A CRISPR FUTURE FOR GENE-EDITING REGULATION: A PROPOSAL FOR AN UPDATED BIOTECHNOLOGY REGULATORY SYSTEM IN AN ERA OF HUMAN GENOMIC EDITING

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Recent developments in gene-editing technology have enabled scientists to manipulate the human genome in unprecedented ways. One technology in particular, Clustered Regularly Interspaced Short Pallindromic Repeat (CRISPR), has made gene editing more precise and cost-effective than ever before. Indeed, scientists have already shown that CRISPR can eliminate genes linked to life-threatening diseases from an individual's genetic makeup and, when used on human embryos, CRISPR has the potential to permanently eliminate hereditary diseases from the human genome in its entirety. These developments have brought great hope to individuals and their families, who suffer from genetically linked diseases. But there is a dark side: in the wrong hands, CRISPR could negatively impact the course of human evolution or be used to create biological weaponry. Despite these possible consequences, CRISPR remains largely unregulated due to the United States's outdated regulatory scheme for biotechnology. Moreover, human embryo research, which is likely critical to maximizing the therapeutic applications of CRISPR, is not easily undertaken by scientists due to a number of federal and state restrictions aimed at preventing such research. This Note examines the possible benefits and consequences of CRISPR and discusses the current regulations in both the fields of biotechnology and human embryo research that hamper the government's ability to effectively regulate this technology. Ultimately, this Note proposes a new regulatory scheme for biotechnology that focuses on the processes used to create products using CRISPR, rather than the products themselves, with a focus on enabling ethical research using human embryos to maximize the potential benefits of CRISPR.

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INTRODUCTION

Twelve weeks after her birth, Layla Richards, an otherwise happy and healthy infant, was taken to the doctor after she began refusing milk.[1] What followed was every parent's worst nightmare: Layla was diagnosed with an aggressive form of leukemia.[2] After several rounds of chemotherapy and a bone marrow transplant failed to slow the disease, Layla's parents and physicians resigned themselves to the inevitable and prepared to make Layla's last few weeks as comfortable as possible.[3] But when a researcher serendipitously located a few doors down from the cancer ward where Layla was admitted got wind of the situation, he proposed a novel treatment that had, up until that point, only been tested in mice.[4] With the consent of her parents, Layla was injected with a vial full of an anonymous donor's white blood cells that were programmed to recognize and kill cancer cells.[5] Layla

1. Madhumita Murgia, *How Scientists in Britain Are Deciding the Future of Humanity*, NEWSWEEK (Dec. 28, 2016, 9:58 AM), http://www.newsweek.com/2017/01/06/gene-editing-dna-crispr-revolution-kathy-niakan-britain-535858.html [https://perma.cc/J59P-EZA4].
2. *Id.*
3. *Id.*
4. *Id.*
5. *Id.*

not only survived the treatment but went into remission within the month and, two years later, remains cancer free.[6]

Until recently, Layla's miraculous recovery would have been relegated to the pages of medical science-fiction novels. Today, however, researchers are closer than ever before to making stories like Layla's more commonplace thanks in large part to a tool called Clustered Regularly Interspaced Short Pallindromic Repeat (CRISPR), which enables scientists to manipulate the human genome with unprecedented precision. Despite its promise, CRISPR is not without controversy. Many of the potentially lifesaving therapies that scientists wish to research using this tool have been delayed or scrapped altogether because of complicated ethical questions and a general lack of regulation surrounding the technology. This Note focuses on one particularly challenging piece of this ethical puzzle—the use of human embryos in CRISPR research—and proposes a path for regulation of the technology that balances ethical concerns with CRISPR's promise to make medical miracles, like Layla's, everyday realities.

Since its discovery in 1993, CRISPR has excited scientists with the possibility that it could make genomic editing more accessible.[7] At the time, researchers hypothesized that because CRISPR technologies are easier to use and more cost-effective than traditional gene-editing techniques,[8] they would ultimately lead to the democratization of human genomic research.[9] It was not until January 2013, however, that scientists working in the Broad Institute announced that they had successfully programmed CRISPR technologies to genomically edit human cells.[10] This breakthrough signaled the beginning of the CRISPR craze and an onslaught of technological development.[11] In 2017 alone, CRISPR technologies enabled researchers to remove HIV from living animals,[12] edit out Huntington's disease in mice,[13] slow the growth of cancerous cells,[14] and open the door to the eradication of mosquito-borne diseases.[15] Despite the incredible impact this technology could have on

6. *Id.*

7. *See* Eric S. Lander, *The Heroes of CRISPR*, 164 CELL 18, 18 (2016).

8. *See, e.g.*, Dipankan Bhattacharya et al., *CRISPR/Cas9: An Inexpensive, Efficient Loss of Function Tool to Screen Human Disease Genes in* Xenopus, 408 DEVELOPMENTAL BIOLOGY 196, 197 (2015).

9. Feng Zhang, *CRISPR: The Democratization of Gene Editing*, SCIENCE, Sept. 26, 2014, at 3, 3.

10. *See generally* Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCIENCE 819 (2013).

11. *See generally* Elizabeth Pennisi, *The CRISPR Craze*, SCIENCE, Sept. 26, 2014, at 15.

12. *See generally* Chaoran Yin et al., *In Vivo Excision of HIV-1 Provirus by saCas9 and Multiplex Single-Guide RNAs in Animal Models*, 25 MOLECULAR THERAPY 1781 (2017).

13. *See generally* Su Yang et al., *CRISPR/Cas9-Mediated Gene Editing Ameliorates Neurotoxicity in Mouse Model of Huntington's Disease*, 127 J. CLINICAL INVESTIGATION 2719 (2017).

14. *See* Zhang-Hui Chen et al., *Targeting Genomic Rearrangements in Tumor Cells Through Cas9-Mediated Insertion of a Suicide Gene*, 35 NATURE BIOTECHNOLOGY 543, 549 (2017).

15. *See generally* Natapong Jupatanakul, *Engineered* Aedes aegypti *JAK/STAT Pathway-Mediated Immunity to Dengue Virus*, 11 PLOS NEGLECTED TROPICAL DISEASES, Jan. 12, 2017, at 1.

human health, recent developments have made the unfettered use of CRISPR controversial. Most notably, scientists from the Oregon Health & Science University (OHSU) announced in August 2017 that they successfully programmed CRISPR to correct a genetic mutation linked to heart failure in human embryos.[16] This news reignited fears of "designer babies" and "playing God" that opponents of stem cell research in the mid-1990s commonly cited.[17] The news also brought the question of CRISPR regulation to the forefront of national debate, as questions surrounding use of human embryos in research are particularly controversial.

Despite these fears, CRISPR remains largely unregulated in the United States because the current regulatory regime for biotechnology is a convoluted system involving a number of different federal agencies, each with overlapping roles, which leads to widespread confusion as to which agency is responsible for a particular area of law. Accordingly, researchers using CRISPR are often in the dark until they are readying products for market approval as to which laws will govern the product in which they have invested millions of dollars. Scientists using human embryos as part of a CRISPR-driven research plan are incapable of receiving federal funding for the project, which leads them to either abandon research involving human embryos or seek private funding.[18] These problems lead to somewhat discordant complications: CRISPR research involving human embryos is stifled because of a lack of funding, yet researchers are free to bend ethical boundaries in the realm of gene editing using CRISPR if they can secure private funding. These conflicting outcomes represent a worst-case scenario. Subsequently, the need to clarify the regulatory scheme for biotechnology products—like CRISPR—that may involve human embryos in the course of researching lifesaving treatments must be prioritized.

This Note is organized in three Parts. Part I begins by giving background information on CRISPR and its applicability to human health. Part I then discusses key moments in the decades-long debate over human embryo research and concludes with an overview of the current biotechnology regulatory regime in the United States. Part II discusses current proposals for biotechnology regulation and human embryo research regulation. Part III evaluates these proposals and ultimately recommends a comprehensive regulatory scheme that will shift the United States away from the end-product focus promulgated by current biotechnology regulations toward a process-oriented regime. These recommendations endeavor to give the government more insight into CRISPR research in the United States without

16. *See* Hong Ma et al., *Correction of a Pathogenic Gene Mutation in Human Embryos*, 548 NATURE 413, 418 (2017).

17. *See, e.g.*, Robert Cook-Deegan & Jane Maienschein, *Listening for the Public Voice*, SLATE (Aug. 16, 2017, 4:17 PM), http://www.slate.com/articles/technology/future_tense/2017/08/the_public_needs_to_weigh_in_on_the_ethics_of_genetically_engineering_humans.html [https://perma.cc/KZC6-CJRZ].

18. Sarah Webb, *A Patchwork Quilt of Funding*, NATURE (Nov. 1, 2007), https://www.nature.com/stemcells/2007/0711/071101/full/stemcells.2007.110.html [https://perma.cc/VZ24-P67H].

unnecessarily hampering biomedical research and to create nationally mandated ethical standards for the use of human embryos in gene-editing research. By offering suggestions for streamlining the regulatory process, this Note hopes to stimulate debate on CRISPR regulation and encourage policymakers to think critically about the future of human genome editing in the United States.

I. THE CURRENT STATE OF AFFAIRS: CRISPR, HUMAN EMBRYO RESEARCH, AND BIOTECHNOLOGY REGULATION WITHIN THE UNITED STATES

CRISPR is a naturally occurring molecule found in bacteria and is considered "the hallmark of a bacterial defense system."[19] In the field of gene editing, however, CRISPR is used as a catchall term for systems that enable researchers to program the CRISPR molecule to make precise cuts along a cell's genome.[20] Using CRISPR technologies, scientists can remove undesirable or harmful genetic sequences and replace them with neutral or beneficial genetic material.[21] Contrasted with earlier "transgenic" techniques, which require the time consuming and expensive process of inserting the genetic material of a different species,[22] CRISPR is much more precise, cost-effective, and straightforward. Accordingly, CRISPR has enabled large numbers of scientists to delve into the world of gene editing, simultaneously raising questions about how this technology should be used. This Part addresses important background information regarding the current regulatory debate surrounding CRISPR by first discussing the development and possible applications of CRISPR, then focusing on the historic and current questions regarding human embryo research. This Part concludes by explaining the current regulatory landscape for biotechnology in the United States.

A. The Who, What, Where, and How of CRISPR

Understanding the need for CRISPR regulation requires a baseline understanding of how CRISPR works and, subsequently, why the development of this technology represents such a meteoric leap in the field of genomic editing. The following section, aimed at a nonscientific audience,

19. *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/P2LK-HJYL] (last visited Aug. 24, 2018).

20. *Id.*

21. *Id.*

22. *See, e.g.*, Michael Hernould et al., *Male-Sterility Induction in Transgenic Tobacco Plants with an Unedited Atp9 Mitochondrial Gene from Wheat*, 90 PROC. NAT'L ACAD. SCI. 2370, 2371 (1993). The oft-cited example of transgenic gene editing is the insertion of jellyfish DNA into rabbit embryos to create glow-in-the-dark rabbits. *See* Amanda Holpuch, *Scientists Breed Glow-in-the-Dark Rabbits*, GUARDIAN (Aug. 13, 2013, 17:49), https://www.theguardian.com/world/2013/aug/13/glow-in-dark-rabbits-scientists [https://perma.cc/L4MN-9H8J].

explains first how CRISPR works and second, possible applications of CRISPR that would require human embryo research.

1. The Nuts and Bolts of CRISPR Technology: How CRISPR Works

In 1993, Spanish scientist Francisco Mojica noticed repeating sequences of genetic code separated by "spacers" in bacteria.[23] Confused by the presence of these sequences, Mojica began investigating and eventually discovered that the spacers were remnants of genetic code from past viral invaders.[24] This system of DNA sequences and spacers is a hallmark of the bacterial defense system and was given the name CRISPR by Mojica and his colleagues.[25] Today, the term "CRISPR" is typically used to refer to the technologies researchers have developed over the past decade that enable genomic editing by manipulating the naturally occurring CRISPR to act as a pair of molecular scissors.[26]

To understand these modern technologies, however, it is important to know how the naturally occurring CRISPR defense system found within bacteria works. When a virus attacks a bacterium, the bacterium's immune system sends out enzymes in response.[27] In instances where the virus is successfully destroyed, the enzymes store a piece of the virus's DNA in the spacers between the CRISPR DNA sequences.[28] Should the same virus attack again, the bacterium's immune system will be able to match the invading virus's DNA with the stored portion and quickly kill the virus by cutting out the stored, matching sequence.[29] To help visualize this process, imagine each portion of viral DNA that the bacterium stores is a barcode. When a new virus enters the cell, the bacterium scans all of the stored barcodes of previous invaders. If one of the barcodes is a match, the bacterium can send out targeted enzymes that "snip" the matching barcode from the viral invader's DNA, thereby killing the invader.

The power of CRISPR stems from this ability to pinpoint and snip a DNA sequence at a precise location along the genome. Indeed, scientists often liken CRISPR to a pair of "molecular scissors" that enables targeted genomic editing.[30] This transformation of gene editing is particularly impressive when compared with earlier transgenic[31] techniques developed in the 1980s.

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23. *See* Lander, *supra* note 7, at 18.

24. *See id.* at 20.

25. *See id.* at 19.

26. Unless otherwise specified, this Note's use of the term CRISPR refers to the technology—not the naturally occurring CRISPR molecule found in a bacterium.

27. *See* Fedor V. Karginov & Gregory J. Hannon, *The CRISPR System: Small RNA-Guided Defense in Bacteria and Archaea*, 37 MOLECULAR CELL 7, 9 (2010).

28. *See id.* at 10.

