Annals of Health Law

Volume 26
Issue 2 *Summer 2017*

Article 5

2017

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I will focus on whether the CRISPR technique could potentially generate risky genome edits that could, intentionally or unexpectedly, have negative effects on human health, genetic traits, and even disrupt entire ecosystems. Researchers note that the technology is easily accessible, the equipment is relatively cheap, and not much training is required.[1] While CRISPR may well prove safe with further understanding of its operation, regulators must worry about unexpected risks and side effects, along with abuses by private parties and governments less careful about research technique and ethical limits on research.

Genetic research risks are special.[2] Unlike environment harms that usually produce a by-product causing long term health effects, harms associated with genetic research present uncertainty about possible catastrophes.[3] As I have previously argued, "[t]he problem of uncertainty is intensified because of the possibility that research into fundamental biological or physical structures may alter those structures in a way that does not normally occur in the natural environment."[4]

Some excellent work has already been done in laying out principles to balance the benefits of CRISPR against possible risks, including summits and National Institutes of Science/Engineering/Medicine reports.[5] We have visited this terrain before in the 1970s and 1980s with the rDNA controversy, where regulatory structures were created and then diminished over time. For some of the worries created by CRISPR, regulation is available in a

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1. Heidi Ledford, *CRISPR, The Disruptor*, 522 NATURE 20, 21 (2015).

2. *See* Barry R. Furrow, *Governing Science: Public Risks and Private Remedies*, 131 U. PA. L. REV. 1403, 1404 (1983) (arguing that the risks of genetic research are in a special category).

3. *Id.*

4. *Id.*

5. *See, e.g.* David Baltimore et al., *A Prudent Path Forward for Genomic Engineering and Germline Gene Modification*, 348 SCI. 36, 36 (2015).

haphazard way.[6] CRISPR critics have already begun to note the range of risks to be considered and to consider how to fit CRISPR within existing regulatory structures like the FDA or NIH.[7] Much conceptual work needs to be done to properly assess the risks (or lack thereof) attendant on this remarkable new genetic tool.

I. CRISPR: A REMARKABLE TOOL

A. The Technology

Genetic engineering holds great promise in treating disease and solving a host of other problems. Editing genomes with molecular tools has been possible for some time.[8] CRISPR, first described in a paper in 2012, turned out to greatly advance the research tools available for genetic research.[9] Its advantages have become clear — it is easy to use, low in cost, and a more precise tool for genetic engineering than earlier tools.[10] It is a gene splicing tool that involves modifying an organism's genetic material to alter or improve its characteristics."[11] CRISPRs are part of the bacterial immune system that defends against invading viruses; they are repeating sequences of genetic code, interrupted by 'spacer' sequences the cell uses to detect and

6. *See generally* SHELDON KRIMSKY, GENETIC ALCHEMY: THE SOCIAL HISTORY OF THE RECOMBINANT DNA CONTROVERSY (1982) (discussing the political and social history of the controversy); *see also* Judith P. Swazey et al., *Risks and Benefits, Rights and Responsibilities: A History of the Recombinant DNA Research Controversy*, 51 S. CAL. L. REV. 1019 (1978) (detailing the legislative proposals to regulate rDNA research); *see also* Barbara J. Culliton, *Recombinant DNA Bills Derailed: Congress Still Trying to Pass a Law*, 199 SCI. 274 (1978) (examining the legislative bills).

7. Sheila Jasanoff et al., *Human Genetic Engineering Demands More Than A Moratorium*, GUARDIAN (Apr. 7, 2015), https://www.theguardian.com/science/political-science/2015/apr/07/human-genetic-engineering-demands-more-than-a-moratorium [hereinafter *Demands*]; *see also generally* Edward Lanphier et al., Comment, *Don't Edit the Human Germ Line*, 519 NATURE 410 (2015); *see also* Ledford, *supra* note 1; *see also* Sara Reardon, *NIH Reiterates Ban on Editing Human Embryo DNA*, NATURE (Apr. 29, 2015), http://www.nature.com/news/nih-reiterates-ban-on-editing-human-embryo-dna-1.17452; *see generally* Daniel Sarewitz, Comment, *Science Can't Solve It*, 522 NATURE 413 (2015).

8. Ledford, *supra* note 1, at 21.

9. *See* Giedrius Gasiunasa et al., *Cas9–crRNA Ribonucleoprotein Complex Mediates Specific DNA Cleavage for Adaptive Immunity in Bacteria*, 109 PROC. NAT'L ACAD. SCI. 15539, 15539–40 (2012), http://www.pnas.org/content/109/39/E2579/1.full; *see also CRISPR Timeline*, BROAD INSTITUTE www.broadinstitute.org/what-broad/areas-focus/project-l spotlight/crispr-timeline (last visited April 17, 2017) (providing a full timeline); *see also* Raheleh Heidari et al., *CRISPR and the Rebirth of Synthetic Biology*, SCI. & ENG. ETHICS (June 20, 2016), https://www.researchgate.net/publication/304171372_ CRISPR_and_the_Rebirth_of_Synthetic_Biology.

10. *See* Michael Specter, *The Gene Hackers*, NEW YORKER (Nov. 16, 2015), 1 http://www.newyorker.com/magazine/2015/11/16/the-gene-hackers ("CRISPR has made a difficult process cheap and reliable. It's incredibly precise.").

