NOTE

LEGISLATIVE RECOMMENDATION FOR REGULATING THE USE OF GERMLINE MODIFICATION TECHNIQUES IN THE UNITED STATES

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INTRODUCTION

Scientific research regarding human health has a long and intricate history of governmental and institutional oversight, along with professional self-regulation.[2] Regulatory regimes, however, often lag behind innovation.[3] At present, this has never been more apparent than in the rapidly-evolving field of genetics, where animals can now be cloned, sick cells can be replaced with healthy ones, and mutated genes can be embryonically modified or replaced prior to birth.[4]

Modern genetic engineering has begun investigating revolutionary technologies through which mutated, defective, or harmful portions of genetic material can be deleted or modified at will.[5] One of these techniques, CRISPR-Cas9 ("CRISPR"),[6] can be used alone for gene deletion, or in conjunction with other techniques for gene modification.[7] To date, CRISPR-Cas9 has been used

[2] *See generally* Todd W. Rice, *The Historical, Ethical, and Legal Background of Human-Subjects Research*, 53 RESPIRATORY CARE 1325 (2008). For example, the Declaration of Helsinki — a set of non-binding ethical guidelines outlining proper treatment of human subjects during scientific experimentation, which still serves as an influential guidepost for scientists and legislators alike — was the international medical community's first significant attempt at self-regulation. *See* Robert V. Carlson et al., *The Revision of the Declaration of Helsinki: Past, Present and Future*, 57 BRIT. J. OF CLINICAL PHARMACOLOGY 695, 695, 703, 709 (2004) ("In its 40-year lifetime the Declaration has been revised five times and has risen to a position of prominence as a guiding statement of ethical principles for doctors involved in medical research.").

[3] *See* Vivek Wadhwa, *Laws and Ethics Can't Keep Pace with Technology*, MIT TECH. REV. (Apr. 15, 2014), https://www.technologyreview.com/s/526401/laws-and-ethics-cant-keep-pace-with-technology/ [https://perma.cc/4WTQ-568K].

[4] Jennifer A. Doudna & Emmanuelle Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*, SCIENCE 2014, 1258066-1, 1258066-4, 5 (reviewing the literature describing how mutated genes can be embryonically modified using CRISPR-Cas9); Shinya Yamanaka, *Induced Pluripotent Stem Cells: Past, Present, and Future*, 10 CELL STEM CELL 678 (2012) (reviewing the literature on the therapeutic stem cell technology called Induced Pluripotent Stem Cells, or iPSCs); I. Wilmut et al., *Viable Offspring Derived from Fetal and Adult Mammalian Cells*, 385 NATURE MAG. 810 (1997) (describing the notable production of 'Dolly' the sheep—the first mammal to be successfully cloned from a differentiated adult mammary cell). Note that authors Doudna and Charpentier are co-discoverers of the CRISPR-Cas9 methodology, the subject of this paper, and their employers the University of Vienna and the University of California Berkeley engaged in a lengthy and ongoing dispute over the patent rights with another, unassociated co-discoverer employed by The Broad Institute. *See supra* notes 55-70 and accompanying text.

[5] *See generally* Doudna & Charpentier, *supra* note 4 (reviewing several seminal articles regarding CRISPR-Cas9 technology).

[6] CRISPR stands for "clustered regularly interspaced short palindromic repeats"; Cas-9 is the associated protein. *Id*. at 1258096-1. *See also* Ruud Jansen et al., *Identification of Genes that Are Associated with DNA Repeats in Prokaryotes*, 43 MOLECULAR MICROBIOLOGY 1565, 1565 (2002) ("To appreciate their characteristic structure, we will refer to this family as the clustered regularly interspaced short palindromic repeats (CRISPR).").

[7] Doudna & Charpentier, *supra* note 4, at 1258096-2-3.

extensively in animal models,[8] and is now being commercialized[9] after lengthy litigation regarding the ownership of CRISPR's underlying intellectual property.[10]

Despite this progress, scientific complexity and federal regulation, among other obstacles, have hampered the domestic progression[11] of the CRISPR-Cas9 technique toward modifying the human germline.[12] Intellectual property ownership notwithstanding,[13] the domestic legality of editing human genes in clinical practice is generally unclear.[14] As a result, the CRISPR editing technique is subject to substantial legal debate in the U.S.[15] While several state, and to some extent federal, regulations tangentially addressing clinical genetic editing exist,[16] the U.S. has yet to enact any legislation explicitly treating this politically charged topic.[17] Moreover, the act of scientifically modifying human

[8] For a description of CRISPR's existing and potential uses, *see generally id*.

