who] receiv[ed] a single injection into the back of the eye of a virus containing the missing gene" that caused their visual impairment, "there was a significant gain in vision across the group of patients as a whole . . . which was sustained for up to five years at the last follow up." *Gene Therapy Breakthrough in Treating Rare Form of Blindness*, NIHR OXFORD BIOMEDICAL RES. CTR. (Oct. 8, 2018), https://oxfordbrc.nihr.ac.uk/gene-therapy-breakthrough-in-treating-rare-form-of-blindness/ [https://perma.cc/VM7M-GH6V].

7. Sheryl Gay Stolberg, *The Biotech Death of Jesse Gelsinger*, N.Y. TIMES MAG., Nov. 28, 1999, at 136, 137–38.

8. Andrew Pollack, *F.D.A. Halts 27 Gene Therapy Trials After Illness*, N.Y. TIMES (Jan. 15, 2003), https://www.nytimes.com/2003/01/15/us/fda-halts-27-gene-therapy-trials-after-illness.html [https://perma.cc/D96D-9J6D].

9. *Id.*

on the other—a biomedical Clash of Titans.[10] Meanwhile, in 2015 a Chinese research team reported the first successful gene-editing intervention in nonviable human embryos,[11] followed last year by a Chinese scientist's claim to have edited the genome of twin baby girls.[12]

The rapid development of CRISPR technology—in particular, the ethically dubious Chinese activities—has spurred consternation, debate, and governance proposals among scientists, bioethicists, lawmakers, and regulators. The contributors to this Symposium are all significant contributors to this emerging discourse. In this Symposium, our contributors explain gene-editing technology and explore its significant implications for law, ethics, regulation, and health policy from their varied perspectives. In this Introduction, I will give a brief, "CRISPR for Lawyers" overview of the technology and then provide a synopsis of each of the contributions to this Symposium.

I. HOW CRISPR WORKS

CRISPR (pronounced "crisper," like the lettuce drawer in the refrigerator) stands for Clustered Regularly Interspaced Short Palindromic Repeats.[13] These are short, repeating sequences in the DNA of *E. coli* and other bacteria that were discovered by Japanese researchers in the 1980s.[14] DNA is made up of long, two-stranded chains of four chemical building blocks, or bases: A,T,C, and G.[15] The specific arrangement, or sequence, of these bases determines the

10. John Conley, *Clash of Titans: The Fight Over the CRISPR Gene-Editing Patent Rights*, ROBINSON BRADSHAW: PRIVACY REP. (Oct. 8, 2018), https://theprivacyreport.com/2018/10/08/clash-of-titans-the-fight-over-the-crispr-gene-editing-patent-rights/ [https://perma.cc/HNF4-TQMD].

11. David Cyranoski & Sara Reardon, *Chinese Scientists Genetically Modify Human Embryos*, NATURE (Apr. 22, 2015), https://www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378 [https://perma.cc/N3PN-JVB4].

12. Dennis Normile, *CRISPR Bombshell: Chinese Researcher Claims to Have Created Gene-Edited Twins*, SCIENCE (Nov. 26, 2018, 1:10 PM), https://www.sciencemag.org/news/2018/11/crispr-bombshell-chinese-researcher-claims-have-created-gene-edited-twins [https://perma.cc/HB4X-F52G].

13. Brad Plumer et al., *A Simple Guide to CRISPR, One of the Biggest Science Stories of the Decade*, VOX (Dec. 27, 2018), https://www.vox.com/2018/7/23/17594864/crispr-cas9-gene-editing [https://perma.cc/N6AM-MBMA].

14. *Id.*

15. Richard J. Roberts et al., *Nucleic Acid*, ENCYCLOPÆDIA BRITANNICA, https://www.britannica.com/science/nucleic-acid#ref594016 [https://perma.cc/8KXY-WVD3].

nature of the organism—in simplest terms, whether it's a bacterium or me.[16]

The CRISPR regions of bacteria were an enigma to the scientists who first noticed them. Their function was unknown for about twenty years, when food scientists using bacteria to make yogurt figured out that they are part of the bacteria's immune system.[17] These scientists realized that the CRISPR sequences resemble the DNA of viruses.[18] In fact, the CRISPR sequences are taken from viral DNA that the bacteria has captured during past viral invasions.[19] When a new viral attack occurs, the bacteria's immune system compares the virus's genetic material to the sequences stored in CRISPR; if it detects a match, it launches enzymes to cut up the incoming viral DNA and repel the invasion.[20]