11. Heidari et al., *supra* note 9.

destroy invaders[12] When the benefits of Cas9 were discovered the CRISPR technology really took off in the research laboratory.[13] The use of Cas9 dramatically improved both the efficiency and accuracy of the CRISPR technology.[14]

The technology, which can be used to make specific changes in the DNA of plants and animals, has become instrumental to studying disease systems in the lab because of its low cost, precision, and ease of use.[15] Unlike other genome editing methods, scientists can use it to change any stretch of DNA in a genome, as long as they know the sequence to target.[16] CRISPR allows for rapid development of mouse models for studying the modification of genetic materials.[17] Previous tools required up to a year —from designing the mutated gene to rounds of mouse breeding to ensure that mouse offspring have the correct genetic mutation.[18] CRISPR is much faster—only two months are needed for a mouse model, since the components are more easily introduced into the embryo without using multiple breeding steps.[19]

CRISPR is an ideal genome engineering technology.[20] Scientists describe the benefits as high potency and specificity, broad application to both in vivo and ex vivo applications, and simple editing tools to speed the process of scaling and optimizing.[21] These traits make CRISPR an incredible tool with the remarkable ability to modulate genes, address any site in the genome, target multiple DNA sites simultaneously, and program them to delete, insert or repair genes.[22]

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12. *Questions and Answers About CRISPR*, BROAD INST., https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/questions-and-answers-about-crispr (last visited April 17, 2017).

13. Ledford, *supra* note 1, at 20.

14. *See generally* Elizabeth Pennisi, *The CRISPR Craze*, 341 SCI. 833 (2013).

15. Ledford, *supra* note 1, at 20.

16. *See* Pennisi, *supra* note 14, at 835 (stating that virtually any gene can be altered with Cas9).

17. *Id.*

18. Angela She, *CRISPR in Neuroscience: How Precision Gene Editing May Unravel How the Brain Works (and Why it Sometimes Doesn't)*, HARV.: BLOG, SPECIAL EDITION ON NEUROTECHNOLOGY (April 6, 2016), http://sitn.hms.harvard.edu/flash/2016/crispr-in-neuroscience-how-precision-gene-editing-may-unravel-how-the-brain-works-and-why-it-sometimes-doesnt/.

19. *Id.*

20. *See* Bruce Booth, *Riding the Gene Editing Wave: Reflections on CRISPR/Cas9's Impressive Trajectory*, FORBES (May 31, 2016), http://www.forbes.com/sites/brucebooth/2016/05/31/riding-the-gene-editing-wave-reflections-on-crisprs-impressive-trajectory/#1abf909c141c ("Its simplicity, and its relatively cheap cost,
make CRISPR an ideal tool to explore myriad genetic manipulations.").

21. *CRISPR/CAS9*, INTELLIA THERAPEUTICS, http://www.intelliatx.com/crispr/ (last visited April 17, 2017).

22. *See generally* F. Ann Ran et al., *Genome Engineering Using the CRISPR-Cas9*

The excitement felt by biologists was well expressed by the Hinxon Steering Committee in its report in its description of the wide range of beneficial uses for CRISPR. Such uses include mitochondrial diseases; early application to complex diseases with single-target solutions; safer treatment and screening of single germ cells; and improving reproductive possibilities where preimplantation genetic diagnosis and in vitro fertilization (PGD-IVF) is not acceptable for medical or personal reasons.[23]

To put it another way, CRISPR genome editing in human sperm, eggs and embryos has tremendous promise in basic research. Embryos can be cultured with better implantation rates and fewer miscarriages; stem-cell lines can be developed for research, miscarriages can be prevented, drugs screened for efficacy, all while reducing the need for using embryos in research; fertility can be enhanced; and genome editing overall can be improved.[24]

CRISPR goes beyond human germline editing. One bioengineer noted that "genome editing shows great promise for next-generation plastics, agricultural products, bioremediation organisms, carbon-neutral fuels, novel enzymes, and better vaccines."[25] CRISPR truly offers a parade of research advantages with clinical, commercial, and agricultural advantages. Who can object to such a technology?

B. The Problem of Rapid Adoption

Biologists have adopted the CRISPR tool with remarkable speed and great enthusiasm.[26] The problem with such a rapid pace of adoption in both public and commercial laboratories is that the full range of ethical and safety concerns have yet to be sorted out.[27] The CRISPR tool of gene editing improves on the older tools such as the recombinant DNA technology (rDNA), which made whole genomes readable.[28] CRISPR holds the promise

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System, 8 NATURE PROTOCOL 2281 (2013).

23. The Nat'l Acads. of Scis. Eng'g & Med., *Applications of Gene Editing Technology: Human Germline Modification* (George Church's address at the International Summit on Human Gene Editing, Dec. 1, 2015), https://vimeo.com/album/3703972/video/149188798.

24. *See* Debra J. H. Mathews et al., *A Path through the Thicket*, 527 NATURE 159, 160 (2015), http://www.nature.com/polopoly_fs/1.18748!/menu/main/topColumns/topLeftColumn/pdf/159-161%20Comment%20-%20Hinxton%20WF.pdf.

25. Daniel M. Gerstein, *How Genetic Editing Became a National Security Threat*, BULL. ATOMIC SCIENTISTS (Apr. 25 2016), http://thebulletin.org/how-genetic-editing-became-national-security-threat9362.

26. *See* Ledford, *supra* note 1, at 21 (stating that CRISPR has led to "rapid progress" within the research community and that in the past two years, several companies have formed to develop CRISPR-based gene therapy).

27. *See id.* (explaining that the fast pace leaves little time for dealing with these concerns before experimentation).