29. Ekaterina Pak, *CRISPR: A Game-Changing Genetic Engineering Technique*, HARV. U.: SCI. NEWS (July 31, 2014), http://sitn.hms.harvard.edu/flash/2014/crispr-a-game-changing-genetic-engineering-technique/ [https://perma.cc/QS9S-9WCG].

30. *See generally* Guy Riddihough, *CRISPR Cas9 Molecular Scissors*, 351 SCIENCE 867 (2016).

31. Transgenic gene editing literally means across-species gene editing and occurs when "a gene is moved from one non-closely related species to another." Keith Edmisten, *What Is*

While transgenic gene editing enabled scientists to insert DNA at specific locations in embryonic cells, "the process was inefficient—requiring selection and screening to identify the one-in-a-million [viable] cells."[32] This process often resulted in DNA insertion at the wrong point along the genome, which led scientists to determine that "[t]he secret to efficient genome editing . . . was to find a reliable method to produce a . . . break at any desired location."[33] With the discovery of CRISPR, scientists finally saw a tool that they believed would help them modernize genomic editing and began working to harness CRISPR's ability to cut DNA sequences at precise locations.[34]

While scientists had long hypothesized that a deeper understanding of CRISPR would advance the field of gene editing, it was not until 2011 that researchers finally discovered all of the components necessary to make this theory a reality.[35] And in 2013, Feng Zhang and his team from the Broad Institute successfully adapted CRISPR for genomic editing in human and mouse cells.[36] No longer was CRISPR simply an obscure immune defense system relegated to bacterial cells—the term now referred to a powerful technology capable of editing the human genome in unprecedented ways.[37]

Broadly, CRISPR technologies rely on two components. The first component is the enzyme Cas9, which is responsible for actually cutting DNA strands.[38] The second component is "a guide [RNA] molecule that directs Cas9 to a specific target like a genetic GPS system."[39] Once the Cas9 enzyme has snipped the DNA sequence at the site directed by the guide molecule, the CRISPR user then has the option to remove, replace, or insert

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the Difference Between Genetically Modified Organisms and Genetically Engineered Organisms, N.C. ST. U., https://agbiotech.ces.ncsu.edu/q1-what-is-the-difference-between-genetically-modified-organisms-and-genetically-engineered-organisms-we-seem-to-use-the-terms-interchangeably/ [https://perma.cc/SNF9-LCPH] (last visited Aug. 24, 2018).

32. Lander, *supra* note 7, at 24.

33. *Id.* at 24.

34. *See id.*

35. *CRISPR Timeline*, BROAD INST., https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-timeline [https://perma.cc/EXR9-3UB9] (last visited Aug. 24, 2018).

36. *See* Cong, *supra* note 10, at 822; *see also* Prashant Mali et al., *RNA-Guided Human Genome Engineering via Cas9*, 339 SCIENCE 823, 823 (2013).

37. Briefly, scientists program CRISPR by "design[ing] and synthesiz[ing] short RNA molecules that match a specific DNA sequence . . . . Then . . . this 'guide RNA' shuttles molecular machinery to the intended DNA target. Once localized to the DNA region of interest, the molecular machinery can silence a gene or even change the sequence of a gene." Pak, *supra* note 29.

38. *See* Josiane E. Garneau et al., *The CRISPR/Cas Bacterial Immune System Cleaves Bacteriophage and Plasmid DNA*, 468 NATURE 67, 69–70 (2010).

39. Ed Yong, *CRISPR's Most Exciting Uses Have Nothing to Do with Gene Editing*, ATLANTIC (Jan. 5, 2016), https://www.theatlantic.com/science/archive/2016/01/the-most-exciting-uses-of-gene-editing-technology-involve-no-editing/422619/ [https://perma.cc/YHX5-EDLQ]; *see also* Haroon Butt et al., *Efficient CRISPR/Cas9-Mediated Genome Editing Using a Chimeric Single-Guide RNA Molecule*, 8 FRONTIERS PLANT SCI. 1441, 1442 (2017).

genomic material into the cell.[40] In this way, CRISPR technologies enable scientists to precisely locate genes they would like to change and program the enzyme to target those genes. These developments make CRISPR the most advanced gene-editing technology currently available and enable scientists to edit the human genome in previously impossible ways, which many believe will lead to the development of lifesaving medical advancements.[41]

2. CRISPR Could Potentially Expedite Medical Advancement for the World's Most Challenging Diseases

Since 2013, scientists around the world have continually refined CRISPR technology to make it even more precise. Today, CRISPR gene editing "can be likened to editing a sentence with a word processor to delete words or correct spelling mistakes."[42] Scientists using the technology have "mutate[d] several suspected cancer genes simultaneously in the somatic cells of adult mice . . . . [They] have also corrected disease-causing gene defects in adult mice, such as the mutations that cause hemophilia and sickle cell anemia."[43] And in July 2017, scientists at OHSU reported that they successfully edited human embryos, removing a genetic mutation that causes heart failure in infants.[44] The success of this experiment brought concerns over gene editing to the forefront of national debate, particularly with regard to the ethics of conducting experiments on human embryos.[45] To illustrate the promise of CRISPR, this section details recent CRISPR experiments as well as potential applications for human health.[46]

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40. *See generally* S. Antony Ceasar et al., *Insert, Remove or Replace: A Highly Advanced Genomic Editing System Using CRISPR/Cas9*, 1863 BIOCHIMICA ET BIOPHYSICA ACTA 2333 (2016).

41. *See, e.g.*, Andrew Scott, *How CRISPR Is Transforming Drug Discovery*, 555 NATURE OUTLOOK, Mar. 7, 2018, at S10, S10; Victor Tangermann, *A CRISPR Future: Five Ways Gene Editing Will Transform Our World*, FUTURISM (Jan. 30, 2018), https://futurism.com/crispr-genetic-engineering-change-world/ [https://perma.cc/5ZBH-XSJY].

42. Pak, *supra* note 29.

43. Jon Cohen, *"Any Idiot Can Do It." Genome Editor CRISPR Could Put Mutant Mice in Everyone's Reach*, SCIENCE (Nov. 3, 2016, 10:00 AM), http://www.sciencemag.org/news/2016/11/any-idiot-can-do-it-genome-editor-crispr-could-put-mutant-mice-everyones-reach [https://perma.cc/S4UN-GAEW].

44. *See* Ma et al., *supra* note 16, at 418.

45. *See, e.g.*, Cook-Deegan & Maienschein, *supra* note 17.

46. Notably, CRISPR has been used extensively to edit crops and animals for food sources and is subsequently a critical component of the discussion surrounding genetically modified organisms (GMOs). For further reading on CRISPR and GMOs, see Sarah Zhang, *CRISPR Could Usher in a New Era of Delicious GMO Foods*, ATLANTIC (Sept. 19, 2016), https://www.theatlantic.com/health/archive/2016/09/gmo-food-crispr-cabbage/500528/ [https://perma.cc/G8ZR-GG3Z].

a. CRISPR's Precision Could Lead to Cures for Monogenic Diseases like Sickle-Cell Anemia

CRISPR's most straightforward therapeutic application is in the field of monogenic[47] diseases—such as cystic fibrosis, sickle-cell disease (SCD), and Duchenne muscular dystrophy.[48] Monogenic diseases are the result of a single mutation along the human genome, which means that absent this mutation, the disease would not exist.[49] Scientists have long hypothesized that gene editing could rid the world of monogenic diseases but have lacked precise tools for the task.[50] The discovery of CRISPR, and its ability to precisely locate and delete genetic mutations, brings the scientific community closer than ever before to the possible eradication of a number of debilitating monogenic diseases.[51]

SCD is one such monogenic disease that is caused by a mutation in a single nucleotide in human DNA that codes for hemoglobin[52]—namely, there is "a T where an A should be."[53] This mutation leads to the creation of sickle-shaped cells that stick together and cause buildups of cells.[54] As a result of these buildups, parts of the body are deprived of oxygen and blood vessels are blocked, which causes an individual with SCD to experience "chronic anemia, severe pain episodes, . . . progressive damage to vital organs such as the brain, lung, and kidney," and, ultimately, premature death.[55] The only cure currently available for SCD involves cell transplantation to the SCD patient from a matching donor, a process that "has been used sparingly because of the difficulty in identifying donors, risks associated with the toxicity of the transplant regimen . . . and potentially fatal graft-versus-host disease."[56]

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47. The World Health Organization defines monogenic diseases as "diseases result[ing] from modifications in a single gene occurring in all cells of the body." *Genes and Human Disease*, WORLD HEALTH ORG., http://www.who.int/genomics/public/geneticdiseases/en/index2.html [https://perma.cc/9RAQ-63L5] (last visited Aug. 24, 2018).

48. *See generally* Hasan Mollanoori & Shahram Teimourian, *Therapeutic Applications of CRISPR/Cas9 System in Gene Therapy*, 40 BIOTECHNOLOGY LETTERS 907 (2018).

49. *See Genes and Human Disease*, *supra* note 47.

50. *See* Matthew Porteus, *Towards a New Era in Medicine: Therapeutic Genome Editing*, 16 GENOME BIOLOGY 286, 286 (2015).

51. *CRISPR: Editing Genes Becomes a Reality*, DERMATOLOGY WORLD (July 29, 2017), https://aadmeetingnews.org/2017-summer-meeting-dailies/crispr-editing-genes-becomes-a-reality/ [https://perma.cc/JHH3-2K4L].

52. "Hemoglobin is the protein contained in red blood cells that is responsible for delivery of oxygen to the tissues." HENRY H. BILLETT, CLINICAL METHODS: THE HISTORY, PHYSICAL, AND LABORATORY EXAMINATIONS 718 (H. Kenneth Walker et al. eds., 1990).

53. Karla Lant, *CRISPR May One Day Cure Sickle-Cell Disease*, FUTURISM (Aug. 24, 2017), https://futurism.com/crispr-may-one-day-cure-sickle-cell-disease/ [https://perma.cc/CC7N-UPVL].

54. *Id.* Normal red blood cells are disc shaped, which enables the cells to slide past each other and decreasing the chances of cell buildup. *See id.*

55. Mark A. DeWitt et al., *Selection-Free Genome Editing of the Sickle Mutation in Human Adult Hematopoietic Stem/Progenitor Cells*, 8 SCI. TRANSLATIONAL MED. 360, 360 (2016).

56. *Id.*

Fortunately, this depressing prognosis may soon be a relic thanks to research conducted by a group of American scientists who, in 2016, successfully edited SCD-afflicted human cells in mice models using CRISPR.[57] In the first stage of this experiment, the researchers found that they could repair up to 25 percent of the affected cells using CRISPR, far surpassing the 2–5 percent threshold at which most patients display clinical improvement.[58] This efficacy dropped to 5 percent in the second stage of the experiment when the corrected cells were then engrafted into mice models,[59] leading one of the study's authors to caution against moving forward with clinical trials in humans and argue that "it would be best to improve efficiency before [this technology] is deployed in people."[60] Undeterred by this warning, SCD patient advocacy groups have pushed for clinical trials in humans, and the National Institutes of Health (NIH) launched a study in 2017 examining current opinions of CRISPR among SDC patients, family members of patients, and SCD-related healthcare providers.[61] SCD is thus an example of one disease that could possibly be eradicated through the use of CRISPR therapeutics.

b. CRISPR's Ability to Permanently Alter Heritable Traits Could Lead to the Complete Eradication of Hereditary Diseases

One of the most significant capabilities of CRISPR as compared to other gene-editing technologies is its ability to create heritable traits that can be passed from generation to generation through the manipulation of what are known as germline cells.[62] Germline cells are responsible for the traits that are passed down from generation to generation and are thus quite different from somatic cells, which are nonheritable and unique to an individual.[63] In Layla Richards's case, only her somatic cells were altered.[64] This means that even though the cancer was successfully edited out of her blood cells, if she developed the cancer because of a genetic predisposition for childhood leukemia, Layla's future children may still be at risk of inheriting the same predisposition.

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57. *Id*; *see also* Heidi Ledford, *CRISPR Deployed to Combat Sickle-Cell Anaemia*, NATURE (Oct. 12, 2016), https://www.nature.com/news/crispr-deployed-to-combat-sickle-cell-anaemia-1.20782 [https://perma.cc/944Q-RD7M].

58. *See* DeWitt et al., *supra* note 55, at 360.

59. *See id.*

60. Ledford, *supra* note 57.

61. Nat'l Human Genome Research Inst., *Examining the Knowledge, Attitudes, and Beliefs of Sickle Cell Disease Patients, Parents of Patients with Sickle Cell Disease, and Providers Towards the Integration of CRISPR in Clinical Care*, CLINICALTRIALS.GOV (2017), https://clinicaltrials.gov/show/NCT03167450 [https://perma.cc/4WHB-77Q6].

62. Press Release, Nat'l Insts. of Health, With Stringent Oversight, Heritable Germline Editing Clinical Trials Could One Day Be Permitted for Serious Conditions; Non-Heritable Clinical Trials Should Be Limited to Treating or Preventing Disease or Disability at This Time (Feb. 14, 2017) [hereinafter NHS Press Release], http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24623 [https://perma.cc/QV8S-TQ3X].

63. *Id.*

64. *See* Murgia, *supra* note 1.