The details of this recognize-and-destroy process have proved critical to developing CRISPR's gene-editing potential. But first a bit more terminology: An organism's *genome* is the entirety of its DNA; *genes* are those DNA sequences that function to build, or *encode*, proteins.[21] Genes account for only a small portion of the DNA in the genome.[22] Other portions of the genome have regulatory functions, controlling when particular genes switch on and off, while other areas have no known current function.[23] *RNA* is a single-stranded cousin of DNA that performs many functions in the cell.[24]

The bacterial CRISPR sequences are always accompanied by genes that code for enzymes (a class of proteins that facilitate chemical reactions) that can cut DNA.[25] The original CRISPR scientists called them Cas (for CRISPR-associated) genes.[26] Later research revealed that when viruses invade a bacterial cell, the

16. *Id.*

17. Plumer et al., *supra* note 13.

18. *Id.*

19. *Id.*

20. *Id.*

21. *Help Me Understand Genetics*, GENETICS HOME REFERENCE (May 14, 2019), https://ghr.nlm.nih.gov/primer [https://perma.cc/72WD-LN52].

22. Jonathan Henninger, *The 99 Percent . . . of the Human Genome*, HARV. U.: SCI. NEWS (Oct. 1, 2012), http://sitn.hms.harvard.edu/flash/2012/issue127a/ [https://perma.cc/ECM6-4HV9].

23. *Id.*

24. Carl Zimmer, *Breakthrough DNA Editor Born of Bacteria*, QUANTA MAG. (Feb. 6, 2015), https://www.quantamagazine.org/crispr-natural-history-in-bacteria-20150206/ [https://perma.cc/3Q9J-D2CE].

25. Plumer et al., *supra* note 13.

26. *Id.*

CRISPR regions produce RNA versions of the viral DNA sequences that it has captured and stored.[27] These RNA sequences are cradled by the Cas enzymes and carried around the cell.[28] When an RNA sequence encounters its viral DNA counterpart, it latches on and the Cas enzyme cuts the DNA, which stops the virus from replicating.[29]

Current CRISPR gene-editing technology mimics this natural process. Researchers at the University of California-Berkeley chose a Cas enzyme called Cas9.[30] They supplied the enzymes with the RNA counterpart of the genetic sequence they wanted to edit—the target gene.[31] The RNA finds and binds to the target DNA and the Cas9 enzymes cut it at its two ends.[32] With the target gene excised, the cell can be induced to make a new one.[33] In the simplest application, the CRISPR mechanism finds and cuts out a "defective" gene—for example, one that causes a single-gene disease such as cystic fibrosis, hemophilia, or sickle cell disease—and the cell replaces it with a normal one.[34] CRISPR technology can also be used to introduce a new gene into the space.[35]

This image provides a simple visual representation of how CRISPR-Cas9 is used to find and cut a target gene (the *g* in gRNA stands for *guide*; PAM is a DNA sequence adjacent to the target sequence that Cas9 recognizes[36]):

27. *Id.*
28. *Id.*
29. *Id.*
30. *Id.*
31. *Id.*
32. *Id.*
33. *Id.*
34. *Id.*
35. Zimmer, *supra* note 24.
36. ADDGENE, CRISPR 101: A DESKTOP RESOURCE 9, 24–25 (2d ed. 2017), https://bit.ly/2uRYyG0 [https://perma.cc/ACU8-SLX3].

CRISPR-Cas9

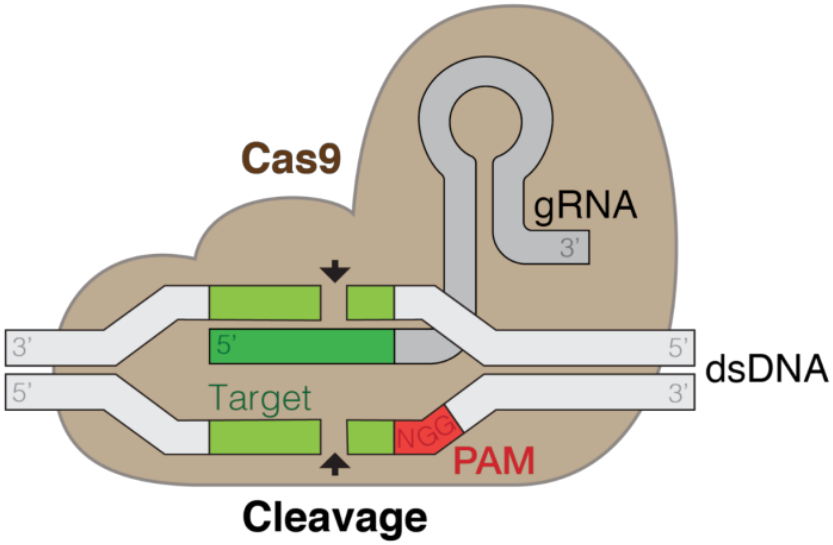

Image Credit: Marius Walter, GRNA-Cas9, WIKIMEDIA COMMONS (Sept. 25, 2017), https://commons.wikimedia.org/wiki/File:GRNA-Cas9.png [https://perma.cc/9RSM-DDL8]. This image is licensed under the Creative Commons Attribution-ShareAlike 4.0 International license. See Attribution-ShareAlike 4.0 International License, CREATIVE COMMONS, https://creativecommons.org/licenses/by-sa/4.0/legalcode [https://perma.cc/65BG-NRTQ].