28. *See generally* Amy Maxmen, *Easy DNA Editing Will Remake the World. Buckle Up.*, WIRED (Aug., 2015), https://www.wired.com/2015/07/crispr-dna-editing-2/.

of cheap, effective editing—it can "cut and alter the DNA of any species" at most genomic sites with precision.[29] I have written about the risks of genetic modification technologies before, and CRISPR presents some of the same risk features of the rDNA controversy, as well as clear benefits for scientific research and medical development as described above.[30]

What are the environments in which such tools are valuable? CRISPR promises the construction of new animals for research, improved bacterial strains in dairy products, and reduction of disease-generating mutations in human genes.[31] As Jasanoff et al. write: "To many it appears all but certain that so precise and powerful a technique will revolutionize the treatment of genetically transmitted human disease, correcting defective genes within diseased bodies, and potentially banishing genetic errors from the germ-line by editing the DNA of human gametes and embryos."[32] Biologists and health care providers are excited.[33] If we can help those with traits for rare genetic diseases, the pressure is enormous to move from the lab into the population with such traits.

Evidence for the rapid rate of take-up by researchers in academia and industry can be found in the increase in publications, patents, and funding.[34] Even stronger evidence is found in the remarkably rapid use of the technology by startup companies such as *Editas*.[35] The field is hot, and its rapid movement leaves risk unanalyzed and under regulated in many areas of the science.[36] Universities want research grants for such research; new biotechnologies are fostered; and another biological arms race begins, driven by market and research benefits.

The rapid emergence of CRISPR has generated calls for a moratorium or slowdown in some areas in which the technology is or may be used.[37] When

29. Sheila Jasanoff et al., *CRISPR Democracy: Gene Editing and the Need for Inclusive Deliberation*, 32 ISSUES IN SCI. & TECH. (2015) [hereinafter *CRISPR Democracy*].

30. *See generally* Furrow, *supra* note 2.

31. *See* Pennisi, *supra* note 14, at 833–34.

32. *CRISPR Democracy, supra* note 29.

33. *See CRISPR Will be a Huge Story in 2017. Here Are 7 Things to Look For*, SCIPOL (Jan. 3, 2017), http://scipol.duke.edu/content/crispr-will-be-huge-story-2017-here-are-7-things-look (asking scientists what they believe are the most exciting ways of changing the world with CRISPR).

34. Ledford, *supra* note 1, at 23.

35. *See* Jordan Paradise, *U.S. Regulatory Challenges for Gene Editing*, 13 SCITECH LAW. (2016), http://www.americanbar.org/publications/scitech_lawyer/2016/fall/us_regulatory_challenges_gene_editing.html ("[*Editas* has a] $43 million capital investment to design clinical trials based on the CRISPR and TALEN platforms.").

36. *See* Ledford, *supra* note 1, at 20–21 ("[S]ome scientists are worried that the field's breakneck pace leaves little time for addressing the ethical and safety concerns such experiments can raise.").

37. *Demands*, *supra* note 7.

Chinese scientists used CRISPR to edit human embryos, controversy erupted over the implications of such research.[38] Worries were expressed about how to involve the public.[39] How do we monitor and gauge risks? What current regulatory regimes can tackle the technology review process? Some critics were concerned that relying on research self-regulation might not be ideal, since scientists do not necessarily represent society's interests, and their own ambition and links to commercialization of the technology may make them suspect decision makers.[40] Researchers have a conflict of interest with regard to proper levels of risk assessment. Can CRISPR research in human embryos be a slippery slope tempting researchers to engage in unsafe, unethical or non-medical uses of the technique? [41] Such research offers huge rewards in research prestige and commercial profitability, fueling possible unsafe research.

II. CRISPR RISKS

CRISPR presents at least three broad areas of regulatory concern about risks: off-target effects; gene drives and biosecurity; and human germline research and "humanness."[42]

A. Off-Target Effects.

The CRISPR-Cas9 gene editing technique works like scissors.[43] CRISPR-Cas9 inserts a protein taken from DNA into the target cell to make cuts near the gene defect that the scientist wants to alter. A properly functioning gene segment is then inserted at that point[44] The cutting however may be imprecise and therefore unpredictable, cutting other genes.[45] The risk is then that the function of a gene might be changed, making the cell cancerous, for

38. David Cyranoski & Sara Reardon, *Embryo Editing Sparks Debate*, 520 NATURE 593, 593 (2015).

39. *See* Heidari et al., *supra* note 9, at 7 (stating that accurate public knowledge, which is difficult to disseminate, is required before democratic legislation can result); *see also generally CRISPR Democracy*, *supra* note 29.

40. Heidari et al., *supra* note 9, at 7 (stating that because scientists are not elected, they do not necessarily represent society's values); *see also generally CRISPR Democracy*, *supra* note 29.

41. *See* Ledford, *supra* note 1, at 21 (stating that because of CRISPR's accessibility and low cost, researchers must be careful in deciding how to use its power).

42. Hank Greely, *Of Science, CRISPR-Cas9, and Asilomar*, STAN. L. SCH.: L. & BIOSCI. BLOG (Apr. 4, 2015), https://law.stanford.edu/2015/04/04/of-science-crispr-cas9-and-asilomar/.

43. Patrick Skerrett, *Experts Debate: Are We Playing With Fire When We Edit Human Genes?*, STAT (Nov. 17, 2015), https://www.statnews.com/2015/11/17/gene-editing-embryo-crispr/?s_campaign=trendmd.