CRISPR opens the door to the possibility of editing out such predispositions before a child is even born through editing germline cells within a human embryo or other precursor cell.[65] The edits made to the embryo or precursor cell would then be passed down from generation to generation, as if they were part of the child's naturally occurring genetic makeup.[66] When it comes to the eradication of diseases like childhood leukemia, this idea sounds like a no-brainer, but scientists warn that in the wrong hands, these types of changes to heritable cells could have disastrous effects on the human genome.[67]

The creation of a gene drive is one such possible application of CRISPR that could permanently alter the human genome. A gene drive occurs when the odds of inheriting a particular trait are manipulated to nearly guarantee that the trait will be inherited.[68] An offspring typically has a 50 percent chance of inheriting a particular trait from its parents, but inserting a gene drive created by CRISPR technologies would "circumvent these traditional rules" and "allow [the targeted traits] to spread to all members of a population."[69] For example, the use of gene drives to limit the reproductive capabilities of a particular species has been proposed for pest management programs and the eradication of mosquitos.[70] But given the disastrous consequences that might befall ecosystems as a result of these changes, scientists have been reluctant to release these altered populations into the wild.[71] The same concerns are present—although to a lesser degree given the slower pace of evolution—for the human species. These concerns, coupled with the general need to conduct gene-drive research on human embryos, present significant ethical questions for policymakers and researchers that have not, as of yet, been addressed.

3. CRISPR and National Security: Global Promise or Global Threat?

Given the widespread effect CRISPR-edited cells could have on global ecosystems, James Clapper, the former Director of National Intelligence, raised concerns that CRISPR might pose national security issues. Clapper contended that "[r]esearch in genome editing conducted by countries with different regulatory or ethical standards than those of Western countries probably increases the risk of the creation of potentially harmful biological agents or products," leading to serious national security implications.[72] The

65. *See* NHS Press Release, *supra* note 62.

66. *See id.*

67. *See id.*

68. *See FAQs: Gene Drives*, WYSS INST., https://wyss.harvard.edu/staticfiles/newsroom/pressreleases/Gene%20drives%20FAQ%20FINAL.pdf [https://perma.cc/SSL9-WWT5] (last visited Aug. 24, 2018).

69. *Id.*

70. Carl Zimmer, *'Gene Drives' Are Too Risky for Field Trials, Scientists Say*, N.Y. TIMES (Nov. 16, 2017), https://www.nytimes.com/2017/11/16/science/gene-drives-crispr.html [https://perma.cc/EXJ2-V7PC].

71. *Id.*

72. James R. Clapper, Director of Nat'l Intelligence, Statement for the Record: Worldwide Threat Assessment of the US Intelligence Community, Senate Armed Services

concern is that the low cost and broad accessibility of CRISPR technology could lead to use of this technology for the creation of biological weapons.[73] One such example posited by the National Academies of Science (NAS) is that use of gene drives could lead to weaponized vectors, such as mosquitos, transmitting not only disease but potentially toxins as well.[74] Accordingly, CRISPR technology in the wrong hands poses significant national security concerns.

CRISPR is categorized as a "dual-use" technology—one that can be used for either ethical or malign purposes. The U.S. government generally tries to influence such technologies "by controlling proliferation through export controls and international agreements . . . and by mitigating the risks of proliferation through other activities such as deterrence, disruption, and preparedness."[75] The Congressional Research Service contends that it is exactly the dual-use nature of CRISPR that makes it less of a threat than Clapper fears—it may increase the likelihood of biological warfare but it will concurrently be the most important tool available in mitigating that threat.[76] Accordingly, a deeper understanding of CRISPR is necessary to counteract potential misuse of the very same technology in bioterrorism.

CRISPR has great potential to cure some of the most vexing diseases of the modern era, from genetically linked afflictions like SCD and Duchenne muscular dystrophy to hereditary cancer.[77] It can potentially eradicate these diseases from the human genome in their entirety through the use of gene drives.[78] These developments are, however, attended by serious ethical quandaries regarding the role humans should play in manipulating the human genome and pose serious threats to national security. Additionally, many of these developments require the use of human embryos as part of the research and development process, which has previously caused strife within the United States[79] and begs the question of how CRISPR research should be regulated.

B. A Historical Overview of Human Embryo Research in the United States

As discussed in Part I.A, many of the most promising medical applications of CRISPR require the use of human embryos for research purposes. However, research involving human embryos has been an ethically fraught

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Committee 9 (Feb. 9, 2016), https://www.dni.gov/files/documents/SASC_Unclassified_2016_ATA_SFR_FINAL.pdf [https://perma.cc/B5KK-E48S].

73. MARCY E. GALLO ET AL., CONG. RESEARCH SERV., R44824, ADVANCED GENE EDITING: CRISPR-CAS9 31 (2017).

74. NAT'L ACADS. OF SCIS., ENG'G, & MED., GENE DRIVES ON THE HORIZON: ADVANCING SCIENCE, NAVIGATING UNCERTAINTY, AND ALIGNING RESEARCH WITH PUBLIC VALUES 159–61 (2016).

75. GALLO ET AL., *supra* note 73, at 31.

76. *Id.*

77. *See generally* Mollanoori & Teimourian, *supra* note 48.

78. *See* NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 74, at 153.

79. *See, e.g.*, Claudia Kalb, *Stem-Cell Research's Controversial Past*, NEWSWEEK (Aug. 24, 2010, 3:48 PM), https://www.newsweek.com/stem-cell-researchs-controversial-past-71475 [https://perma.cc/9MXE-6EES].

issue for a number of decades, which has resulted in the erection of a number of federal barriers in the United States. This section discusses the reasoning behind objections to human embryo research throughout recent American history to give a comprehensive picture of the current considerations policymakers must take into account when weighing the possible medical advancements made possible by CRISPR against concerns of constituents.

1. Key Issues for Opponents of Human Embryo Research

Opponents of embryonic research typically cite moral and ethical concerns as the driving motivations for their disapproval. These ethical concerns are founded in three main areas: ways in which human embryos are acquired, how embryos are treated during research, and processes for destroying embryos when research is complete. These points of opposition are discussed in turn.

a. Opponents of Human Embryo Research Are Concerned with How Embryos for Research Are Acquired

Human embryos used for medical research are often acquired from in vitro fertilization (IVF) labs in situations where the owners of the embryos decide that particular embryos are unwanted.[80] These embryos may be deemed unwanted for a number of reasons, including the finding of a serious, life-threatening medical condition or the successful implantation of another embryo during a previous round of IVF (making the "extra" embryos created for the intended parent or parents unnecessary).[81] Many endocrinologists estimate that there are roughly one million such embryos in storage facilities throughout the United States frozen in liquid nitrogen as families, clinics, and courts decide their fates.[82] For some, the question of what to do with the unused embryos presents challenging questions about the definition of life,[83]

80. Thomas Douglas & Julian Savulescu, *Destroying Unwanted Embryos in Research*, 10 EUR. MOLECULAR BIOLOGY ORG. REP. 307, 307 (2009).

81. *See* Tamar Lewin, *Industry's Growth Leads to Leftover Embryos, and Painful Choices*, N.Y. TIMES (June 17, 2015), https://www.nytimes.com/2015/06/18/us/embryos-egg-donors-difficult-issues.html [https://perma.cc/9L4L-2UB5]. The question of what to do with "extra" embryos leads to challenging moral questions for those that initially commissioned the embryos. To illustrate, consider a recent article in the *New York Times* describing the Watts family's struggle with exactly this issue. Using eggs from a donor, the couple received ten viable embryos, four of which were implanted in Angel Watts, resulting in the births of the couple's children. On advice from their doctor, the couple decided not to have any more children and took to Facebook to find someone who would want the six leftover embryos, posting: "We have 6 good quality frozen six-day-old embryos to donate to an amazing family who wants a large family . . . . We prefer someone who has been married several years in a steady loving relationship and strong Christian background, and who does not already have kids, but wants a boat load." *Id.*

82. *See id.*

83. These questions have troubled some people to such an extent that a small number of women opt for a procedure known as compassionate transfer in which "a doctor place[s] the embryos in the womb of the woman who made them, at a time of the month when she will not become pregnant." *Id.*

and for others the decision to donate the embryos to research labs is fairly straightforward. Unfortunately, "[t]here are no national statistics on what happens with these leftover embryos."[84] Accordingly, trying to determine what the consensus surrounding use of unused embryos would—or should—be poses challenges. As a practical matter, fertility clinic employees report that many embryos "sit in storage indefinitely . . . costing $300 to $1,200 a year" in storage fees.[85]

The debate surrounding the acquisition of human embryos for research mirrors the abortion debate. Many religious organizations, including the Catholic Church, are opposed to the creation of embryos for IVF altogether because of a staunch belief that life begins at conception, while many "evangelicals accept in vitro, but believe frozen embryos have the right to full lives."[86] The U.S. legal system is of no help to individuals who are involved in disputes over embryos because the domestic IVF market remains largely unregulated,[87] which often leaves those who would like to donate unused embryos in questionable legal territory.

b. Concerns Arise Surrounding the Physical Handling of Human Embryos During the Course of Research

The debate over ethical use of human embryos continues even after the embryos have been donated for research. Unlike other forms of human tissue, human embryos carry a more significant moral weight because of their potential for life.[88] In a cross-cultural study, researchers found that the most common reason for donation was "a willingness to contribute to potentially curative medical research."[89] As the authors of the study point out, however, the reason behind the donation "raises a separate *ethical* concern about the patients' understanding of the information they were given about the research goals,"[90] underscoring the question of whether donors should be able to earmark embryos for certain types of research.

There is also concern that fertility clinic employees may put undue pressure on people considering donation of embryos for research by essentially coercing them into the donation using their relative position of authority. For this reason, researchers at Stanford University's biobank came up with a process that enables "people to make this decision in the privacy of their own homes—without any interaction with clinic personnel or scientists who might benefit from the research."[91] The two-part procedure

84. *Id.*
85. *Id.*
86. *Id.*
87. *See id.*
88. *See* Jackie Leach Scully et al., *Donating Embryos to Stem Cell Research*, 9 J. BIOETHICAL INQUIRY 19, 21 (2012).
89. *Id.* at 22.
90. *See id.*
91. Krista Conger, *New Approach to IVF Embryo Donations Lets People Weigh Decision*, STAN. MED. (Apr. 7, 2011), https://med.stanford.edu/news/all-news/2011/04/new-approach-to-ivf-embryo-donations-lets-people-weigh-decision.html [https://perma.cc/S7ZP-AQ3L].

advocated by the Stanford team begins with the clinic providing written information pertaining to embryo donation that the potential donor is free to take home or discard. If the potential donor decides to move ahead with the donation, then she engages with a biobank staff member who follows a script to confirm the donor's purported choices, including confirming the type of research the donor would like to support.[92] Clinics across the country have adopted similar processes to ensure the decision to donate embryos to scientific research is done of the donor's own volition and that the embryos are going towards research the donor personally supports. But given the lack of regulation in the field, it remains an open question whether the donor would have any recourse should it be discovered that the embryos were used in a manner contrary to the donor's wishes.

c. Many Groups Worry About How Embryos Are Destroyed at the Conclusion of Research

Finally, there is controversy surrounding the ways in which embryos are destroyed after they have been used for scientific research. Tracking the earlier debate surrounding acquisition of human embryos,[93] opponents of embryo donation decry the destruction of embryos following research and claim a moral interest in the value of life they believe is inherent to embryos.[94]

The immorality ascribed to destruction of embryos by opponents of this research is typically supported by one of three beliefs. First, many opponents believe that beings with certain mental capacities should not be killed, often citing "consciousness, self-consciousness, sensitivity to pleasure and pain, and rationality" as components of this mental capacity.[95] In the debate over embryonic research, however, this argument falls flat because scientists have shown that embryos do not develop feelings of pleasure or pain until sixteen weeks, consciousness until twenty-four weeks, development of self-consciousness or rationality until after birth, and, in fact, "lack even the beginnings of a nervous system" until two weeks after conception.[96]

Second, opponents often cite species membership as a reason for shying away from embryonic research and claim that, because these are human

92. *See* Tasha Kalista et al., *Donation of Embryos for Human Development and Stem Cell Research*, 8 CELL STEM CELL 360, 360–62 (2011). The form used by the Stanford biobank gives potential donors the option of donating unused embryos to one or both of the following classes of research: (1) human development research, which "uses embryos to learn more about early human development, embryo quality, and improving IVF clinical outcomes, including projects such as embryo imaging studies or culture media comparisons"; or (2) stem cell research, which "uses embryos for embryonic stem cell research by making cell lines, which might be used to develop therapies to treat injured tissue, diseases, and disorders." *Id.* at 361.

93. *See supra* Part I.B.1.a.

94. *See* Douglas & Savulescu, *supra* note 80, at 307–08.

95. *Id.* at 309.

96. *Id.* at 309–10.

embryos, they have greater moral value than embryos from other species.[97] But researchers are quick to point out that species membership should not have any more significance because "the assignment of beings to different species depends on various biological criteria that seem to lack any moral content or relevance."[98]

Finally, opponents often condemn the deprivation of a valuable future for an embryo as a reason for banning embryonic research.[99] It is very unlikely, however, that embryos will go on to become humans capable of leading valuable lives; unused embryos are often "destined to languish in freezers until they are destroyed for some other reason."[100] Accordingly, the foundational concerns of opponents of embryonic research are untethered from the realities of embryonic life.

Despite the foundational flaws of many opponents' arguments, there are serious reasons to be concerned about unregulated embryonic research, particularly when embryos move beyond the early stages of development and into phases in which sensations of pain, pleasure, and consciousness begin developing. To this end, researchers and governments around the world have long supported the fourteen-day rule, which draws a "legal and regulatory line in the sand" after which continued research on human embryos is impermissible.[101] This rule mandates that after fourteen days in vitro, an embryo used for research must be destroyed—this timing was originally proposed because it "represents the earliest point at which an embryo's biological individuation is assured."[102] The rule was not, however, "intended to be a bright line denoting the onset of moral status in human embryos" but was designed as "a public-policy tool . . . to carve out a space for scientific inquiry and simultaneously show respect for the diverse views on human-embryo research."[103] In this regard, the fourteen-day rule has been considered successful, as evidenced by its international adoption.[104] Additionally, the existing rule assuages some of the concerns surrounding the destruction of human embryos at the conclusion of research.