[9] *See* John Divine, *CRISPR Stocks to Buy: How to Invest in a Medical Miracle*, YAHOO! (July 12, 2017), https://www.yahoo.com/news/crispr-stocks-buy-invest-medical-miracle-133824298.html [https://perma.cc/M2JJ-EWFR] (discussing CRISPR and the ways in which "the biotech industry is taking notice of . . . [its] commercial possibilities").

[10] *See infra* Part II.

[11] *But see* Hong Ma et. al., *Correction of a Pathogenic Gene Mutation in Human Embryos*, 548 NATURE 413, 413–19 (2017) (United States); Lichun Tang et. al., *CRISPR/Cas9-Mediated Gene Editing in Human Zygotes Using Cas9 Protein*, 292 MOLECULAR GENETICS & GENOMICS 525, 525–33 (2017) (China).

[12] *See* Doudna & Charpentier, *supra* note 4, at 1258096-7. "Germline" is "the cellular lineage of a sexually reproducing organism from which eggs and sperm are derived; also: the genetic material contained in this cellular lineage which can be passed to the next generation." *Germline*, MERRIAM-WEBSTER, https://www.merriam-webster.com/dictionary/germline [https://perma.cc/W3CN-V8US] (last visited Jan. 19, 2019).

[13] For a discussion of the intellectual property issues surrounding CRISPR, *see generally* Kristin Beale, *The CRISPR Patent Battle: Who Will be "Cut" Out of Patent Rights to One of the Greatest Scientific Discoveries of Our Generation?*, B.C. INTELL. PROP. & TECH. F. 1 (2015).

[14] Heidi Ledford, *The Landscape for Human Genome Editing*, NATURE 15 October 2015, at 310, 310–11 (outlining the various means by which different countries are addressing the "promise and perils of editing the genome of a human embryo").

[15] *Id*.; *see also infra* Part V.

[16] *See* Ledford, *supra* note 14, at 310-11.

[17] *See* Amy Harmon, *Human Gene Editing Receives Science Panel's Support*, N.Y. TIMES (Feb. 14, 2017), https://www.nytimes.com/2017/02/14/health/human-gene-editing-panel.html [https://perma.cc/8SN9-FP9N]; *see also infra* Parts V-VI. While the U.S. has yet to explicitly regulate clinical genetic editing, a number of other countries have. *See* Ledford, *supra* note 14, at 310-11.

deoxyribose nucleic acid ("DNA")[18] raises substantial bioethical concerns.[19] These concerns are especially salient as they relate to the implementation of assisted reproductive technologies — a practice for which CRISPR may have particular utility.[20] Despite the absence of legislation in the U.S., the topic is being actively considered both domestically and internationally.[21] Several countries have already enacted legislation, and the U.S. recently formed a committee to analyze the matter and publish recommendations for domestic legislation.[22]

This note evaluates the current international regulatory landscape concerning the modification of human genetics and provides domestic legislative solutions to the increasingly important[23] issue of clinical genetic editing.[24] Part I provides a general description of the scientific principles underlying the CRISPR-Cas9 gene editing technique and introduces the intellectual property dispute over the rights to it — a dispute which Part II discusses in further detail. Part III examines the bioethical and political concerns regarding the practice of modifying the human germline. Part IV surveys current regulatory approaches to CRISPR, both in the U.S. and abroad. Part V summarizes the U.S. Committee on Human Gene Editing's 2017 recommendations. Finally, Part VI undertakes a critical analysis of the preceding parts and utilizes the results of that analysis to propose domestic regulatory approaches to CRISPR.

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[18] "DNA," or deoxyribonucleic acid, is the self-replicating carrier of genetic information that is present in nearly all living organisms. *DNA*, OXFORD DICTIONARIES, https://en.oxforddictionaries.com/definition/dna [https://perma.cc/UWC4-HK94] (last visited Jan. 19, 2019).

[19] *See* Harmon, *supra* note 14 ("This type of human gene editing has long been seen as an ethical minefield."); *see also infra* Part III.