44. *Id.*

45. *Id.*

example[46] The off-target effects could create larger risks than the editing technique aims to fix.[47] The human genome can be altered with unknown consequences.[48]

B. Gene Drives and Biosecurity

CRISPR provides a precise method of targeting, snipping, and inserting exact pieces of a genome.[49] The trait then becomes transmissible from generation to generation. This means that the use of such "gene drives" could, for example, reprogram mosquito genomes to eliminate malaria—this would reverse mosquito resistance to herbicides and pesticides, wiping out invasive species.[50] Transgenic mosquitoes could be released to limit the spread of mosquito–borne diseases such as malaria and dengue fever.[51] CRISPR Cas9 allows for precise cutting of sequences specified by guide RNA molecules to "edit nearly any gene in sexually reproducing populations."[52]

Preferred traits can rapidly enter a species population; as a result, it is possible, for example, to reengineer mosquitos so they cannot spread malaria or plants for drought resistance.[53] Populations of organisms can be altered by "adding, disrupting, or editing genes or suppressed by propagating treatise that reduce reproductive capacity."[54]

The problem of biosecurity is multi-faceted.[55] CRISPR's ease of use and access to materials means that dangerous outcomes can result from Do-It-Yourself (DIY) biology, biohacking, and neighborhood labs.[56] Second, research on animal species can have effects on entire ecosystems, such as an altered organism escaping into the wild.[57] Finally, what about weaponization and the threat of bioterrorism?[58] Pathogens could be engineered for biological attacks on a large scale against humans or against the food supply

46. *Id.*
47. *See* Gerstein, *supra* note 25 ("Subtle changes, for example, intended to affect only genetic diseases, could have unknown consequences….").
48. *Id.*
49. *Id.*
50. Kenneth A. Oye et al., *Regulating Gene Drives*, 345 SCI. 626, 626 (2014).
51. *Id.*
52. *Id.*
53. Gerstein, *supra* note 25.
54. Oye et al., *supra* note 50, at 626.
55. *See generally id.*
56. *See* Gerstein, *supra* note 25 (The parade of horribles is quite impressive: creating diseases in humans, producing disease susceptibility through changes in the immune system, causing expression of harmful factors for health, to list a few.)
57. *See* Gerstein, *supra* note 25.
58. *Id.*

with devastating effects.[59] Diseases could be created—engineered pathogens could sicken or even kill thousands."[60] Some of these concerns require a halt to practical use of the CRISPR tool until the ecosystem risks are properly assessed. Bioterror uses fall under the purview of military assessment, which may be quite capable of evaluating and blocking some uses.[61] The problem is always one of uncertain risks at the beginning of the spread of new tools like this.

Gene drives create a wide range of risks.[62] Targeting wild organisms requires understanding population dynamics and how to maintain stability.[63] Second, alterations could spread to nontarget or related populations.[64] What are the unintended side effects?[65] Can drive capabilities occur in populations not originally targeted?[66] Third, could populations of agricultural plants or livestock be harmed intentionally by bad actors?[67] While this may be difficult in industrialized farming, it is more possible in developing countries.[68] The risk is less for altering human populations because of long generation times.[69]

Oye et al. recommend a set of risk management steps to protect against gene drive hazards.[70] Current regulation of gene drives rely on approaches such as "listed-agent-and-toxin approaches," neither of which really cover the attributes of gene drive risks.[71] Likewise, U.S. environment regulations for animal applications are ambiguous; international environmental conventions fail to define the standard for assessing effects or mitigating harms; and U.S. security policies fail to cover gene drives within the scope of the oversight by Dual Use of Research of Concern (DURC).[72] International security conventions rely on narrow lists and fail to address gene drive risks, and the authors note that "[g]ene drives and most other advanced applications of genomic engineering do not use proscribed agents or create regulated toxins and hence fall beyond the scope of operational

59. *See id.*
60. *Id.*
61. *See id.* (suggesting international laws and treaties that currently govern terrorism and bioterrorism should incorporate misuse of synthetic biology).
62. *See generally* Oye et al., *supra* note 50.
63. *Id.* at 626–27.
64. *Id.* at 627.
65. *Id.*
66. *Id.*
67. *Id.*
68. *See id.* (explaining that "[d]eveloping countries that do not use centralized seed production and artificial insemination could be more vulnerable.").
69. *Id.*
70. *See id.*
71. *Id.* at 627-28.
72. *Id.* at 628.

regulations and agreements."[73]

The authors want "lead time" to assess these genomic technologies: they propose "adopting a function-based approach that defines risk in terms of the ability to influence any key biological component the loss of which would be sufficient to cause harm to humans or other species of interest."[74] They advocate a safety control that slows the risk vector release, proposing that "…concepts and applications should be published in advance of construction, testing, and release."[75] This is a good idea that needs an effective risk management regulatory body to implement.

C. Human Germ Line Research: The Effect on "Humanness"

Greely summarizes the reasons why human germline genomic modification is unlikely to be pursued: safety issues, low medical demand and non-medical demand, and its controversial nature.[76] Such modifications are constrained by public controversy and unease over manipulating the human genome.[77] Critics worry about the side effects of such manipulation for society, such as the fostering of inequality as rich parents seek to create enhanced children with improved intelligence or other traits as a result of germline editing.[78] Is the power of CRISPR to alter genetic makeup going to outstrip evolution and normal mating? Or is choice and enhancement part of what we need to survive as the world changes rapidly around us?

Some critics see human germline modification as playing God with core dimensions of humanness, an action that should not be undertaken without a robust ethical discussion about what it means.[79] In fact, one critic has argued in fact that nothing "short of a complete and total ban on human germline modification will do…."[80] On the other hand, proponents of CRISPR such as Steven Pinker note that parental selection of offspring traits is nothing new, and, in his words, "…[g]enetic editing would be a droplet in the maelstrom of naturally churning genomes."[81] For example, we allow in vitro

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73. *Id.*
74. *Id.*
75. *Id.*
76. Greely, *supra* note 42.
77. *See id.*
78. Skerrett, *supra* note 43 (statement by Steven Pinker regarding parents who want to select the traits for their offspring as a risk of germline editing) ("We affect the genetic makeup of our offspring, and the species, every time we choose one sex partner over another. And each of us introduces dozens of mutations into our own germlines by exposing ourselves to everyday radiation and chemical mutagens. Genetic editing would be a droplet in the maelstrom of naturally churning genomes.").
79. *See generally* Robert Pollack, *Eugenics Lurk in the Shadow of CRISPR*, 348 SCI. 871 (2015) (discussing concerns that modification opens the door for eugenics).
80. *Id.*
81. Skerrett, *supra* note 43.