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97. *Id.* at 310.
98. *Id.*
99. *Id.*
100. *Id.*
101. Insoo Hyun et al., *Embryology Policy: Revisit the 14-Day Rule*, NATURE (May 4, 2016), https://www.nature.com/news/embryology-policy-revisit-the-14-day-rule-1.19838 [https://perma.cc/724W-93KS].
102. *Id.* Biological individuation occurs when an embryo can no longer "split in two or fuse together," and is thus considered by some to be the "stage [that] a morally significant individual comes into being" because the organism is no longer capable of twinning. *Id.*
103. *Id.*
104. *See id.* In addition to internationally agreed-upon guidelines issued by the International Society for Stem Cell Research, at least twelve countries have incorporated the fourteen-day rule into law, and five others have nationally commissioned scientific guidelines specifying the fourteen-day rule. *Id.*

2. Historic and Current Restrictions on Human Embryo Research

In the United States, research on human embryos has long been the subject of unease with the government responding to popular apprehension by instituting a variety of regulations and legislation intended to slow or halt embryonic research. With the advent of CRISPR, however, this type of research is even more critical than ever before for to realize the promised benefits of this technology.[105] With this tension in mind, this section explores historical attitudes surrounding research on human embryos and restrictions that both federal and state governments have placed on this type of research.

a. Restrictions at the Federal Level Focus on Cutting Off Funding Sources for Human Embryo Research

In 1973, the U.S. Department of Health, Education, and Welfare[106] instituted a ban on research involving live human embryos that Congress expanded the following year to include embryos created using IVF.[107] In 1979 the federal advisory board responsible for reviewing "federally funded research on human sperm, eggs, and embryos" was disbanded because of pressure from anti-abortion groups.[108] Presidents Ronald Reagan and George H. W. Bush later issued executive orders blocking all federal funding for research on human embryos, bowing to similar anti-abortion sentiments.[109]

This ban was lifted in 1993 under President Bill Clinton, who, in an effort to effectuate embryo research, tasked the NIH with drafting guidelines for such research.[110] The Human Embryo Research Panel presented these guidelines ten months later, recommending that human embryo research "should be allowed only if the embryos were less than 14 days old, if the studies could not be performed with animal embryos, and . . . if scientists could demonstrate a compelling reason why the studies should be performed."[111] This panel also determined that researchers should be allowed to create embryos specifically for medical research, meaning researchers would not be limited to surplus embryos from assisted

105. *See* Douglas & Savulescu, *supra* note 80, at 307.

106. In 1980, the Department of Health, Education, and Welfare became the Department of Health and Human Services ("HHS"). *HHS Historical Highlights*, U.S. DEP'T HEALTH & HUM. SERVICES, https://www.hhs.gov/about/historical-highlights/index.html [https://perma.cc/67HM-LMZH] (last visited Aug. 24, 2018).

107. Miriam Reisman & Katherine T. Adams, *Stem Cell Therapy: A Look at Current Research, Regulations, and Remaining Hurdles*, 39 PHARMACY & THERAPEUTICS 846, 846 (2014).

108. Phillip B. C. Jones, *Funding of Human Stem Cell Research by the United States*, 3 ELECTRONIC J. BIOTECHNOLOGY (Apr. 15, 2000), http://www.ejbiotechnology.info/index.php/ejbiotechnology/article/view/v3n1-3/839 [https://perma.cc/9KJ7-FRL4].

109. *Id.*

110. *Id.*

111. *Id.*

reproductive technology (ART) clinics.[112] On the day the NIH met to vote on these guidelines, however, "President Clinton issued an Executive Order that government funded scientists would not be allowed to create human embryos for research."[113] As a result, the topic of embryonic research entered the spotlight, and politicians across the country—attempting to harness the political goodwill of anti-abortion groups—manifested their intentions to ban embryonic research.

To this end, Congress passed the 1996 Dickey-Wicker Amendment as a bill rider to the annual omnibus appropriations bill, which prohibited the Department of Health and Human Services ("HHS") from providing federal funding for research involving the "(1) creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death."[114] Congress has renewed this bill rider every year since, creating substantial roadblocks for U.S. scientists looking to use human embryos in CRISPR research.[115] To make matters even more complex, in 2016 the House of Representatives added an additional rider to the annual consolidations bill that prohibits the FDA from acknowledging applications "for an exemption for investigational use of a drug or biological product . . . in research in which a human embryo is intentionally created or modified to include a heritable genetic modification."[116] This means that the FDA must refrain from acknowledging that it even received such a submission.

In 2011, President Obama attempted to lessen these restrictions on stem cell research by issuing Executive Order 13,505.[117] This order underscored the importance of stem cell research and the need to support it with federal funding.[118] Accordingly, the order directed the director of the NIH to "review existing NIH guidance and other widely recognized guidelines on human stem cell research, including provisions establishing appropriate safeguards, and issue new NIH guidance on such research that is consistent with this order."[119]

The NIH complied and new guidelines went into effect on July 7, 2009.[120] These guidelines loosened restrictions on human embryo research and enabled researchers to obtain federal funding for human embryo research, so

112. *Id.*

113. *Id.*

114. Balanced Budget Downpayment Act, Pub. L. No. 104-99, § 128, 110 Stat. 26, 34 (1996).

115. *See* Julia Franz & Katie Hiler, *New Developments in Human Gene Editing Face an Ethical and Regulatory Quagmire in the US*, PUB. RADIO INT'L (Aug. 27, 2017, 10:00 AM), https://www.pri.org/stories/2017-08-27/new-developments-human-gene-editing-face-ethical-and-regulatory-quagmire-us [https://perma.cc/JJ3N-H2ML].

116. Consolidated Appropriations Act, Pub. L. No. 114-113, § 749, 129 Stat. 2242, 2283 (2016).

117. Exec. Order No. 13,505, 3 C.F.R. 229 (2009).

118. *See id.*

119. *Id.*

120. National Institutes of Health Guidelines for Human Stem Cell Research, 74 Fed. Reg. 32,170 (July 7, 2009).

long as the embryos "were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose; [and] were donated by individuals who sought reproductive treatment . . . and who gave voluntary written consent for the human embryos to be used for research purposes."[121] The guidelines did note, however, that funding projects where stem cells have been derived from human embryos remained prohibited because of the funding moratorium mandated by the Dickey-Wicker Amendment.[122] Importantly, these guidelines have been interpreted to apply to CRISPR-based research due to the similar ethical conundrums posed by both fields.[123]

b. Restrictions at the State Level Are Wide-Ranging in Scope

In addition to federal bans, many states regulate human embryo research. State approaches range from the statutes in eight states that actively encourage embryonic research to statutes that strictly forbid all forms of embryonic research.[124] Massachusetts, for example, prohibits research on a live embryo or fetus and prohibits the creation of a fertilized embryo solely for research.[125] Taken together, the state and federal restrictions that researchers must navigate when attempting to conduct research on human embryos erect substantial roadblocks, significantly slowing scientists' abilities to advance therapeutic applications of gene-editing breakthroughs like CRISPR.

3. Current Funding Configurations for Human Embryo Research

Despite the federal ban on funding for research on human embryos, private donations from foundations, organizations, and individuals have enabled researchers within the United States to conduct research on human embryos.[126] Privately funded studies are subject to neither federal oversight nor state regulations, which means that the government is limited in its ability to control the research plans of these studies should researchers choose to ignore consensus-driven ethics in the field of genomic editing.[127] In 2001, the American Academy of Pediatrics criticized this lack of oversight, stating that it "does little to address many of the ethical concerns, and . . . may limit the potential for this research to be valuable to large segments of society,

121. *Id.* at 32,175.

122. *See id.* at 32,173. For more on the Dickey-Wicker Amendment, see *supra* note 114 and accompanying text.

123. *See* Francis S. Collins, *Statement on NIH Funding of Research Using Gene-Editing Technologies in Human Embryos*, NAT'L INSTITUTES HEALTH (Apr. 28, 2015), https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos [https://perma.cc/32AN-MPDQ].

124. *Embryonic and Fetal Research Laws*, NAT'L CONF. ST. LEGISLATURES (Jan. 1, 2016), http://www.ncsl.org/research/health/embryonic-and-fetal-research-laws.aspx [https://perma.cc/4RRC-E2KH].

125. *See* MASS. GEN. LAWS ch. 112, § 12J (2018).

126. Comm. on Pediatric Research & Comm. on Bioethics, *Human Embryo Research*, 108 PEDIATRICS 813, 814 (2001).

127. *See id.*

such as children."[128] But in the sixteen intervening years since this critique, government officials have taken no further steps to limit gene editing funded by private entities. Indeed, the OHSU study that reignited this debate in the CRISPR context was privately funded.[129] This lack of oversight leads to serious questions about how exactly the U.S. government should regulate research to ensure abusive use of CRISPR technologies does not threaten either societally endorsed applications of the technology or national security.[130]

Ultimately, the current state of regulation surrounding human embryo research leaves scientists in this field with one option: seek private funding. Absent private funding, human embryo research will be unlikely to get off the ground, which is particularly unfortunate in the CRISPR context because a number of research projects that could eradicate life-threatening diseases from the human genome may be abandoned. Moreover, even if scientists were to successfully circumvent this hurdle, they would still be forced to navigate the incredibly convoluted regulatory regime the United States cobbled together decades ago to have a chance of getting a product to market.

C. The Current State of Affairs for Regulation of Biotechnology in the United States

The United States's current regulatory regime for biotechnology is woefully ineffectual and, despite recent efforts to modernize this process, remains outdated and inefficient. This section gives a snapshot of the current state of biotechnology regulation, beginning with a brief historical overview and ending with the most recent updates to the system recommended by the Obama administration.

In 1986, the White House Office of Science and Technology Policy ("OSTP") was tasked with determining how to regulate the then-hot-ticket biotechnology trend, recombinant DNA.[131] The OSTP decided that writing new regulatory laws was unnecessary and opted instead for a system known as the "Coordinated Framework,"[132] which gave regulatory authority to three federal agencies: the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act; the Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide

128. *Id.*

129. John F. Sargent, Jr. et al., *CRISPR Gene Editing Research in Embryos Generates Scientific and Ethics Debate*, CRS INSIGHT (Sept. 12, 2017), https://fas.org/sgp/crs/misc/IN10773.pdf [https://perma.cc/LFU5-RW47].

130. *See supra* Part I.A.3.

131. Recombinant DNA technology was introduced in the 1970s and was the first known biotechnology capable of artificially introducing genetic material from one organism into another. *Herbert J. Boyer and Stanley N. Cohen*, SCI. HIST. INST., https://www.chemheritage.org/historical-profile/herbert-w-boyer-and-stanley-n-cohen [https://perma.cc/ZJH8-3W4S] (last updated Aug. 24, 2018).

132. Brooke Borel, *The U.S. Regulations for Biotechnology Are Woefully Out of Date*, SLATE (Apr. 21, 2017, 7:08 AM), http://www.slate.com/articles/technology/future_tense/2017/04/u_s_biotechnology_regulations_are_woefully_out_of_date.html [https://perma.cc/LC2T-APZF].

Act, the Toxic Substances Control Act, and pollution-control statutes; and the U.S. Department of Agriculture (USDA) under the Federal Plant Pest Act.[133] The OSTP reasoned that this framework would "ensur[e] the safety of biotechnology research and products" because it was thought to comprehensively cover the relevant federal agencies and provide a clear framework for the responsibilities of each.[134] This framework "was expected to evolve in light of experience, and modifications to the framework were anticipated."[135] Since its publication in 1986, however, the framework has remained largely the same.[136]

Recognizing that the rapid advancement of biotechnology required a new, modern system capable of adapting to future products, the Obama administration directed the OSTP to revisit the framework and propose updates.[137] Unfortunately, these updates, published shortly before President Obama left office in January 2017, do not propose any substantive changes to the Coordinated Framework. Rather, the lengthy document "lists a series of hypothetical biotech products and explains how each agency *might* regulate them."[138] And given the length of time it took for President Trump to name an OSTP director,[139] it appears unlikely that major changes to the Coordinated Framework will take place in the near future.

Understanding the current state of biotechnology regulation, restrictions on human embryo research, and promise of CRISPR-developed therapeutics illuminates the need for clearer regulation aimed at enhancing scientific discovery without compromising ethical boundaries. This background information is also critical to understanding and evaluating proposals for streamlining biotechnology regulation.

II. PROPOSALS FOR REGULATION OF BIOTECHNOLOGY AND PATHWAYS FOR ETHICAL HUMAN EMBRYO RESEARCH

Given the extraordinary promise of CRISPR, as well as the possibility for abuse of the technology, its regulatory pathway demands a comprehensive overhaul. Strong, clear regulatory oversight is often seen by the biotechnology industry as one of the necessary components for high levels of investment and innovation.[140] A recent report on the state of

133. Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment, 57 Fed. Reg. 6753, 6754 (Feb. 27, 1992).

134. *Id.*

135. *Id.*

136. Borel, *supra* note 132.

137. *Id.*

138. *Id.*

139. Ben Guarino, *Trump Desperately Needs a Science Adviser, Experts Say. He Just Doubled the Record for Time Without One.*, WASH. POST (July 27, 2018), https://www.washingtonpost.com/news/speaking-of-science/wp/2018/07/27/trump-just-doubled-the-record-for-time-without-a-science-and-technology-adviser/ [https://perma.cc/3LEW-MMDK].

140. *See* PUGATCH CONSILIUM, BUILDING THE BIOECONOMY 2015: EXAMINING NATIONAL BIOTECHNOLOGY INDUSTRY DEVELOPMENT STRATEGIES GLOBALLY 26 (2015).

biotechnology globally states, "[a] strong regulatory environment creates the conditions for the production and sale of high quality products and technologies."[141] Part II.A examines the regulatory options available for CRISPR—and biotechnology as a whole—by looking at the status quo and current proposals for modernization. Part II.B considers proposals for regulating human embryo research, and Part II.C details a proposal that attempts to merge the two.