CRISPR is not the first gene-editing technology. Other approaches include Zinc-finger nucleases ("ZFN") and transcription activator-like effector nucleases ("TALENs").[37] ZFN, which dates to the early 1990s, employs custom-engineered proteins that find, bind to, and cut target DNA sequences.[38] ZFN improved on prior technology by significantly improving the accuracy of gene editing, in particular by reducing "off-target" edits that hit the wrong DNA sequences with unpredictable consequences.[39] However, ZFN's

37. *Id.* at 53.

38. Thomas Gaj, Charles A. Gersbach & Carlos F. Barbas III, *ZFN, TALEN, and CRISPR/Cas-Based Methods for Genome Editing*, 31 TRENDS BIOTECHNOLOGY 397, 398–99 (2013).

39. *Id.* at 400–01.

custom engineering of proteins for each new target gene makes it slow, expensive, and inefficient.[40] TALENs, which appeared in 2009, is generally similar to ZFN but simpler and more efficient.[41] CRISPR represents a major advance over both in terms of efficiency and accuracy.[42]

There is a long way to go before CRISPR gene editing becomes part of everyday patient care, but it has the potential both to "fix" the causes of single-gene diseases and to contribute to the prevention or treatment of diseases that are caused by a complex interaction of genes and environmental factors, including cancer and heart disease.[43] Such uses seem—at least at first glance—to be ethically unproblematic, though there are worries about such safety issues as off-target edits.[44] But other possible uses are already engendering profound ethical concerns. Those uses include enhancement, or gene editing to improve on normal human traits;[45] editing human sperm or egg cells, which raises concerns about the intergenerational protection of those who might inherit edited genomes;[46] gene editing of embryos, the subject of the recent Chinese claims;[47] gene editing of animals, for a variety of purposes;[48] and attempting to alter ecology, as in the proposed use of CRISPR to eliminate malarial mosquitoes.[49] Such concerns are the subject of many of the Articles in this Symposium.

40. ADDGENE, *supra* note 36, at 8.

41. J. Boch et al., *Breaking the Code of DNA Binding Specificity of TAL-Type III Effectors*, 326 SCIENCE 1509, 1509–12 (2009); Gaj et al., *supra* note 38, at 399.

42. ADDGENE, *supra* note 36, at 9.

43. *See id.* at 15; Mark Shwartz, *Target, Delete, Repair*, STAN. MED. (2018), https://stanmed.stanford.edu/2018winter/CRISPR-for-gene-editing-is-revolutionary-but-it-comes-with-risks.html [https://perma.cc/QVZ5-ZLZZ].

44. Gaj et al., *supra* note 38, at 402.

45. *See, e.g.*, Shwartz, *supra* note 43.

46. *See, e.g.*, Jianhua Luo, *Here's What We Known About CRISPR Safety – And Reports of 'Genome Vandalism'*, WASH. POST (Sept. 3, 2018), https://www.washingtonpost.com/national/health-science/heres-what-we-know-about-crispr-safety--and-reports-of-genome-vandalism/2018/08/31/2ed90212-9735-11e8-a679-b09212fb69c2_story.html?noredirect=on&utm_term=.9ed673af0653 [https://perma.cc/6ZGT-LZHW].

47. *See, e.g.*, Normile, *supra* note 12.

48. *See, e.g.*, Preetika Rana & Lucy Craymer, *Big Tongues and Extra Vertebrae: The Unintended Consequences of Animal Gene Editing*, WALL ST. J. (Dec. 14, 2018), https://www.wsj.com/articles/deformities-alarm-scientists-racing-to-rewrite-animal-dna-11544808779 [https://perma.cc/BYJ3-U87M]; *see also* THE NETH. COMM'N ON GENETIC MODIFICATION (COGEM), CRISPR & ANIMALS: IMPLICATIONS OF GENOME EDITING FOR POLICY AND SOCIETY 5–6 (2018).