fertilization to proceed with little regulatory oversight. This is a central concern, and one that the new NAM Report tackles with some strong recommendations for regulating such germline enhancement.[82]

III. GOVERNING THE RISKS OF NEW SCIENTIFIC TECHNOLOGIES

A. Why Does It Matter?

1. Self-Regulation is Admirable....and Suspect.

If self-regulation has some value in science, it is unclear how it offers any security in the world of start-up biotech companies or DIY science by individuals. Earlier controversies surrounding genetic editing, such as the recombinant DNA debates of the 1970s, involved claims of the trustworthiness of scientific self-regulation in scientific research.[83] Scientists claimed then that self-governance was effective. If that was so, then freedom from outside regulation was justified.[84] However, the history of the earlier rDNA controversy over the risks and uncertainties of gene engineering does not offer much encouragement for reliance on scientific self-regulation. Susan Wright's conclusion, after her exhaustive historical review of both the U.S. and British regulatory approaches, was as follows:

> The original policies of the United States and the United Kingdom, although framed narrowly, were unusual in attempting to forestall the emergence of unknown hazards from a novel form of technology and in requiring a degree of international cooperation for their success. The abandonment of those policies signified a return to laissez-faire development of technology driven primarily by the interests of its funders and creators and by the conditions of international industrial and scientific competition.[85]

Some of the reasons for the abandonment of regulation, according to Wright, included the structure of American research—serial competitive funding made it hard for university researchers to tolerate any form of regulatory activity which might slow down or limit their access to research

82. *See generally,* Comm. on Human Gene Editing: Scientific, Medical, and Ethical Considerations, Nat'l. Acad. of Sci. and Nat'l. Acad. of Med., Human Genome Editing: Science, Ethics, and Governance (2017) (prepublication), https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance [hereinafter the NAM Report].

83. *See* Furrow, *supra* note 2, at 1409–11.

84. *Id.* at 1412.

85. SUSAN WRIGHT, MOLECULAR POLITICS: DEVELOPING AMERICAN AND BRITISH REGULATORY POLICY FOR GENETIC ENGINEERING 456 (1994).

grants.[86] For the industry, global competitive pressures meant a similar reluctance to tolerate regulatory slowdowns for long.[87] Eventually both industry and academic researchers aligned to reduce NIH power and return to so-called self-regulation.[88]

The story of CRISPR is likely to follow the path of rDNA technology of the 70s and 80s. The ferocious frenzy created by a new technology such as CRISPR that promises patents, riches, and academic fame and celebrity status is hard to resist. The promises of such a tool tend to suppress long term efforts at mindful reflection about pace and risks, and cancels out objectivity even among the best of scientists who hope to benefit from the remarkable efficiency of CRISPR.

We cannot say that CRISPR does not present a range of risks, and we cannot safely feel comfortable with the claims of researchers to self-regulatory autonomy in such a case. We need even more with CRISPR – a systematic theory of institutional regulation of research hazards is required for differing levels of hazards. The CRISPR controversy, just like the rDNA controversy before it,[89] requires outside oversight to deal with the problem of research uncertainty in its many dimensions.

2. Patent Licenses Have Potential. . .and Limits.

CRISPR is still free to be used by industry and academia with few legal or regulatory constraints, given the slow pace of regulatory developments. This is changing rapidly as patents are developed for various CRISPR technologies. Patent disputes and their resolution may affect which of the commercial entities pursing CRISPR research benefits win and which are forced to stop.[90] The same result may occur with academic research institutions.[91] Additionally, litigation over and enforcement of patent rights may shift the functions of research universities from pure research to commercialization and profit.[92] In the words of one commentator, "[t]aken together, these shifts may complicate the future of gene editing."[93]

One response to the above critique is to suggest that the use of CRISPR

86. *Id.* at 454.

87. *See id.* at 454 ("[T]he most powerful factor, the structure of global industrial competition, transmitted by corporations that are free to move personnel and capital across national boundaries, set nations in competition to attract and keep new sources of innovation, industry, and employment.").

88. *Id.*

89. *Id.*

90. Jacob S. Sherkow, *Who Owns Gene Editing? Patents in the Time of CRISPR*, 38 BIOCHEMIST 26, 28 (2016).

91. *Id.* at 28–29.

92. *Id.* at 29.

93. *Id.*

patent licenses provides a beneficial form of self-regulation, reducing the need for external government regulation.[94] The use of patent licensing to limit applications of CRISPR has not previously been considered in the policy discussions to date.[95] Entering this policy vacuum, the Broad Institute, which holds several key patents on the CRISPR technology, has begun to license its CRISPR patent portfolio, first to Monsanto.[96] Their license restricts socially controversial applications, as they define such applications.[97] During the period of the patent term, a research entity may not develop an invention without first seeking and receiving a license from the Broad Institute.[98]

The Broad Institute will license non-exclusive research and commercial use of its patented CRISPR use in agriculture, subject to three limits.[99] First, the technology may not be used for gene drive.[100] Second, it may not be used to create sterile seeds.[101] Third, it may not be used to modify tobacco for any uses except creating a model organism and manufacturing non-tobacco products.[102]

This kind of licensing agreement effectively limits potentially controversial uses of patented technologies.[103] The benefits are real. The process is relatively quick, as the patent holder holds the decisional power and can anticipate some negative uses of the patient.[104] The license is enforceable in court and penalties can be built into the license.[105] The license can be specifically tailored to the concerns of both parties.[106] Lastly, the license is negotiated between the parties, rather than through the fractious

94. *See* Christi J. Guerrini et al., *The Rise of the Ethical License*, 35 NATURE BIOTECHNOLOGY 22, 23 (2017) (explaining that a solution may exist in "using patent licenses to restrict socially controversial applications of a technology") [hereinafter *Ethical License*].