A. Proposals Aimed at Maintaining or Altering the Current System of Biotechnology Regulation Within the United States

A number of proposals have been put forth for updating the current system of biotechnology regulation in the United States. This section looks at some of the more promising ideas that could be fairly and easily incorporated into the existing regulatory structure.

1. Regulators Could Opt to Maintain the Existing Regulatory Framework to Avoid Disturbing the Status Quo

The first option for regulating CRISPR is to maintain the status quo—the Coordinated Framework approach. Under this approach, the FDA, EPA, and USDA would continue to share responsibility for regulating new biotechnologies, including CRISPR. The FDA, for instance, would continue to regulate CRISPR-based therapeutic regimes, the USDA would continue to regulate genetically modified organisms (GMOs) related to livestock and agricultural crops, and the EPA would continue to regulate crops with enhanced pesticidal traits.[142] Importantly, the U.S. regulatory scheme would maintain its *product*-oriented focus, with the critical attention paid to the end product, as opposed to the regulatory scheme in, for example, Canada is *process*-oriented with a focus on how the biotechnology product is created.[143]

Proponents of the Coordinated Framework believe that this regulatory scheme has two distinct advantages: First, a number of existing laws cover the products that could be affected by CRISPR.[144] Accordingly, the

141. *Id.* at 27.

142. *See* Emily Waltz, *CRISPR-Edited Crops Free to Enter Market, Skip Regulation*, 34 NATURE BIOTECHNOLOGY 582, 582 (2016).

143. Thorben Sprink et al., *Regulatory Hurdles for Genome Editing: Process- vs. Product-Based Approaches in Different Regulatory Contexts*, 35 PLANT CELL REP. 1493, 1501 (2016); *see infra* note 179 and accompanying text (discussing product- versus process-oriented regulatory systems).

144. Some of the existing laws considered by the OSTP when the Coordinated Framework was originally proposed include the Toxic Control Substances Act; the Federal Insecticide, Fungicide, and Rodenticide Act; the Occupational Health and Safety Act; the Comprehensive Environmental Response, Compensation, and Liability Act; the Resource Conservation and Recovery Act; the Marine Protection, Research, and Sanctuaries Act; the Federal Meat Inspection Act; the Poultry and Poultry Products Inspection Act; the Hazardous Materials Inspection Act; the Federal Plant Pest Act; the Federal Noxious Weed Act; the Export Administration Act; the Federal Seed Act; the Clean Water Act; the Plant Variety Protection Act; the Safe Drinking Water Act; the National Environmental Policy Act; and the Endangered

Coordinated Framework, both at its conception and today, has "the advantage that [the agencies] provide more immediate regulatory protection and certainty for the industry than [is] possible with the implementation of new legislation."[145] Second, proponents of the framework believe that its stated objectives are well supported by the existing regulatory scheme, namely that there is a "[c]onsistency of definitions and regulatory scope[, c]lear establishment of lead and supporting agencies with a mechanism for effective interagency communication[, c]onsistency of statements of information to support review[, c]omparably rigorous reviews[, and t]ransparency of [the] review process."[146] Consequently, advocates of the framework see no pressing reason to overhaul the current regulatory scheme.

Conversely, opponents of the Coordinated Framework contend that it is outdated, inflexible, and incomprehensive, particularly when it comes to evaluating genetic engineering technologies.[147] In criticizing the 2017 update to the Coordinated Framework, Professor Jennifer Kuzma of North Carolina State University stated, "New [genetic engineering] technologies, like . . . gene-editing, and gene-drive systems, as well as novel [genetic engineering] products, are challenging regulatory definitions, highlighting inadequacies in health and environmental assessments, and revealing gaps in agency jurisdiction."[148] Kuzma further contends that the irony of subjecting groundbreaking scientific discoveries to an archaic regulatory scheme is causing many researchers to lose faith in the system.[149]

In leveraging this critique, Kuzma gives the recent example of the FDA's approval of the first genetically engineered mosquito as an Investigational New Animal Drug (INAD).[150] This mosquito is capable of mating with wild mosquitos but, because of a technologically modified gene, most of the resulting offspring die in early development.[151] Researchers hope that by releasing these modified mosquitos into the wild, the overall mosquito population will decline and, with it, the prevalence of diseases transmitted by mosquitos such as dengue fever, Zika virus, and malaria.[152] While the FDA has jurisdiction over INADs under the Coordinated Framework, applications for this designation typically involve chemicals that are "injected, topically applied, or fed to animals to treat or prevent disease . . . [and] are primarily reviewed based on safety and efficacy to the target animal."[153] Clearly, an

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Species Act. *See* Coordinated Framework for Regulation of Biotechnology; Establishment of the Biotechnology Science Coordinating Committee, 50 Fed. Reg. 47,027, 47,174–95 (Nov. 14, 1985).

145. Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,302–03 (June 26, 1986).

146. COMM. ON GENETICALLY MODIFIED PEST-PROTECTED PLANTS, GENETICALLY MODIFIED PEST-PROTECTED PLANTS: SCIENCE AND REGULATION 156 (2000).

147. *See generally* Jennifer Kuzma, *A Missed Opportunity for U.S. Biotechnology Regulation*, SCIENCE, Sept. 16, 2016, at 1211.

148. *Id.* at 1211.

149. *Id.*

150. *Id.*

151. *Id.*

152. *Id.*

153. *Id.*

INAD that is genetically engineered to bring about the demise of its own population does not fit within these regulatory standards.[154] Moreover, the eradication of a species could have serious environmental impacts that the FDA does not have jurisdiction to evaluate.[155] These issues led Kuzma to conclude that the status quo for biotech regulation is "outdated, and confusing, especially for newer biotechnology products" and "is bound to get worse."[156]

Other recent regulatory submissions of genetically altered organisms have similarly drawn the ire of Coordinated Framework opponents. One such example is an "anti-browning" white button mushroom engineered at Pennsylvania State University,[157] which many believed would be regulated by the USDA under the Plant Protection Act, an act that gives the agency jurisdiction to regulate genetically engineered crops.[158] Historically, GMO crops such as this mushroom have been modified using transgenic techniques in which a "plant pest" is inserted into the genetic material of the original crops.[159] The vast majority of these types of crops "were made using a soil bacterium to deliver a new gene, were modified with a gene taken from a bacterium, or both," which "triggered the 'plant pest' regulatory mechanism."[160] Many of these techniques are no longer used because CRISPR allows scientists to modify the genome of agricultural products without inserting DNA from another species.[161] This technological shift means that crops edited using CRISPR fall outside of the USDA's definition of GMO, and subsequently out of the USDA's jurisdiction.[162] But because of the underinclusiveness of the Coordinated Framework, neither the FDA nor the EPA had jurisdiction over these sorts of GMOs, which enabled the mushroom to escape regulation.[163] While the mushroom itself may not pose health threats, it has hit a nerve among opponents of the Coordinated

154. *Id.*
155. *See id.*
156. *Id.* at 1213.
157. Mike Orcutt, *Who Approved the Genetically Engineered Foods Coming to Your Plate? No One.*, MIT TECH. REV. (Apr. 21, 2016), https://www.technologyreview.com/s/601295/who-approved-the-genetically-engineered-foods-coming-to-your-plate-no-one/ [https://perma.cc/234P-Q6TF].
158. *Id.*
159. *Id.*
160. *Id.*
161. *See id.*
162. *See id.*
163. *See* Emily Waltz, *Gene-Edited CRISPR Mushroom Escapes US Regulation*, NATURE (Apr. 14, 2016), http://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754 [https://perma.cc/MYW5-8TZF]. This problem is not unique to the United States. In a multinational evaluation of current regulations on genetic engineering, the authors of a recent study found that "[i]n the majority of cases . . . vague or narrow terminology has inadvertently created barriers or ambiguities that may allow for interpretations or practices to circumvent or hinder the intent of the policy, without violating its literal interpretation." Rosario Isasi et al., *Editing Policy to Fit the Genome?*, 351 SCIENCE 337, 338 (2016).

Framework who worry that future CRISPR-created products may not be so harmless.[164]

Finally, there is a camp in the Coordinated Framework corner that does not necessarily advocate for the system but rather recognizes that an overhaul of either domestic or international policy is unlikely given lawmakers' current unwillingness to prioritize this sort of regulation.[165] These "pragmatists" generally believe that the discussion of possible regulatory solutions is important but note that "without a change in the current atmosphere there is little likelihood of success."[166] When pressed to consider the possible ethical and national security consequences of this deterministic attitude, these pragmatists contend that widespread use of the technology will enable rapid mitigation of potential threats, whereas overregulation would limit the ability of the government to respond quickly in the face of such threats and thus hold that the current state of affairs is sufficient, even if it is less than ideal.[167]

2. The National Academies of Science Recommend Restructuring the Regulatory System to Allow for a Single Point of Entry for All Biotechnology Product Applications

An alternative to scrapping the entirety of the Coordinated Framework is to revamp the existing framework to improve the efficiency of the approval process. The NAS adopted this position in the 2016 report *Preparing for Future Products of Biotechnology*.[168] In evaluating the current state of the U.S. biotechnology regulatory system, the NAS found the overall regulatory regime to be effective but identified as a major concern the ability of the system to evaluate new products quickly as biotechnology product applications proliferate.[169] Accordingly, the NAS recommends a stratified regulatory scheme where a single point of entry categorizes the proposed products based on risk-analysis methodology:

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164. *See* Borel, *supra* note 132.

165. *See* Adam J. Gross, Comment, *Dr. Frankenstein, or: How I Learned to Stop Worrying and Love CRISPR-Cas9*, 56 JURIMETRICS J. 413, 415 (2016).

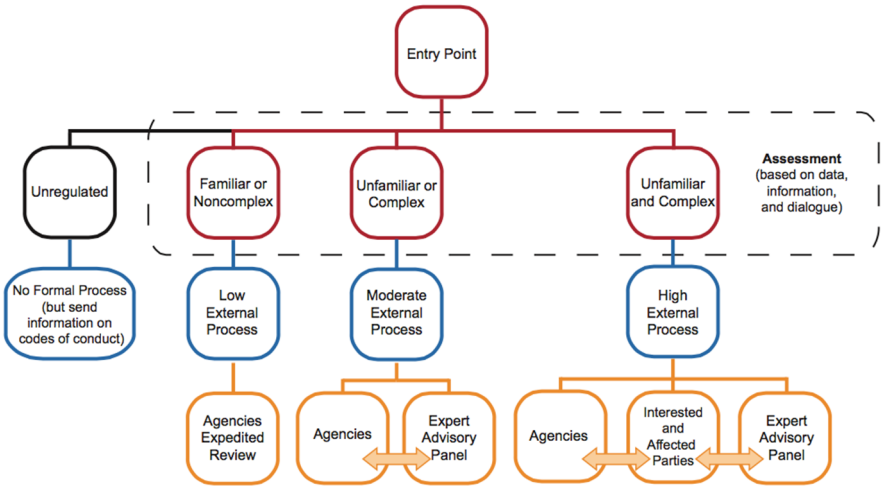
166. *Id.* at 447.

167. *See id.*

168. *See generally* NAT'L ACADS. OF SCI., PREPARING FOR FUTURE PRODUCTS OF BIOTECHNOLOGY (2017) [hereinafter NAS REPORT 2017]. Interestingly, this report was commissioned to provide a framework for the regulatory update required by President Obama's executive order. *See supra* note 117 and accompanying text. In the final report issued by the executive branch, however, the stratification system critical to the NAS proposal is absent. *See generally* MODERNIZING THE REGULATORY SYSTEM FOR BIOTECHNOLOGY PRODUCTS: FINAL VERSION OF THE 2017 UPDATE TO THE COORDINATED FRAMEWORK FOR THE REGULATION OF BIOTECHNOLOGY (2017), https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/2017_coordinated_framework_update.pdf [https://perma.cc/3BY7-KFJH].

169. *See* NAS REPORT 2017, *supra* note 168, at 8 ("[G]iven the profusion of biotechnology products that are on the horizon, there is a risk that the capacity of the regulatory agencies may not be able to efficiently provide the quantity and quality of risk assessments that will be needed.").

Figure 1[170]



As depicted in Figure 1, the advisory body at the entry point would categorize proposed products as either unregulated,[171] familiar or noncomplex, unfamiliar or complex, or unfamiliar and complex in comparison to already approved biotechnology products.[172] Each group is then subject to various levels of scrutiny based on the potential risk the product category poses, with unfamiliar and complex product applications subject to the most rigorous review process.[173] Conversely, more familiar products would be eligible for "a more expedited process . . . under the assumption that relevant risk-analysis processes are well established."[174]

The NAS proposal also provides for postapproval monitoring systems that mirror the initial categorization of the products. The unfamiliar and complex products, for example, would be subject to higher standards of reporting and audit once they are on the market than would the familiar or less complex products.[175] Given the more stringent requirements both pre- and post-approval for unfamiliar and complex products, one potential problem concerns how the products are categorized. To deal with conflicts that may

170. *Id.* at 142. Reprinted by permission of the publisher.
171. Due to the complexity of the Coordinated Framework, it can often be challenging for product developers to determine which products do not fall under federal statute. Accordingly, the single point of entry "provides a voluntary opportunity to get input from the regulatory agencies" for confused developers, and also gives the federal government the opportunity to provide these developers with "information about voluntary stewardship programs [when] available." *Id.*
172. *Id.* at 9–10.
173. *Id.*
174. *Id.* at 9.
175. *Id.* at 143.

arise during this categorization process, the NAS recommends evaluating the products using additional objective criteria, including:

> the degree of confinement and/or containment (greater confinement/containment should reduce the likelihood of environmental exposure), whether it is living or nonliving (a living product may increase uncertainty and unpredictability of the assessment), and reversible or nonreversible product deployment (a nonreversible deployment may increase the complexity of risk-management measures to mitigate adverse effects).[176]

Moreover, the NAS prescribes an increased role for participation by multiple stakeholders as a way to deal with one of the key criticisms of federal agencies: lack of complete information.[177] The higher the degree of complexity or novelty ascribed to a product, the greater the participation of external stakeholders will be. For instance, an unfamiliar and complex product would likely require the input of a peer review board, expert panel, and possibly the public to ensure that the agency is not evaluating the product based on incomplete information.[178]

The system suggested by the NAS is similar to Canada's regulatory regime for biotechnology products. In Canada, regulatory authorities assess products by first determining whether the genetically modified traits have been seen in this species before.[179] If the trait is deemed novel, then the product will undergo a stringent regulatory process to assess human and environmental safety, whereas products with nonnovel traits are expedited through the review process.[180] Proponents of this regulatory scheme claim the system "promotes efficiency, coherence and uniform application of standards because no matter what technologies are used, regulatory intervention will apply only to novel plants and foods."[181] Notably, this system does not specifically regulate products created using human embryo research but does provide a conceptual framework for one of the ways in which government actors may think about such regulation.