49. *See, e.g.*, Megan Molteni, *Here's the Plan to End Malaria with CRISPR-Edited Mosquitos*, WIRED (Sept. 24, 2018, 11:00 AM), https://www.wired.com/story/heres-the-plan-to-end-malaria-with-crispr-edited-mosquitoes/ [https://perma.cc/XTE4-FU9Q]; *see*

II. SUMMARY OF THE ARTICLES

The Articles in this issue are ordered generally according to theme. The first three deal in various ways with the ethics and legality of human gene editing. In *Human Gene-Editing Research*, Nancy King's primary concern is the creation of inheritable gene changes. Her worries include the perpetuation of dangerous outcomes and the use of gene editing for enhancement rather than treatment. Expressing skepticism about global enforcement mechanisms, she argues rather for transparency, ongoing discussion, and the development of best practices.

Next, Vence Bonham and Lisa Smilan's *Somatic Genome Editing in Sickle Cell Disease* uses the history of sickle cell disease to explore the issue of equitable access to gene-editing treatments. Sickle cell disease is a prime candidate for the early application of somatic gene editing, but, as the authors document, the history of the treatment of people living with the disease is one of discrimination and health inequities. They offer ethical prescriptions for policymakers in an effort to avoid a repeat of that tragic story.

Then, in *Editing Humanity*, Paul Enríquez examines the legality of human germline editing from multiple legal perspectives. He concludes that the Food and Drug Administration has ample current authority to regulate the practice but offers an innovative constitutional argument against efforts to ban germline gene-editing technologies. He proposes organizing possible uses of germline editing along an ethical continuum and using this continuum as a blueprint for future regulation.

A second group of Articles addresses gene editing in relation to animals and the environment. Rebecca Walker and Matthias Eggel focus on the ethics of using animals to model potential human applications of CRISPR. In *Replacement or Reduction of Gene-Edited Animals in Biomedical Research*, they identify the inherent ethical tension in the trend toward reducing the number of animals used while at the same time replacing mice and rats with more "complex"—and thus more humanlike—species such as primates.

In *Before We Make a Pig's Ear of It*, Karen Meagher and Paul Thompson use recent nuisance suits against the North Carolina hog-

also Dylan Matthews, *The Bold Plan to End Malaria with a Gene Drive*, VOX (Sept. 26, 2018, 5:03 PM), https://www.vox.com/science-and-health/2018/5/31/17344406/crispr-mosquito-malaria-gene-drive-editing-target-africa-regulation-gmo [https://perma.cc/HG2Q-RZ39].

farming industry as a vehicle for thinking about the ethics of the gene editing of livestock. They argue for new bioethical frameworks that combine divergent perspectives as policymakers grapple with ethical problems at the intersection of the environment, public health, and the legitimate needs of agriculture.

Governing Extinction in the Era of Gene Editing, by Jonas Monast, explores CRISPR technology as a conservation tool, including such uses as improving the genetic diversity of endangered species, controlling invasive species, and even reviving extinct species. The problem is that, whereas traditional conservation methods allow time and space for debating competing values, CRISPR-based conservation may move too fast. Monast offers a framework based in the Endangered Species Act to ensure that conservation uses of gene editing undergo appropriate public policy analysis.

Three more Articles examine some of the health implications of gene editing. *Legal and Ethical Implications of CRISPR Applications in Psychiatry*, by Alexandra Foulkes and colleagues, addresses psychiatry's increasing focus on the genomic correlates of many conditions. The authors identify some of the conditions that are especially promising for gene-editing treatment, as well as the special clinical challenges that CRISPR presents in the mental-health context. They conclude with some thoughts about the ethical and legal issues that are likely to arise, focusing particularly on the vulnerability of psychiatric patients who are likely to enlist in gene-editing research.

In *DIY CRISPR*, Christi Guerrini, Evan Spencer, and Patricia Zettler explore the overlooked and unregulated world of "citizen scientists" doing CRISPR research on their own, and sometimes on themselves. The authors' extensive interview study reveals a surprisingly robust—and generally effective—self-regulatory regime. But their interviews also identify emerging challenges that may portend an increase in risky experimentation.

Then, in *Gene Therapy's Field of Dreams*, Laura Hercher and Anya Prince consider the critical question of who will pay for gene therapy. It is expensive and, because it is individualized, it is likely to remain so. Consequently, cost should be a fundamental concern, lest we slip into a world of "genetic haves and have-nots," a world in which health inequalities are even more profound than they are now.

In our final Article, *The Pick-and-Shovel Play*, Jacob Sherkow and Christopher Scott take a bioethical perspective on the role of patents in the development of gene-editing technology. While the

debate thus far has been largely limited to the propriety of patents on gene-editing technologies themselves, the authors urge greater attention to the vectors that are used for introducing gene-editing mechanisms into the body. They contend that some commercial players have shrouded their vector information in secrecy, raising serious ethical and safety issues about the therapies in which those vectors are used.