95. *See id.* ("Notably, the use of patent licensing to limit applications has not yet entered the national or international policy conversation.").

96. *Monsanto Licenses CRISPR/Cpf1 from Broad Institute*, GENOMEWEB (Jan. 4, 2017), https://www.genomeweb.com/business-news/monsanto-licenses-crisprcpf1-broad-institute.

97. *See* Christi Guerrini, *Licensing 'CRISPR' Patents to Promote Public Interests*, BAYLOR C. OF MED. (Jan. 18, 2017), https://blogs.bcm.edu/2017/01/18/licensing-crispr-patents-promote-public-interests/ (explaining that Broad's license to Monsanto contains various restrictions on use).

98. *Ethical License, supra* note 94, at 23.

99. Issi Rosen, *Licensing CRISPR for Agriculture: Policy Considerations*, BROAD INST. (Sept. 29, 2016), https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations.

100. *Id.*

101. *Id.*

102. *Id.*

103. *Ethical License*, *supra* note 94, at 23.

104. *Id.*

105. *Id.*

106. *Id.*

process required by administrative regulations and statutes.[107] As a model of contract law regulation, it can effectively constrain some negative lines of research through enforcement of breach of the licensing agreement.

The limitations from a public policy perspective are also substantial.[108] The value of the patent will be affected by the license constraints, weakening the market value of the patent.[109] Second, the patent holder has to assess often competing ethical and risk perspectives of other stakeholders.[110] This puts the patent holder in an uncomfortable quasi-regulatory position, and is likely to limit the effective use of such licensing agreements.[111] After all, most patent holders want to make money from their patents, not regulate their use by others.[112] It is unlikely that we can rely on patent licensing agreements to resolve concerns about the risks of CRISPR or to control them in any significant way.

3. Summits and Academy Reports Are a Start. . .but Are Not Regularized

Regulatory bodies are involved in various aspects of CRISPR applications.[113] The FDA regulates genetic technologies;[114] NIH and NSF funding control the flow of research by amplifying its reach through grants.[115] This regulatory environment is inescapably chaotic—agencies with overlapping jurisdictions, regulations developed for other rather different technologies, and often with no coherent central process for evaluating and collecting data on the risks of this genomic editing tool.[116] Given the ease of application of CRISPR to DIY researchers, there can be a parade of horribles that moves far beyond human germline editing to produce "improved" biological entities.[117] We can acknowledge that there are effective regulatory

107. *Id.*
108. *Id.*
109. *Id.*
110. *Id.*
111. *Id.*
112. *Id.*
113. *See e.g.* Paradise, *supra* note 35; *see also* Alta R. Charo, *The Legal and Regulatory Context for Human Gene Editing*, 32 ISSUES SCI. & TECH. 39, 39 (2016) (explaining that gene editing is regulated by "an ecosystem that is made up of government, the public, and private industry. . .").
114. *See* Charo, *supra* note 113, at 40 (explaining that the FDA regulates gene therapy and the sale of genetically modified food like salmon).
115. *See* Furrow, *supra* note 2, at 1405.
116. *See* R. Alta Charo & Henry T. Greely, *CRISPR Critters and CRISPR Cracks,* 15 AM. J. BIOETHICS 11, 14-15 (2015), (describing the difficulty of determining the correct regulatory body to address CRISPR).
117. *See generally* Skerrett, *supra* note 43 (experts discussing potential harms); *see also generally* Charo & Greely, *supra* note 116 (discussing range of problems with the use of CRISPR for uses outside of human germ line editing).

islands—the FDA has power to regulate curative genetic tools, NIH certainly imposes controls through its control of funding streams, and so on, but we must acknowledge that large gaps still exist.[118]

The flurry of meetings, "summits," and other linked activities makes it appear that wise scientists and academics are indeed sorting through the risks and downsides of CRISPR. But many of the participants are scientists with a long term interest in the success of CRISPR in enhancing their own research success. Such ad hoc processes are just that, called into action briefly but without the capacity of in-depth review or continuity.

B. Renewing the Power of Technology Assessment

Given the limits of self-regulation and the peculiar uncertainties attendant upon research, a regulatory vacuum is undesirable. Some systematic means of evaluating risks is necessary. I will develop five criteria for evaluating a genetic tool such as CRISPR.[119] First, a brake or governor is needed to slow rapid development, whether through scientists' own restraint or outside pressures from government or professional organizations. A means to trigger that "governor"—a method by which the expansion of research can be checked in order to allow more careful evaluation of risks, benefits, and future developments—will also be necessary. Public control through funding agencies such as NIH certainly provides some regulatory controls and brakes potentially hazardous research. However, most industrial research is not touched by these funding streams, and as basic research is done either by industry or through industrial-academic cooperation, any controls through funding are weakened. It is also clear that federal funding decisions represent the value judgments of the scientific community involved in the peer review process, and the earlier rDNA controversy showed that the attitude of the U.S. funding agencies became one of speeding up research, not waiting for analysis of uncertain risks.[120]

Uncertainty in scientific research like CRISPR includes a range of risks—from human germline modification effects to agricultural harms. We need an institutional mechanism that can suspend or slow some kinds of research while thorough study is undertaken as to the nature of the research risks and modes of reduction, if any. What I earlier advocated with regard to rDNA research is equally applicable to CRISPR varieties of research: we need "…a more deliberate, explicit, and somewhat more pessimistic consideration of the area of uncertainty as to potential hazards, triggered by some mechanism