[20] *See* Pam Belluck, *Gene Editing for 'Designer Babies'? Highly Unlikely, Scientists Say*, N.Y. TIMES (Aug. 4, 2017), https://www.nytimes.com/2017/08/04/science/gene-editing-embryos-designer-babies.html [https://perma.cc/7C7M-KQYH] (addressing bioethical concerns regarding "designer babies," which refers to an individual's hypothetical option to utilize commercial clinical genetic editing to select their child's physical and mental traits prior to that child's birth).

[21] *See, e.g.* Ledford, *supra* note 14, at 310-11 (outlining how different countries are addressing the "promise and perils of editing the genome of a human embryo"); *see also infra* Part IV.

[22] *See generally* NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., HUMAN GENOME EDITING: SCIENCE, ETHICS, & GOVERNANCE (2017) (ebook) (outlining the Committee on Human Gene Editing's recent recommendations); Harmon, *supra* note 17 (reporting that the National Academy of Sciences and the National Academy of Medicine had formed an advisory group on clinical genetic editing); see also infra Part V.

[23] Gina Kolata, Sui-Lee Wee & Pam Belluck, *Chinese Scientist Claims to Use Crispr to Make First Genetically Edited Babies*, N.Y. TIMES (Nov. 26, 2018), https://www.nytimes.com/2018/11/26/health/gene-editing-babies-china.html.

[24] Note that the word "editing" can be alternately used to describe both modification and deletion. When written here, the term will refer to the more broad "modifying", rather than the more specific "deleting".

I. THE SCIENCE, BACKGROUND, AND HISTORY OF THE CRISPR-CAS9 METHODOLOGY.

While CRISPR has had a presence in the contemporary zeitgeist, that presence has in many ways been largely ethical, legal, and commercial in nature.[25] As a result, discussion focusing on the technology's scientific progress is relatively limited. Nevertheless, numerous scientists continue to apply the technology in new and innovative ways.[26] Within the last decade, CRISPR has swiftly swept into many different fields of biological study.[27] Often compared to a word processing program's "find and replace" function, CRISPR's utility lies in its ability to "find and replace" specific portions of DNA.[28] It is this relative simplicity that makes the CRISPR-Cas9 technology appealing to scientists[29] and investors[30] alike.

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[25] *See, e.g.*, Brad Plumer et al., *A simple guide to CRISPR, one of the biggest science stories of the decade*, VOX (Dec. 27, 2018, 2:45 PM), https://www.vox.com/2018/7/23/17594864/crispr-cas9-gene-editing [https://perma.cc/8ZEX-BBYN] (devoting a substantial portion of a comprehensive, high-level, overview of CRISPR to the ethical, legal, and commercial issues attendant to the technology).

[26] *See* Brad Bergan, *11 Amazing Feats the Gene-Editing Tool CRISPR Just Made Possible*, NBC NEWS: MACH (Aug. 8, 2017, 4:22 PM), https://www.nbcnews.com/mach/science/11-amazing-feats-gene-editing-tool-crispr-just-made-possible-ncna790911 [https://perma.cc/8NYB-T9XM] (reviewing the developments in the CRISPR field of genome editing occurring in 2017).

[27] *See, e.g.*, Martin Jinek et al., *A Programmable Dual-RNA – Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816, 821 (2012) (revealing a use for CRISPR); Eric S. Lander, *The Heroes of CRISPR*, 164 CELL 18, 18 (2016) ("fill[ing] in the backstory" of CRISPR technology).

[28] Rae Ellen Bichell, *Science Rewards Eureka Moments, Except When It Doesn't*, NAT'L. PUB. RADIO (Nov. 2, 2016, 5:03 AM), https://www.npr.org/sections/health-shots/2016/11/02/500331130/science-rewards-eureka-moments-except-when-it-doesnt [https://perma.cc/4CEM-6ZVA] (analogizing CRISPR to word processing's "cut and paste" functionality); Francis Collins, *Find and Replace: DNA Editing Tool Shows Gene Therapy Promise*, NAT'L INST. OF HEALTH: NIH DIRECTOR'S BLOG (Jan. 24, 2017), https://directorsblog.nih.gov/2017/01/24/find-and-replace-dna-editing-tool-shows-gene-therapy-promise/ [https://perma.cc/K5QC-E38Q] (referring to CRISPR-Cas9 as "'find and replace' for the genome").