3. Some Experts Call for the Expansion and Adoption of International Agreements Governing Gene-Editing Technologies

Given the cross-border effects CRISPR research could have, many have called for an international regime to govern the use of CRISPR. This section details the current and proposed international agreements aimed at global cooperation.

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176. *Id.* at 144.
177. *Id.* at 147.
178. *Id.* at 145–47.
179. Gary E. Marchant & Yvonne A. Stevens, *A New Window of Opportunity to Reject Process-Based Biotechnology Regulation*, 6 GM CROPS & FOOD 233, 235–36 (2015).
180. *See id.*
181. *Id.* at 236.

In international law, the most widely accepted agreement is the United Nations Convention on Biological Diversity,[182] which is set forth in the Cartagena Protocol on Biosafety ("Cartagena Protocol"), and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization ("Nagoya Protocol").[183] The Cartagena Protocol, adopted in 2000, "aim[ed] to ensure the safe handling, transport and use of living modified organisms (LMOs) resulting from modern biotechnology that may have adverse effects on biological diversity, taking also into account risks to human health."[184] The Nagoya Protocol, adopted in 2011, is essentially a follow-up to the Cartagena Protocol, setting out further compliance provisions in an effort to even the genetic engineering playing field.[185]

The United Nations developed the Cartagena Protocol in an effort to address concerns about the impact genetically modified organisms may have on the environment.[186] The terms of the agreement require parties to "notify one of the U.N.'s International Biosafety Clearing-Houses and any affected nations about activities that may lead to movement of living modified organisms with potential adverse effects on biological diversity or human health."[187] Today, policymakers are exploring whether this language can be extended to govern the use of genetic engineering for therapeutic purposes.[188] Because of the sheer number of countries that are parties to the agreement, some policymakers argue that this "modernization" approach would be a relatively efficient way to regulate CRISPR on a global scale.[189]

Critics of this approach caution that the modernization of existing protocols may not make a huge impact on the international framework of biotechnology regulations for three reasons. First, many of the signatories to these protocols are middle- or low-income countries, and while these countries have used these agreements as frameworks for their own national regulatory regimes, many of them lack the resources to enforce these regulations.[190] Second, nations with high rates of CRISPR research, such as the United States, are not signatories to the agreements, which means that "the United States does not have a clear policy for collaborating with other countries with divergent systems of governance."[191] Finally, those with

182. NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 74, at 153.
183. *Id.* at 8–9.
184. *About the Protocol*, CONVENTION ON BIOLOGICAL DIVERSITY, https://bch.cbd.int/protocol/background/ [https://perma.cc/X5FA-M39W] (last visited Aug. 24, 2018).
185. *See* Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from Their Utilization to the Convention on Biological Diversity (Oct. 29, 2010), https://treaties.un.org/doc/Treaties/2010/11/20101127%2002-08%20PM/XXVII-8-b-Corr-Original.pdf [https://perma.cc/F85R-GK4U].
186. *See The Cartagena Protocol on Biosafety*, CONVENTION ON BIOLOGICAL DIVERSITY, https://bch.cbd.int/protocol [https://perma.cc/L54S-2758] (last visited Aug. 24, 2018).
187. NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 74, at 154.
188. *See id.* at 145.
189. *See id.* at 154.
190. *See id.*
191. *Id.* at 8.

malicious intent would be unlikely to operate within the confines of international—or even domestic—agreements, rendering these sorts of agreements ineffective at dealing with national security problems.[192]

Critics further argue that the jurisdiction of the Cartagena and Nagoya Protocols is not comprehensive enough to cover modern biotechnology; that "it is difficult to integrate social, political, and ethical norms of different countries into a single policy[;] and that developing international systems of governance may require substantial resources that may take away from developing strong national-level oversight."[193] These concerns led experts to call for new transnational governance based on concepts of soft power at the International Summit on Human Gene Editing in 2015.[194] And while policies stemming from a soft power would not be legally enforceable, "[t]heir advantages include the fact that they are voluntary, cooperative and reflexive; can be adopted or revised relatively quickly; allow many different approaches to be tried simultaneously; and can be gradually 'hardened' into more formal regulatory oversight."[195] Proponents of this approach argue that mobilizing the international community and enacting these sorts of policies may give these international agreements a foundational position, which means that individual nations would look to these agreements as they draft their own individual regulations.[196] This scenario would increase the efficacy of such policies given the general lack of enforcement power inherent to international agreements.[197]

4. Rather than Give Specific Structural Recommendations, Some Groups Advocate for General Criteria-Based Regulatory Regimes

A final approach to biotechnology regulation could be to encourage the adoption of frameworks that meet a defined set of criteria as opposed to advocating for a one-size-fits-all model. In attempting to define what this set of flexible criteria might look like, researchers for the International Food Policy Research Institute (IFPRI) recommended exploration of the following categories: effectiveness, economics, good governance, conformity, and legitimacy.[198] These categories are further explicated in Table 1 below.

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192. *Id.* at 152–53. For more on CRISPR and national security, see *supra* Part I.A.3.

193. *See* NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 74, at 153.

194. *See id.* at 156–57. A country exercises "soft power" when it uses nongovernmental institutions such as companies, universities, and foundations to get another country to follow a particular path. *See* G. John Ikenberry, Review, *Soft Power: The Means to Success in World Politics*, FOREIGN AFF. (May/June 2004), https://www.foreignaffairs.com/reviews/capsule-review/2004-05-01/soft-power-means-success-world-politics [https://perma.cc/H9QY-KZR7].

195. NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 74, at 156.

196. *Id.* at 157.

197. *See id.*

198. REGINA BIRNER & NICHOLAS LINACRE, REGIONAL BIOTECHNOLOGY REGULATIONS: DESIGN OPTIONS AND IMPLICATIONS FOR GOOD GOVERNANCE 17 (2008).

Table 1[199]

Criterion	Aspects
Effectiveness criteria	• Effectively ensuring desired levels of environmental and food safety • Effectively avoiding regulatory failure
Economic criteria	• *Cost-effectiveness*: Achieving desired levels of environmental and food safety at lowest possible costs • *Optimal "intensity" of regulation*: Expected marginal benefits from regulation equaling expected marginal costs • *Dynamic efficiency*: Creating/protecting incentives for innovation
Good governance criteria	• *Control of special interest capture*: Regulation is not captured by special interest groups (biotechnology industry, environmental groups) • *Fairness*: Acceptable balance of different societal interests, and acceptable distribution of costs and benefits • *Voice and accountability*: Processes are transparent and provide scope for citizen participation; regulatory agencies are accountable to citizens and their political representatives • *Control of corruption*: Regulation does not create incentives for corruption/has safeguards against corruption • *Rule of law*: Regulations can be enforced
Conformity criteria	• Regulation conforms with international agreements (Cartagena Protocol, WTO) • Regulation conforms with regional treaties and national constitutions • Regulation conforms with international good practice standards
Legitimacy criteria	• *Input legitimacy*: Regulatory process is considered fair, transparent, participatory, and accountable • *Output legitimacy*: Performance of regulatory process is considered satisfactory, regulatory failures are avoided, and problem-solving capacity is in place

199. *Id.* at 17 tbl.2.

The IFPRI concludes that balancing the perspectives of stakeholders—such as government, consumers, and industry—with these criteria may be a particularly effective approach because introduction of the criteria may "help[] rationalize emotional debates, and may narrow down the number of options on which different groups disagree."[200]

* * *

The four proposals discussed are representative of the wide range of options policymakers must consider, and there are important pros and cons for each of these options. Maintaining the Coordinated Framework, for instance, would be the path of least resistance but may contribute to greater inefficiencies over time. Restructuring the Coordinated Framework to incorporate a single point of entry may be better for product developers but would require political will that may be challenging to rustle up in the current political climate. International consensus building would mitigate fears of misuse of gene-editing technology in developing nations but lacks the force of law. And finally, criteria-based governance approaches are good for establishing norms but lack structural recommendations. Policymakers must prioritize the outcomes they wish to see from a restructured regulatory regime and mix and match the aforementioned proposals to maximize the potential of achieving those outcomes.

B. Regulatory Options for Increasing Oversight of Human Embryo Research

In addition to the general debate over how to increase the efficiency of the U.S. biotechnology regulatory system, there is great need to clarify the laws and regulations governing the use of human embryos in scientific and medical research. This issue is made even more challenging by the general lack of information available regarding current research being done on human embryos because "[n]o country is systematically making public any overview of the embryo research performed on its territory."[201] This section first explores the option of banning human embryo research entirely, then discusses licensing systems implemented by the United Kingdom and Belgium, and concludes with a discussion of possible ways in which scientists may secure funding for such research.

1. Opponents of Human Embryo Research Advocate for a Complete Ban

The first option is to simply not allow research on human embryos, which is a position endorsed by "[s]ome scientists and public interest groups, including the United Nations Educational Scientific and Cultural

200. *Id.* at 38.

201. Guido Pennings et al., *Human Embryo Research in Belgium: An Overview*, 108 FERTILITY & STERILITY 96, 96 (2017).

Organization (UNESCO)."[202] Opponents of human embryo research, who advocate this approach, note that it is not necessary for medical purposes because of the ability to prescreen embryos for genetic defects.[203] Proponents of human embryo research, in response to this position, state that current IVF procedures do not guarantee that all embryos will be free of genetic defects.[204] These proponents also argue that gene editing has the potential to not only eradicate disease in the immediate offspring of a couple, but also in future generations of the genetic line because of its unique ability to alter heritable traits.[205]

Opponents of human embryo research also argue that the research is morally impermissible because of the harm that may befall what many see as potential life.[206] Moral philosophers question the soundness of this proposition, however, by asking how it is that an embryo—an entity that is devoid of experiences or desires—can be harmed.[207] These philosophers also point out that many jurisdictions allow for both abortion and elimination of unwanted embryos following IVF, which underscores their position that many current practices would not be upheld if the concern of harming embryos were paramount.[208] Finally, the philosophers of this camp point to the fourteen-day rule[209] as a means of ensuring that no "future people" are harmed by genetic research.[210] Even still, questions persist as to whether use of human embryos for genetic research inappropriately puts scientists in divine shoes.

2. Internationally, Government-Run Licensing Programs Have Been Effective at Monitoring Human Embryo Research

The European Union's position on human embryo research is set forth in the European Convention on Human Rights and Biomedicine, which bans the creation of human embryos for research purposes.[211] Several countries within the European Union, notably Belgium and the United Kingdom, declined to sign the Convention because they found the terms too restrictive.[212] Belgium in particular wanted the freedom to establish its own regulatory regime regarding human embryo research, which it did in 2003 with the enactment of the Law on Research on Embryos In Vitro.[213] This law created a federal commission charged with evaluating proposed research

202. Christopher Gyngell et al., *The Ethics of Germline Gene Editing*, 34 J. APPLIED PHIL. 498, 498–99 (2017).
203. *Id.* at 499.
204. *Id.* at 500.
205. *See id*; *supra* Part I.A.2.b.
206. *See* Gyngell et al., *supra* note 202, at 504.
207. *See id.* at 504.
208. *See id.*
209. *See supra* Part I.B.3.
210. *See* Gyngell et al., *supra* note 202, at 505.
211. Pennings et al., *supra* note 201, at 97.
212. *Id.*
213. *Id.*

projects involving the use of human embryos and determining which projects meet the law's stringent requirements.[214] The law includes:

> [A] number of applications that are forbidden, such as reproductive cloning, eugenics, sex selection for nonmedical reasons, implantation of human embryos in animals, and creation of chimeras or hybrids. Research on embryos is allowed for up to 14 days (freezing period excluded) and must be based on the most recent scientific findings and conducted according to the appropriate scientific methods. The research must be performed in a laboratory of a university that is recognized as a center for reproductive medicine. No other research method can be equally effective to obtain the same results. Embryos subjected to research must be destroyed unless the research had a therapeutic goal for the embryo, or when it concerns mere observation that does not harm the embryo's integrity.[215]

Once a proposed research project meets these requirements, it is free to conduct the planned research.