118. Charo & Greely, *supra* note 116, at 14.

119. This discussion of criteria is heavily based on my earlier discussion in Governing Science. Furrow, *supra* note 2.

120. *See* Wright, *supra* note 85, at 456 (explaining that the abandonment of early policies exemplified the importance of industrial advancement and scientific achievement).

to focus attention on the putative hazards of research and to mobilize resources for further inquiry, while dampening the momentum which a promising line of research accumulates."[121]

Second, scientific bias in favor of a hot new technology needs to be counteracted. Some external entity, like the former Office of Technology Assessment, can offer a systematic approach to risk assessment. Researchers in academic and industry have a vested interest in the research, inescapably, and their biases needed to be counterbalanced by a neutral regulatory body.[122]

Third, an external review organization needs the time and resources to conduct the technology assessment, to generate a full and complete record on the risks, and to give voice to all the interests involved, including the public.

Fourth, public participation in some form is needed, as Jasanoff et al. suggest.[123] The extent of public participation has often been cited as a goal against which to measure various approaches to technological problems.[124] Public participation has many benefits.[125] First, alternative viewpoints may offer new perspectives.[126] Second, in a partisan political world where elites are viewed with suspicion, real public participation may increase public confidence in the decision-making process.[127] Third, we want to find ways to give individuals some form of say in risks, even if the conclusion of a public process is that the risks are low, or are well worth encountering once understood.[128] Fourth, an ethical framework is needed to consider the long-term effects of CRISPR on human populations, where germline editing allows the transfer of new traits to future generations.[129]

Suppose we consider a moratorium such as Hank Greely has suggested.[130] Will the academic laboratories be joined by the private companies who have gambled with venture capital money on the possibilities of breakthrough treatments? It is easier to outline relevant values to consider in assessing a

121. Furrow, *supra* note 2, at 1421 (surveying the problem of regulating emerging risks in the face of uncertainty).

122. *Id.*

123. *See generally CRISPR Democracy*, *supra* note 29.

124. *See generally* DOROTHY NELKIN, TECHNOLOGICAL DECISIONS AND DEMOCRACY: EUROPEAN EXPERIMENTS IN PUBLIC PARTICIPATION (1977).

125. Furrow, *supra* note 2, at 1422.

126. *Id.*

127. *Id.*

128. *See generally* Charis Thompson, *Governance, Regulation, and Control: Of Which People, By Which People, For Which People?* International Summit on Human Gene Editing, Washington, D.C. December 2015 (explaining that these conversations need to include everyone, not just stakeholders).

129. We have seen some excellent first steps with the NAM Report sections written by bioethicists on the Committee, as well as some earlier writings, *e.g.* Charo & Greely, *supra* note 116, at 14-15; Niklaus H. Evitt, et al., *Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework*, 15 AM. J. BIOETHICS 25, 25 (2015).

130. Greely, *supra* note 42.

new technology than it is to imagine a regulatory structure that could apply them effectively. Today's regulatory environment in the U.S. consists of agencies with overlapping jurisdictions coupled with international agreements with a taxonomy of limitations and signatories.[131] Lacking a central oversight authority, CRISPR risks may be disregarded or not detected.

IV. 2017 REPORT OF THE NATIONAL INSTITUTES OF SCIENCE, ENGINEERING, AND MEDICINE (NAM REPORT).

The CRISPR technology has been analyzed by summits, conferences, and finally, a Consensus Statement development process by the Academies of Sciences, Engineering, and Medicine.[132] This has been an impressive assault on the uncertainty issues raised by CRISPR. But is it representative? Is it critical of aspects of this remarkably efficient tool? Is public participation considered in the membership of the panel?[133]

The expert process created by the NAS and the NAM has culminated in a lengthy monograph on the variety of dimensions of CRISPR.[134] It is, in the words of the NAS and NAM, a study conducted by a committee of experts.[135] The directive for the study was as follows:

> It will perform its own independent and in-depth review of the science and policy of human gene editing by reviewing the literature and holding data-gathering meetings in the U.S. and abroad to solicit broad input from researchers, clinicians, policymakers, and the public. The committee will also monitor in real-time the latest scientific achievements of importance in this rapidly developing field. Finally, while informed by the statement issued by the organizing committee for the international summit, the study committee will have broad discretion to arrive at its own findings and conclusions, which will be released in a peer-reviewed consensus report.[136]

The NAM Report, issued early in 2017, focuses exclusively on human applications of CRISPR.[137] The three academies that issued the NAM Report work together, in their words, "…to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies also

131. Charo & Greely, *supra* note 116, at 14–15.

132. The NAM Report, *supra* note 82.

133. *CRISPR Democracy*, *supra* note 29.

134. *See generally* The NAM Report, *supra* note 82.

135. *Id.* at iv.

136. *Human Gene Editing: Scientific, Medical, and Ethical Considerations*, NAT'L ACAD. MED. (2016) https://nam.edu/event/human-gene-editing-scientific-medical-and-ethical-considerations/.