[29] Christopher A. Lino et al., *Delivering CRISPR: a review of the challenges and approaches*, 25 DRUG DELIVERY 1234, 1239 (2018) ("This simplicity makes the CRISPR/Cas9 system the most convenient, simple, and flexible tool for site-directed gene editing currently available.").

[30] Allison Gatlin, *This Biotech Stock Could Launch Its First CRISPR Drug In 2022*, INVESTOR'S BUS. DAILY (Nov. 30, 2018), https://www.investors.com/news/technology/crispr-stock-biotech-stocks-gene-editing/ [https://perma.cc/J88S-SE67] ("'[W]e believe Crispr [sic] is uniquely positioned to succeed in the space, given rights are wholly owned and the simplicity and flexibility of CRISPR technology to make multiple simultaneous edits'").

Indeed, CRISPR is dominant among gene-editing technologies.[31] It has generated an enormously lucrative potential market for large-scale manufacturing of cost-effective gene therapies, and has been tested in industries ranging from agriculture to biotechnology to drug therapy.[32] Market participants have taken notice.[33] The commercial value of the technology is projected to measure in the billions of dollars by 2023,[34] and some of the biggest pharmaceutical companies in the world, including Bayer AG, Vertex, Novartis, Johnson & Johnson, Allergan, Celgene, Glaxo Smith-Kline, Biogen, Amgen, Baxter, and AstraZeneca, have invested in future, commercially-available versions of CRISPR.[35]

To understand why CRISPR is potentially lucrative, as well as potentially controversial, one must understand the technology's scientific underpinnings. In its natural state, CRISPR is an immune response system present in microbes and other single-celled organisms, such as prokaryotes,[36] that helps the organisms protect against foreign viruses or bacterial DNA strands.[37] In what can be

[31] *See, e.g.*, Katelyn Brinegar et al., *The Commercialization of Genome-Editing Techniques*, 37 CRITICAL REVIEWS IN BIOTECHNOLOGY 924, 924 (2017) ("In our analyses, we evaluated the patent landscape of gene-editing technologies and found that in comparison to earlier gene-editing techniques, CRISPR has gained significant traction and this has established dominance.")

[32] *Id*. at 925, 927-28 (2017).

[33] *See* Brinegar, *supra* note 23.

[34] *CRISPR Technology Market*, MARKETSANDMARKETS RES. (Nov. 2018), https://www.marketsandmarkets.com/Market-Reports/crispr-technology-market-134401204.html [https://perma.cc/N5W9-KRLE]; KNOWLEDGE SOURCING INTELLIGENCE, GLOBAL CRISPR MARKET FORECASTS FROM 2018 TO 2023 (2018), *discussed in Global CRISPR Market Forecasts from 2018 to 2023*, BUS. WIRE (Sept. 20, 2018, 2:11 PM), https://www.businesswire.com/news/home/20180920005758/en/Global-CRISPR-Market-Forecasts-2018-2023-Profiles [https://perma.cc/VP7K-GUR4] ("Global CRISPR market is estimated to grow at a CAGR of 33.26% during the forecast period to reach a total market size of US$3086.697 million by 2023 from US$551.242 million in 2017.").

[35] Scientist of Fortune, *Big Biotech in the CRISPR Game: Novartis and Vertex Lead the Pack*, SEEKING ALPHA (Oct. 23, 2017, 10:04 AM), https://seekingalpha.com/article/4115418-big-biotech-crispr-game-novartis-vertex-lead-pack [https://perma.cc/JM32-R5V8].

[36] A prokaryote is a "unicellular microorganism[] that lack[s] a distinct nucleus and membrane-bound organelles." *Prokaryote*, MERRIAM-WEBSTER, https://www.merriam-webster.com/dictionary/prokaryote [https://perma.cc/8GQY-64UD] (last visited Jan. 19, 2019).