The United Kingdom's Human Fertilisation and Embryology Authority (HFEA) similarly regulates the use of human embryos in research.[216] The HFEA requires that researchers obtain a license for every project; research meets one of the purposes of the Human Fertilisation and Embryology Act of 1990;[217] donors have consented to donating for research purposes; embryos involved in research cannot be implanted in a woman; and embryos are not permitted to develop past fourteen days.[218] This process also mandates approval from an HFEA-approved ethics committee before submitting an application for a license.[219] Once a research team submits an application, the HFEA then commissions peer reviews and carries out clinic inspections to ensure the standards of the Human Fertilisation and Embryology Act are met.[220] If these criteria are fulfilled, the research team is granted a license—valid for up to three years—to conduct the planned human embryo research.[221]

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214. *See id.*

215. *Id.*

216. Ewen Callaway, *UK Scientists Gain Licence to Edit Genes in Human Embryos*, NATURE (Feb. 1, 2016), https://www.nature.com/news/uk-scientists-gain-licence-to-edit-genes-in-human-embryos-1.19270 [https://perma.cc/W5C5-HD7Y].

217. Proper research purposes under the Act include: increasing knowledge about serious disease or other serious conditions; developing treatments for serious diseases or other serious medical conditions; increasing knowledge about the causes of congenital diseases; promoting advances in the treatment of infertility; increasing knowledge about the causes of miscarriages; developing more efficient techniques of contraception; developing methods for detecting gene, chromosome or mitochondrion abnormalities in embryos before implantation; and increasing knowledge about the development of embryos. HUMAN FERTILISATION & EMBRYOLOGY AUTH., CODE OF PRACTICE 202 (8th ed. 2017).

218. *Id.* at 200.

219. *See id.* at 214–20.

220. Callaway, *supra* note 216.

221. *See* HUMAN FERTILISATION & EMBRYOLOGY AUTH., *supra* note 217, at 202.

3. Revamping Funding Restrictions Could Lead to Greater Government Oversight of Human Embryo Research

Funding is one of the largest issues surrounding human embryo research in the United States. As discussed, the Dickey-Wicker Amendment currently bans federal funding of human embryo research.[222] Researchers within the United States may, however, conduct gene-editing research provided they obtain private funding. Critics of this system argue that enabling private funding of human embryo research diminishes the government's ability to regulate research that could have far-reaching impacts on the country and the world.[223] They argue that lifting the federal funding ban would give American regulators "greater scientific and ethical oversight," permit "greater scrutiny of the value of this research through the peer review system," and potentially "create incentives to direct research toward health issues that have important implications for children."[224] Indeed, a recent survey of scientists found that the scientific community writ large supports both federal funding of human embryo research and the creation of human embryos for such research purposes.[225] This change would require legislative overhaul, however, and it is unlikely that politicians at this juncture in time will champion the cause of human embryo research, which means that there is very little political will to effectuate such a change. This stubbornness persists despite findings from as recently as 2016 that 60 percent of Americans find "[m]edical research using stem cells obtained from human embryos" morally acceptable.[226]

C. The Evitt Proposal Advocates for a Comprehensive Overhaul That Incorporates Human Embryo Research Within the Broader Biotechnology Regulatory Framework

Rather than have two disparate systems—one for human embryo research and one for biotechnology regulation—Stanford University researchers proposed a unified system in which government regulation begins at the research stage and continues through the distribution phase.[227] The researchers argue that a separate framework is necessary for CRISPR technologies, as opposed to other forms of biotechnology, because of its "unprecedented promise and peril."[228] This framework, referred to here as

222. *See supra* Part I.B.2.a.

223. *See* Comm. on Pediatric Research & Comm. on Bioethics, *supra* note 126, at 814.

224. *Id.*

225. Kirstin R. W. Matthews & Sharon Tsao, *Contrasting Views on Embryo Research and Funding: A Survey of U.S. Physicists and Biologists*, RICE UNIVERSITY'S BAKER INST. FOR PUB. POL'Y (2016), https://www.bakerinstitute.org/media/files/Research/eb06d8b5/STP-Poster-ISSCR2016-Embryo.pdf [https://perma.cc/674Z-7YQB].

226. Art Swift, *Birth Control, Divorce Top List of Morally Acceptable Issues*, GALLUP (June 8, 2016), http://news.gallup.com/poll/192404/birth-control-divorce-top-list-morally-acceptable-issues.aspx [https://perma.cc/G8BZ-KCKJ].

227. *See* Niklaus H. Evitt et al., *Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework*, 15 AM. J. BIOETHICS 25, 28 (2015).

228. *Id.* at 29.

the "Evitt proposal," is divided into five phases: before preclinical research, during preclinical research, prior to clinical development, during clinical development, and distribution.[229]

Phase I occurs during the preclinical research stage, at which point researchers must engage with agencies and CRISPR-specific oversight committees to ensure that the proposed CRISPR application has a reversal mechanism, does not contain a gene drive,[230] and will address either monogenic diseases with no treatment alternative or diseases in which CRISPR technologies will drastically decrease embryonic loss due to genetic screening.[231] If these research objectives are met, product developers move onto Phase II—the "during preclinical research" phase.[232] Here, researchers would need to show proof of concept to give the research team a chance to refine study design in nonhuman cells and animal models, which would also "lower the ethical burden of [these] experiments by minimizing embryo destruction."[233]

Phase III—preclinical development—requires that the research team obtain the consent of the individuals providing genetic material, and Phase IV—clinical development—essentially mirrors the drug-approval process currently mandated by the FDA.[234] Finally, in Phase V, mandatory multigenerational surveillance trials should be established to monitor the long-term effects of CRISPR therapeutics.[235] The Stanford team contends that this robust regulatory framework will de-risk CRISPR research in human embryos in a manner that balances the lifesaving benefits these therapeutics may have with the serious risks posed to the human genome.[236] Moreover, the team contends that this framework deals with many of the ethical dilemmas posed by CRISPR, and, accordingly, once this is in place there will no longer be a need for the federal funding ban.[237]

* * *

The options on the table for regulation of CRISPR in relation to its reliance on human embryo research range from an overhaul of the current Coordinated Framework system to embryo-specific licensing programs completely separate from the biotechnology regulatory process to integrated regulatory schemes like the Evitt approach that endeavor to bridge human embryo licensing with biotechnology regulation. Given the importance of CRISPR, and the rapid pace at which the technology is developing, it is important to settle on a regulatory scheme soon to ensure readiness for some

229. *Id.* at 26–28.
230. *See supra* Part I.A.2.b.
231. Evitt et al., *supra* note 227, at 28. The final criterion is meant to serve as a proxy for an ethical test to ensure that CRISPR research is being done in accordance with the public interest. *Id.* at 26.
232. *Id.* at 26–28.
233. *See id.* at 26.
234. *See id.* at 27.
235. *See id.* at 27–28.
236. *See id.* at 29.
237. *See id.* at 26.

of the tough ethical and scientific questions that CRISPR will inevitably pose.

III. REGULATION OF CRISPR-CREATED GENE-EDITING PRODUCTS SHOULD BE GOVERNED BY AN UPDATED REGULATORY REGIME THAT STREAMLINES THE APPLICATION PROCESS FOR PRODUCT DEVELOPERS WHILE SIMULTANEOUSLY GIVING THE GOVERNMENT INCREASED OVERSIGHT

Given the numerous proposals available to policymakers, it is important to consider which options will increase the efficiency of product applications without sacrificing the standards of safety and efficacy that are the hallmarks of the current Coordinated Framework regime. This Part discusses why the status quo must be overhauled to allow for regulation and proposes a regulatory scheme that incorporates licensing for human embryo research as a component of a process-oriented regime.

A. The Current Coordinated Framework Regime Is Outdated and Inefficient

Critics of the Coordinated Framework are correct that this regulatory system is impractical given the current acceleration of biotechnology development across the United States[238] for four reasons. First, the current regime is incapable of comprehensive regulation. As evidenced by the ability of the nonbrowning mushroom to slip through the cracks, the Coordinated Framework does not comprehensively regulate all new products made using CRISPR.[239] These products escape regulation because they do not fit the USDA's outdated definition of GMOs—the current framework requires that some form of "plant pest" be introduced into the product to trigger regulatory oversight. Because CRISPR does not require that the DNA of another species be engrafted into the plant or crop at issue—and typically only alters the product's own DNA—it may be argued that there is a much lower risk involved and thus regulation is not as critical. This position dangerously assumes (or at least makes it seem very unlikely) that any alterations made within the DNA of a product are incapable of leading to adverse health outcomes for humans and animals that ingest the product. Study of the modern genome shows that small genetic mutations—even the alteration of just one base pair within a DNA sequence—can have disastrous effects on the health of an organism, and there is no research indicating that these poor health outcomes will not be passed on to end users of the product. Accordingly, regulation of the process used to create products intended for consumption is critical.

Moreover, the Coordinated Framework cannot, at present, regulate the products of research using human embryos because the three relevant federal

238. For an overview of this position, see *supra* Part II.A.1.

239. *See supra* note 163 and accompanying text (discussing the development of the non-browning mushroom).

agencies do not have jurisdiction over embryos. Human embryo research clearly falls outside the purview of the USDA and EPA, and the FDA is currently blocked from even considering proposals that involve human embryo research at any point.[240] This means that Congress has blinded the FDA to work that is being done in this field, thereby limiting the agency's ability to meaningfully regulate any product or research process involving human embryos. Additionally, there is no one to hold accountable for the lack of regulation because there have not yet been any laws passed regarding human genomic editing, and the only real restrictions placed on scientists stem from consensus-driven agreements in the global scientific community that lack the force of law.[241]

Second, the current regime is confusing for product developers. Because of the number of federal agencies involved, and their overlapping statutory jurisdictions and mandates, developers are left in the dark as to which laws might govern the regulation of their products. This inability to plan for regulation is extremely unfair to developers who invest millions—if not billions—of dollars researching and developing[242] groundbreaking and potentially lifesaving products. This regulatory opaqueness has three important ramifications. First, product developers are unable to design research in ways that will meet the standards of the agency they will eventually defend their products to, which means small technicalities in a research design plan that leave the researcher unable to answer questions pertinent to the applied statute may result in a denied application. Second, on top of the exorbitant sums spent on research and development, product developers expend additional money to determine which federal agency is the appropriate regulatory body for their product, and may, in the end, be told that because of the novelty of the product, none of the relevant federal agencies have jurisdiction. In this way, product developers may be dissuaded from creating novel therapeutics. Finally, product developers, particularly those using human embryo research, are at the mercy of their investors. To successfully fund a project, the developers need to have an informed plan for how the product will be priced, marketed, and distributed postregulation. The Coordinated Framework's opaqueness muddies a developer's ability to estimate the restrictions that may be placed on the product, which in turn affects the product's end-distribution network and drives up research and development costs. These costs are then passed on to the consumer and

240. *See generally* Consolidated Appropriations Act, Pub. L. No. 114-113, 129 Stat. 2242 (2016).

241. *See supra* Part II.A.3; *see also* Sarah Ashley Barnett, *Regulating Human Germline Modification in Light of CRISPR*, 51 U. RICH. L. REV. 553, 576–77 (2017) (discussing the present lack of regulation and subsequent norms developed within the scientific community to fill this gap).

242. In 2016 alone, pharmaceutical companies spent $157 billion on research and development. *Total Global Pharmaceutical Research and Development (R&D) Spending from 2008 to 2022 (in Billion U.S. Dollars)*, STATISTA (May 2018) [hereinafter *Pharma R&D*], https://www.statista.com/statistics/309466/global-r-and-d-expenditure-for-pharmaceuticals/ [https://perma.cc/74KA-KQ57].

contribute to the exorbitant prices of medication in the United States. This system is consequently unfair to developers, investors, and consumers.

Third, the current regime results in unnecessary delays, which will only worsen as biotechnology applications increase. Because the regulatory jurisdictions of the FDA, EPA, and USDA overlap under the Coordinated Framework, some product applications require agencies to spend an unnecessary amount of time determining who is the most appropriate regulatory body. It is not hard to imagine scenarios in which one regulatory body nears the end of regulatory review only to realize that another agency should have been reviewing the product, which resets the entire process. These inefficiencies are likely to increase as biotechnology product applications increase in the coming decade and lead to misused government funds and unnecessary delays in getting lifesaving treatments to consumers.

Finally, the Coordinated Framework is too focused on the end product. It ignores the process used to create these products to the detriment of the public. As evinced by the long-standing debates surrounding human embryo research, there is a significant amount of public investment in the question of how a product is developed. The current system does not enable federal agencies to consider the process used as part of their review, which could lead to oversight of important health and safety consequences when compared to systems that pay more attention to process. In the Canadian system, for example, the regulatory scheme is essentially product-focused but regulators put a large emphasis on the novelty of the trait introduced through gene editing.[243] This inquiry requires that Canadian regulators spend more time considering the development process and, subsequently, gives them greater insight into some of the ethical concerns that may arise out of approval of a gene-edited product. The current regulatory system in the United States ignores process to its detriment.

Accordingly, the Coordinated Framework is outdated and in desperate need of an overhaul to address unique problems associated with gene-edited products in the twenty-first century.

B. Regulation Is Necessary to Keep American Product Developers Competitive in the Global Environment and to Protect the Health and Safety of Consumers

Leaving the gene-editing market to regulate itself is an unwise strategy because it will exacerbate the ethical and national security questions concerned with modification of the human genome. To date, the scientific community has done a laudable job of regulating the use of gene-editing technology despite the global absence of law mandating that they do so. For example, following the International Summit on Gene Editing in 2015, the organizing committee released a statement supporting a ban on any CRISPR research that would permanently alter the human germline until there has been further proof of the safety and efficacy of such procedures, and broad-

243. *See supra* notes 179–81 and accompanying text.

based societal consensus has been reached regarding the ethics of germline editing.[244] While scientists around the world have, to date, respected this moratorium, it is only a matter of time before enterprising labs or companies resolve to push the barriers in the name of either innovation or profit. Without legal consequences for these actions, there is no assurance that important ethical boundaries will remain intact. Moreover, given the widespread accessibility and low cost of CRISPR, a complete ban on use of these technologies will be ineffective and undesirable because of the promising outcomes they could have—if properly regulated—on human health.