137. The NAM Report, *supra* note 82, at 1.

encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine."[138] The NAM Report was written by a committee of twenty-two experts (legal academics, bioethicists, biologists, and bioengineering company leaders).[139] It was reviewed by twelve excellent academics and lawyers to ensure that review comments were considered.[140] It is a first class document: it summarizes the science clearly, it outlines the issues for human germline editing, and it makes specific recommendations. It is a one-off document by a working group under the NAM/E/S auspices.[141] The authors note that other studies are underway by the NAS and the NAM, including agricultural uses, gene drive issues, animal genome modification, and future biotechnology products.[142]

The report starts with a sanguine observation about the lack of need for regulation of human genome editing: it notes that CRISPR research requires high quality laboratories and medical facilities and this inevitably ensures regulatory oversight.[143] The report then observes that marketing of therapies using human genome editing products will need regulatory review and approvals. Such marketing will require regulatory bodies with the legal authorship, commitment and political support to block marketing of unapproved genome editing products.[144]

The Report takes the position that existing regulatory infrastructure and processes are sufficient for evaluating gene therapy using genome editing.[145] Uses should however be limited to treatment or prevention of disease or disability.[146] And the Report proposes public participation in some form before CRISPR can be used beyond disease treatment or prevention.[147]

The use of inheritable germline editing is viewed as problematic at this point.[148] The Report notes the disquiet that surrounds this use that can affect multiple generations and asks whether "enhancement" uses should be limited or prohibited.[149] Recommendation 6-1 proposes a moratorium on somatic or germline editing, while Recommendation 6-2 wants public discussion and

138. *Id.* at iii.
139. *See Id.* at v.
140. *Id.* at vi.
141. *Id.* at 1.
142. *Id.* at 13–15.
143. *Id.* at 80.
144. *Id.* at 81.
145. *Id.* at 83 (See Recommendation 4-1).
146. *Id.* (See Recommendation 4-2).
147. *Id.* (See Recommendation 4-4).
148. *See id.* at 118.
149. *Id.*

policy debate.[150]

The Report offers a detailed look at public participation—theory, existing practice, and possibilities in the CRISPR context.[151] The Report ultimately proposes a strong public participation model, to be developed. Recommendation 7-1 states: "Extensive and inclusive public participation should precede clinical trials for any extension of human genome editing beyond treatment or prevention of disease or disability."[152]

V. REINVENTING THE OFFICE OF TECHNOLOGY ASSESSMENT

Can we do better than using the National Institutes? The NAM Report is a thorough and well documented look at a worrisome aspect of the CRISPR tool, with other reports to follow. The authors are a well-respected and diverse group. I argue, however, that we need a standing agency that (1) promotes strong versions of public engagement in its design, (2) has an institutional memory, and (3) a staff familiar with a wide range of technology assessment problems would be preferable.

I propose that we reconstitute a new and improved Federal Office of Technology Assessment to provide a coherent framework for evaluating the risks of technologies like CRISPR in all of its possible applications.[153] The original Office of Technology Assessment (OTA) issued a wide range of valuable reports to assist Congress in evaluating thorny issues, but in 1995 it was closed.[154] Congress can now use the Congressional Research Service and the General Accounting Office in the absence of the now defunct OTA, but these offices do not provide the detail that is needed for difficult technological assessments, the depth of research, or the range that scientific uncertainty requires.[155] As Sclove writes: "Congress is indeed awash in information and analysis, including scientific and technical analysis, but lacks a trustworthy mechanism for evaluating, distilling and synthesizing this information."[156]

Adding another regulatory body to the world of U.S. government regulation will be met with political opposition. On the other hand, the model

150. *Id.* at 123.

151. *Id.* at 127-29, 130-31, 134.

152. *Id.* at 136.

153. Jathan Sadowski, *The Much-Needed and Same Congressional Office that Gingrich Killed Off and We Need Back*, THE ATLANTIC (Oct. 26, 2012), https://www.theatlantic.com/technology/archive/2012/10/the-much-needed-and-same-congressional-office-that-gingrich-killed-off-and-we-need-back/264160/; *see generally* RICHARD SCLOVE, WOODROW WILSON INT'L CTR. FOR SCHOLARS, REINVENTING TECHNOLOGY ASSESSMENT: A 21ST CENTURY MODEL, (April 2010) (proposing an improved model of the Office of Technology Assessment).

154. *See* SCLOVE, *supra* note 153, at page vii (Executive Summary).

155. *See Id.* at 18-19.

156. *Id.* at 19.

of an agency of technology assessment is based on solid experience with the OTA of the past, a form which can be improved to better serve the needs of scientific and technological assessment.[157] And it would better integrate the current morass of regulatory initiatives that govern the uncertain risks of CRISPR only glancingly, leaving large regulatory holes in the risk analysis.

Congress can use the Congressional Research Service and the General Accounting Office in the absence of the now defunct OTA, but neither provides the staff and the long-term attention span needed for difficult technological assessments. The need for an independent agency review and ongoing investigation of a technology like CRISPR is justified by the wide range of possible misfires of the technology may create. Sclove notes that all realms of human experience might be affected, and "…[a] well-crafted TA capability can assist citizens and decision-makers in understanding these kinds of broad and deep implications of technological innovation – implications that might otherwise escape attention until well after they, too, have become entrenched."[158]

An improved model of the Office of Technology Assessment offers a coherent model for an agency with broad experience with a range of technologies and with public engagement, one better equipped to counterbalance the biases of those who are fans of the technology as a research tool. A central purpose of a revived OTA would be to justify and propose moratoria on new research developments that may pose risks that need to be studied.[159] Since CRISPR may just be the first in a series of technologies with huge benefits and uncertain risks; a federal capacity to assess such new technologies is sorely needed under any political administration, regardless of political affiliation.

157. John Dunlop, *The Limits of Legal Compulsion*, 27 LABOR L. J. 67 (1976) (representing a classic article on a critical view of creating new regulatory agencies in response to perceived national problems).

158. SCLOVE, *supra* note 153, at 3.

159. *See generally* Matthew T. Wansley, *Regulation of Emerging Risks*, 69 VAND. L. REV. 401 (2016) (describing a model of regulation where agencies have the power to impose moratoria on emerging technologies).