[37] *See* Yoshizumi Ishino et al., *Nucleotide Sequence of the 'iap' Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in 'Escherichia Coli,' and Identification of the Gene Product*, 169 J. BACTERIOLOGY 5429, 5429-33 (1987); Luciano A. Marraffini & Erik J. Sontheimer, *CRISPR Interference Limits Horizontal Gene Transfer in Staphylococci by Targeting DNA*, 322 SCIENCE 1843, 1843-45 (2008); Francisco J. M. Mojica et al., *Biological Significance of a Family of Regularly Spaced Repeats in the Genomes of Archaea, Bacteria and Mitochondria*, 36 MOLECULAR MICROBIOLOGY 244, 244-46 (2000); Francisco J. M. Mojica et al., *Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements*, 60 J. OF MOLECULAR EVOLUTION 174, 174-82 (2005); Francisco J. M. Mojica et al., *Long Stretches of Short Tandem Repeats are Present in the Largest Replicons of*

described as a natural adaptive immune response, the organisms integrate short fragments of an invader's DNA[38] sequence into their own genetic material.[39] The integrated sequence is then transcribed like normal DNA, and the output is processed to form short CRISPR RNAs ("crRNA").[40] When paired with CRISPR associated protein 9 ("Cas9"), a DNA nuclease, the organism can target the threatening foreign DNA for destruction.[41] Once the foreign sequence is integrated into the cell's CRISPR sequence, the organism can then quickly target similar invading DNA again in the future — a process much like an immune response antibody system.[42] Together, CRISPR and Cas-9 are directed by the crRNA to accurately edit, or "cleave,"[43] specific segments of the foreign DNA.[44] The 2011 discovery of tracrRNA, another type of RNA, gave geneticists the final element necessary to create this genetic engineering tool. TracrRNA was

the 'Archaea Haloferax Mediterranei' and 'Haloferax Volcanii' and Could be Involved in Replicon Partitioning, 17 MOLECULAR MICROBIOLOGY 85, 85-93 (1995); Francisco J. M. Mojica et al., *Transcription at Different Salinities of 'Haloferax Mediterranei' Sequences Adjacent to Partially Modified Pst I Sites*, 9 MOLECULAR MICROBIOLOGY 613, 613-21 (1993); C. Pourcel et al., *CRISPR Elements in Yersinia Pestis Acquire New Repeats by Preferential Uptake of Bacteriophage DNA, and Provide Additional Tools for Evolutionary Studies*, 151 MICROBIOLOGY 653, 653-63 (2005). *See also* Jacob S. Sherkow, *Law, History and Lessons in the CRISPR Patent Conflict*, 33 NATURE BIOTECHNOLOGY 256, 256-57 (2015) (providing a useful overview of how the CRISPR-Cas9 system works).

[38] For a definition of DNA, see OXFORD DICTIONARIES, *supra* note 18.

[39] *See* Lander, *supra* note 27, at 18.

[40] "RNA," or ribonucleic acid, is a nucleic acid, one function of which is to act as a messenger in all living cells by carrying instructions from DNA to make proteins. *RNA*, OXFORD DICTIONARIES, https://en.oxforddictionaries.com/definition/rna [https://perma.cc/BEJ3-9HRM] (last visited Jan. 19, 2019). For a further discussion of cRNA, see generally Stan J. J. Brouns et al., *Small CRISPR RNAs Guide Antiviral Defense in Prokaryotes*, 321 SCIENCE 960 (2008).

[41] Alexander Bolotin et al., *Clustered Regularly Interspaced Short Palindrome Repeats (CRISPRs) Have Spacers Extrachromosomal Origin*, 151 MICROBIOLOGY 2551, 2551 (2005) (utilizing the terminology of earlier CRISPR studies, the protein cas9 was called cas5 or csn1); Josiane E. Garneau et al., *The CRISPR/Cas Bacterial Immune Sys. Cleaves Bacteriophage & Plasmid DNA*; 468 NATURE 67, 67 (2010); Kira S. Makarova et al., *Putative RNA-Interference-Based Immune System Prokaryotes: Computational Analysis Predicted Enzymatic Machinery, Functional Analogies with Eukaryotic RNAi, & Hypothetical Mechanisms Action*, 1 BIOL. DIRECT 1, 1 (2006); Prashant Mali et al., *Cas9 as Versatile Tool for Engineering Biology*, 10 NATURE METHODS 957, 957–63 (2013). *See generally* Doudna & Charpentier, *supra* note 4.

[42] Rodolphe Barrangou, *CRISPR Provides Acquired Resistance Against Viruses Prokaryotes,* 315 SCIENCE 1709, 1711 (2007); Jansen et al., *supra* note 27, at 1573. *See* Doudna & Charpentier, *supra* note 4, at 1258096-1–2.