There may be a fear among scientists that forcing regulations on CRISPR will result in increased attention to the technology, subsequent public outcry, and ultimately a legislative ban on the technology. While there is always a risk of backlash when new technologies are brought to the attention of the public, recent studies indicate that Americans are more open to gene editing than ever before.[245] Additionally, careful framing of the need for regulation, which is grounded in promoting safety and is ethically reasonable, will likely quell the fears of members of the public who may perceive CRISPR as a threat. Accordingly, prior to launching a campaign for regulation, careful consideration should be placed on messaging the need for regulation, but concerns regarding public outcry should not dissuade scientists from seeking regulation. Thus, the best path forward is to regulate the use of CRISPR technology. But if the Coordinated Framework is ineffective, what is the best path forward?

C. Specific Regulatory Recommendations Focus on Creating a Single Point of Entry for Biotechnology Products and Creating a Licensing Subcommittee for Human Embryo Research

While a novel or updated regulatory regime should consider the criteria outlined by the IFPRI,[246] a criteria-based system in and of itself leaves too much room for interpretation. Rather, these criteria should be considered foundational components of a regulatory regime that incorporates both the NAS proposal for a single point of entry and the Evitt proposal. Using this approach, the United States would be able to regulate CRISPR—and other emerging biotechnologies—in a manner that accounts for both the safety concerns associated with CRISPR-created products and the ethical dilemmas posed by the processes relied upon by CRISPR researchers, particularly in the field of human embryo research. Accordingly, the new regulatory regime should incorporate a licensing program for human embryo research on the

244. *See* Press Release, Nat'l Acads. of Scis., Eng'g, & Med., On Human Gene Editing: International Summit Statement (Dec. 3, 2015), http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a [https://perma.cc/7KKX-PZ2J].

245. *See* Jon Cohen, *Americans Are Becoming More Open to Human Genome Editing, Survey Finds, but Concerns Remain*, SCIENCE (Aug. 10, 2017, 2:40 PM), http://www.sciencemag.org/news/2017/08/americans-are-becoming-more-open-human-genome-editing-survey-finds-concerns-remain [https://perma.cc/B5US-BX29].

246. *See supra* Part II.A.4.

front end of the single-entry-point framework, giving the federal government greater oversight of human embryo research. The following framework is organized as a comprehensive, beginning-to-end approach with an eye toward incorporation of CRISPR into the larger biotechnology regulatory scheme, a desire to utilize as many of the existing regulatory bodies as possible, and recognition that the government must be involved in the research process for germline cell editing.

1. Increasing Efficiency Is Dependent on the Creation of a Single Point of Entry for All Product Applications

The most important component of an updated regulatory system for biotechnology, and CRISPR in particular, is a single point of entry. Researchers affiliated with academic institutions and companies looking to develop novel therapeutics using CRISPR need a straightforward path for determining which regulatory body is responsible for the regulation of either a research plan or a new drug. Given the high overhead costs[247] associated with drug development, institutions looking to break into this field should not be additionally burdened by excess legal fees that are expended with the sole goal of trying to determine which regulatory body is the most appropriate. Rather, the government should perform this sorting function.

The single-point-of-entry framework would not only increase the efficiency of the biotechnology application process for product developers but would also be the most appropriate for CRISPR given the technology's wide-ranging applicability. As discussed, CRISPR's ability to alter the genes of any organism means that some of the resulting products may appropriately fall under the regulatory purview of the USDA, FDA, or EPA. Moreover, certain products may escape regulation altogether because the authority delegated by Congress via statutory mandates was not specifically written with technologies like CRISPR in mind and may therefore be underinclusive.[248] Accordingly, the creation of a single point of entry for all CRISPR-based product applications would enable regulators to more appropriately assess which federal agencies and corresponding legislation govern the approval process of such products.

a. The Single-Point-of-Entry Committee Should Be Staffed with Individuals from a Diverse Set of Backgrounds to Ensure Ethical, Scientific, and Regulatory Integrity

The success of a single-entry-point regulatory scheme is highly dependent on a purposeful structuring of the entry point itself. Creation of an entirely new federal agency, for instance, would be imprudent because it would not solve the problems of efficiency—seemingly inherent to federal agencies—that currently slow approvals of biotechnology. Rather, the single entry point

247. *See Pharma R&D*, *supra* note 242.

248. *See supra* note 163 and accompanying text (discussing the development of the non-browning mushroom).

should be structured to allow for maximum flexibility, and therefore efficiency, without compromising scientific integrity. Accordingly, this Note proposes the creation of a central committee that serves as the gatekeeping body at the mouth of the single entry point. The following section first elaborates on the benefits of such a committee followed by a discussion on the suggested membership.

A committee comprised of leading ethicists, scientists, regulators, and legislators would be the most effective way to manage the single-entry-point system. By putting scientific thought leaders familiar with the cutting edge of technology on such a panel, developers would be assured that product applications are not misunderstood for lack of scientific knowledge. At the same time, the public at large would be appeased by the presence of ethicists and legislators, knowing that the conversation surrounding possible gene-editing products would include discussion on the ethical questions posed by such technologies. Finally, seasoned regulators would be able to weigh in on which federal agency has authority to regulate such a product, adding a level of regulatory know-how other committee members might lack.

The Australian Research in Human Embryos Act (RIHE Act) mandated the creation of a similar committee tasked with granting—or withholding—licenses for human embryo research.[249] By law, the committee must be comprised of an expert in the regulation of ART, a member of the Australian Health Ethics Committee, an expert in research ethics, an expert in a relevant area of research, an expert in a relevant area of law, an expert in consumer health issues relating to disability and disease, an expert in consumer issues relating to ART, and an embryology expert.[250] Of course, the single point of entry proposed here would require committee members to cover a broader array of biotechnology proposals, but subcommittees with targeted expertise, like the one created by the RIHE Act, could be created ad hoc for particularly complex product applications.

The biggest drawback to such a committee is that it would need to be created by new legislation,[251] and given the current political climate it is unlikely that bipartisan support sufficient to approve such a bill could be mustered. This sort of legislation would likely require grassroots support and substantial media coverage to gain traction, and given the complexity of CRISPR research in particular it seems unlikely that such a movement will take shape organically. Rather, more research like the trials conducted by OHSU in 2017[252] will need to be published to push this conversation to the forefront of national debate and encourage citizens to put pressure on legislators to more effectively regulate CRISPR. At such time, the ability of legislators to quickly draw on regulatory proposals will be critical.

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249. *Embryo Research Licensing Committee*, NAT'L HEALTH & MED. RES. COUNCIL, https://www.nhmrc.gov.au/about/nhmrc-committees/embryo-research-licensing-committee [https://perma.cc/B9EF-HJ2V] (last updated Aug. 24, 2018).

250. *Id.*

251. *See* NAS REPORT 2017, *supra* note 168, at 144.

252. *See generally* Ma et al., *supra* note 16.

b. The Single Point of Entry Will Allow for Tailored Oversight Following the Initial Categorization of the Proposed Research Plan

In addition to giving product developers more insight into the regulation of CRISPR-created products, the single-entry-point sorting function enables regulators to appropriately scale up or scale down oversight of research plans depending on the novelty of the proposals. The Evitt proposal, for instance, recommends that regulation take place in each of the following five phases: before preclinical research, during preclinical research, prior to clinical development, during clinical development, and distribution.[253] For novel, complex research plans, including those involving human embryos and germline editing, the government's level of involvement at each of these stages should be relatively high. For less complex, more familiar proposals, however, there is no need to burden product developers with unnecessary regulation. Subsequently, the Evitt proposal is bolstered by an incorporation of the NAS's proposed single point of entry because the single-entry-point committee can weigh the risks of the proposed CRISPR research and tailor the necessary level of oversight accordingly.

2. Proposals for Research Involving Human Embryos Should Be Submitted to the Committee at the Single Point of Entry to Increase Government Oversight from the Beginning

Beyond increasing efficiency and ensuring appropriate expertise, a single entry point also enables regulators to more easily move to a process-oriented regulatory system, which is critical for establishing a beginning-to-end regulatory scheme for CRISPR research involving human embryos.[254] As currently implemented, the Coordinated Framework focuses purely on end products. It is the product alone that is evaluated for safety and efficacy once it has been submitted for review with no attention paid to the processes used to create that product. For biotechnologies that do not pose significant process-related ethical dilemmas, this system is appropriate. But for technologies like CRISPR that may implicate ethical questions because of the process used to create the end product, the Coordinated Framework is wholly inapt.

Given CRISPR's great potential for curing debilitating diseases, and the need for the use of human embryos in developing lifesaving therapeutic techniques, it is imperative that researchers be allowed to use human embryos in research. A complete ban of human embryo research would not only prevent lifesaving cures from being developed, but also harm the United States's competitive position in the world of biotechnology. Because of the possible misuse and abuse of human embryos in this research, however, it is critical that the government be involved.

253. *See* Evitt et al., *supra* note 227, at 28.
254. *See supra* notes 179–81 and accompanying text.

Under this proposed framework, any researcher intending to use CRISPR technology to develop therapeutics using human embryos during the research process would be required to first submit an application to the single-entry-point committee. The committee, or more appropriately a subcommittee dedicated to evaluating proposals involving human embryo research, would then evaluate the application and balance the need for the proposed therapeutic against ethical concerns. If the application is accepted, the committee would then be responsible for stipulating the licensing terms for human embryo research and ensuring these terms are adhered to throughout the course of the research.

Involving regulatory bodies at the outset of product research and development—particularly when the research involves human embryos—is an important step for regulating CRISPR technology. Use of CRISPR to edit human germline cells could possibly lead to severe long-term consequences for human evolution,[255] and passively allowing scientists to engage in this sort of research, provided they obtain private funding, does little to assuage concerns. Society would be better off in the long run if regulators were involved from the outset of research, particularly when scientists plan to engage in research that could permanently alter the human genome. This enhanced oversight may even lead to broader public approval of such research if citizens are assured that the regulatory system takes into account ethical and long-term considerations when evaluating product development proposals involving human embryo research.

a. The Licensing Program for Human Embryo Research Should Mirror Those Adopted in the United Kingdom and Belgium

Outside of funding restrictions, the federal government largely leaves oversight of human embryo research up to the states.[256] This disparate system is inappropriate because CRISPR research, and gene editing more broadly, are not contained by state boundaries. Rather, the effects of this research on the human genome are of critical importance both domestically and internationally. Accordingly, greater oversight by the federal government is required when researchers propose studies that could permanently alter the human germline.

To this end, the United States should adopt a licensing program in the same vein as Belgium's system.[257] The licensing program would cover all proposed studies involving human embryos and ensure that criteria intended to prevent unethical research are met. A licensing system is preferable to the status quo because it would enable the government to intervene in possibly dangerous research regardless of the funding source. Moreover, a licensing system allows the government to evaluate whether the hypothesized outcome of proposed research would lead to significant improvements in modern

255. *See supra* Part I.A.2.b.
256. *See supra* Part I.B.2.b.
257. *See supra* Part II.B.2.

medicine and supports this research when the possible health benefits outweigh the research risks.

b. The Federal Funding Restriction for Human Embryo Research Should Be Lifted

An additional strategy for increasing government involvement in the regulation of human embryo research is to lift the ban on federal funding of research projects involving human embryos. At present, human embryo research in the United States must be privately funded, but if the federal government were the only permissible funding source, all proposed studies involving human embryos would have to be run by the government for approval. This change would increase government oversight and is an important component of the proposed embryo research licensing program.

Ultimately, a shift away from the Coordinated Framework and toward a regulatory system comprised of components from the NAS and Evitt proposals will serve citizens, industry, and academia well. Moreover, enabling researchers to obtain licenses and funding through the federal government to pursue CRISPR research on human embryos will not only give the government more control over the human embryo "market," but also possibly enable researchers to completely eradicate life-threatening diseases from the human genome. Accordingly, the United States should aggressively move towards revamped regulation of CRISPR to increase scientific innovation and decrease the risks posed by unregulated use of gene-editing technologies on the human germline.

CONCLUSION

CRISPR is arguably the most important development in the field of gene editing to date because of the technology's accuracy, cost-efficiency, and ease of use. These same factors are, however, what make CRISPR dangerous in the wrong hands, potentially leading to harmful manipulation of the human genome. Accordingly, the great power of this technology should not be taken lightly. Rather, governments around the world need to act quickly to rein in unethical use of this technology.

Within the United States, this reconsideration of how biotechnology is regulated requires a fresh look at restrictions currently governing human embryo research and an increase in the government's involvement in all trials involving human embryo research, particularly when those trials may involve permanent alterations to the human genome using CRISPR. To this end, the government should consider eliminating the current Coordinated Framework for biotechnology regulation because it is inefficient and simultaneously over- and under-inclusive in scope. In its place, policymakers should consider a regulatory framework that enables regulators, experts, and the public to be involved from the initial planning stages of products involving gene editing.

A single-entry-point system in which products are categorized by a specialized regulatory body would serve to increase the efficiency of the sorting process, lead to more transparency for product developers, and also give the government the ability to quash potentially dangerous experiments. As a subcomponent of this committee, the government should consider the addition of a human embryo research licensing body tasked with evaluating proposals involving human embryo research and monitoring these studies to ensure ethical boundaries are not crossed. Then, depending on the initial complexity of the study and the novelty of the processes proposed by the researchers, the government can choose to either scale up or scale down monitoring processes. In this way, the government will allow for greater innovation in the medical field without unnecessarily burdening product developers, leading to better health outcomes—and possibly the eradication of some of the world's most vexing diseases.