[43] Cas9 is a nuclease, meaning that is can "catalyze the cleavage of phosphodiester bonds." Tatsuya Nishino & Kosuke Morikawa, *Structure and function of nucleases in DNA repair: shape, grip and blade of the DNA scissors*, 21 NATURE 9022, 9022 (2002).

[44] Brouns et al., *supra* note 40, at 963*;* Garneau et al., *supra* note 41, at 67, 69.

found to be essential to both the processing of the crRNA and in the cleavage of DNA by the Cas9 nuclease complex.[45] Using tracrRNA, crRNA, and the Cas-9 nuclease complex, the CRISPR system causes double-stranded breaks in the invader's DNA, and then has the ability to use the cell's own DNA repair mechanism to make precise changes in the DNA sequence.[46]

Once scientists understood CRISPR's internal operating mechanisms, they quickly sought to expand its utility. As early as 2008, biologists Luciano Marraffini and Erik Sontheimer began to investigate whether it was possible to control CRISPR's adaptive immune response properties externally, writing "From a practical standpoint, the ability to direct the specific addressable destruction of DNA . . . could have considerable functional utility, especially if the system could function outside of its native . . . context."[47]

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[45] Elitza Deltcheva et al., *CRISPR RNA Maturation by Trans-Encoded Small RNA & Host Factor RNase III*, 471 NATURE 602, 602–03 (2011); Giedrius Gasiunas et al., *Cas9-crRNA Ribonucleoprotein Complex Mediates Specific DNA Cleavage for Adaptive Immunity Bacteria*, 109 PROC. NATL. ACAD. SCI. USA E2579, E2580–81 (2012); Jinek et al., *supra* note 27, at 816, 820.

[46] Doudna & Charpentier, *supra* note 4, at 1077.

[47] Marraffini & Sontheimer, *supra* note 37, at 1845. In fact, Marraffini even filed a patent application claiming the use of CRISPR on eukaryotic cells. U.S. Patent App. No. 14/324,960 (filed July 7, 2014). Though outside the scope of this note, there is another facet of the CRISPR patent dispute: A 2012 patent application named both Marraffini and Feng Zhang as inventors, but the 2013 applications that eventually became the Broad Institute patents at issue in the central CRISPR dispute only named Zhang. Kerry Grens, *That Other CRISPR Patent Dispute*, THE SCIENTIST (Aug. 31, 2016), https://www.the-scientist.com/?articles.view/articleNo/46921/title/That-Other-CRISPR-Patent-Dispute/ [https://perma.cc/NG2M-NMPM]. Rockefeller University, Marraffini's employer, felt that Marraffini had been snubbed on the 2013 applications and filed the cited 2014 application, which repeats the claims of the 2013 patents verbatim but omits Zhang as an inventor. *Id*. However, Rockefeller University and Marraffini might have the last laugh. In 2018, due to a quirk in European patent law, Zhang's patent applications were denied. Phil Taylor, *Broad Institute Knocked Back by European CRISPR Patent Ruling*, FIERCEBIOTECH (Jan. 19, 2018, 10:13 AM), https://www.fiercebiotech.com/biotech/broad-institute-knocked-back-by-european-crispr-patent-ruling [https://perma.cc/3N8L-YHLR]. Since the original application included Marraffini and Rockefeller University, for Zhang to receive a patent Rockefeller University would have needed to assign their rights to him and the Broad Institute. *Id*. Whether by error or refusal, Rockefeller University did not make this assignment, and Zhang's European CRISPR patent applications were denied. *Id*. However, Marraffini's claim was unsuccessful as his application lacked sufficient experimental evidence that CRISPR could successfully function in eukaryotic cells. Lander, *supra* note 27 at 23; *see infra*, Part II. The subject matter of Marraffini's claim is at issue in the dispute over CRISPR's patent rights, which began in 2016 and was between two separate groups of inventors. Alessandra Potenza, *Who Owns CRISPR — One of the Most Important Genetic Inventions of Our Time?*, THE VERGE (Dec. 6, 2016, 5:52 PM), https://www.theverge.com/2016/12/6/13857674/crispr-gene-editing-patent-dispute-berkeley-broad-mit-jennifer-doudna-feng-zhang [https://perma.cc/7L9G-YNYH].

Further, despite knowing that the CRISPR system occurs naturally in certain types of single-celled organisms,[48] scientists believed the technology could also potentially apply to multi-cellular systems, such as the eukaryotic[49] systems present in plants and animals.[50] The first step toward effectuating this idea was to verify that it was possible to transfer the requisite CRISPR components — Cas9 nuclease, crRNA, and tracrRNA — from cells in which CRISPR naturally occurs to those where it does not.[51] In 2011, a group of scientists led by Lithuanian biochemist Virginijus Siksnys successfully reconstituted an entire, fully functional, CRISPR locus, which they had taken from *S. thermophilus*[52] in *E. Coli*, a distantly-related microbe.[53] Shortly thereafter, the same group demonstrated that Cas9 could be successfully reprogrammed to cleave a targeted DNA strand *in vitro*.[54] In other words, they were able to successfully (1) transfer the components necessary for CRISPR's functionality from cells in which those components naturally exist to cells in which they do not; and (2) successfully control the CRISPR-Cas9 system externally.

At the same time that Siksnys was conducting his study, another group of scientists — led by the University of California, Berkeley's Jennifer Doudna and Emmanuelle Charpentier, then of the University of Vienna— were working on the same process.[55] The Doundna and Charpentier study, which was published a mere two weeks after the Siksnys study,[56] not only replicated the results of the Siksnys study, but also discovered an important method of fusing crRNA and tracrRNA into a single-guide RNA ("sgRNA").[57] This discovery was significant in that it simplified CRISPR, increasing the likelihood that scientists might successfully apply CRISPR in more complex organisms such as humans and other

[48] *See supra* notes 36-37 and accompanying text.

[49] *Eukaryotic Cells*, NATURE, https://www.nature.com/scitable/topicpage/eukaryotic-cells-14023963 [https://perma.cc/8BMY-2AW2] (last visited Feb. 1, 2019) (explaining that eukaryotic cells are those cells, present in plants and animals, that contain nuclei and other organelles).

[50] *See* Rimantas Sapranauskas et al., *The Streptococcus thermophilus CRISPR/Cas System Provides Immunity in Escherichia coli*, 39 NUCLEIC ACIDS RES. 9275, 9275–9282 (2011).

[51] Lander, *supra* note 27, at 24.

[52] Short for *Streptococcus thermophilus*, this bacterium "is necessary for commercial purposes" including the production of dairy products. *Streptococcus thermophilus,* BIOLOGY ONLINE DICTIONARY, https://www.biology-online.org/dictionary/Streptococcus_thermophilus [https://perma.cc/3EL8-XBQK] (last visited Jan. 20, 2019).

[53] Rimantas Sapranauskas et al., *The Streptococcus thermophilus CRISPR/Cas System Provides Immunity in Escherichia coli*, 39 NUCLEIC ACIDS RES. 9275–9282, 9275 (2011).

[54] Gasiunas et al., *supra* note 45, at E-2579, E-2581. In March of 2013, Sikysnys employer, Vilnius University, filed a patent on his method of preprogramming Cas9. U.S. Patent. No. 9,637,739 (filed Mar. 15, 2013) (issued May 2, 2017).

[55] Bichell, *supra* note 28.

[56] Gasiunas et al., *supra* note 45 ("Siknsys"; Aug. 1, 2012); Jinek, *supra* note 27 ("Doudna and Charpentier"; Aug. 17, 2012).

[57] Jinek et al., *supra* note 27, at 820.

mammals.[58] Indeed, subsequent modifications of Charpentier and Doudna's discovery are what enabled the CRISPR-Cas9 complex to edit genomes of multicellular organisms.[59] Absent this scientific breakthrough, CRISPR would never have become as available and commercially useful as it is today,[60] and it also may never have become the center of a hotly-contested patent dispute.[61]

Charpentier and Doudna were not the only individuals seeking to propel CRISPR into more complex systems. Biochemist Feng Zhang, who had devoted much of his career to the novel application of genetic techniques, was likewise at the center of CRISPR's progress toward increasing utility.[62] In 2011, for example, Zhang successfully repurposed another genome editing technique called TALENs[63] — a precursor to CRISPR — in order to activate, repress, or edit genes within mammalian cells.[64] Later that year, Zhang became aware of the CRISPR system and began efforts to create a version of the system for use in human cells.[65] In 2012, Zhang and his team reported that it was possible to accurately and efficiently mutate both human and mouse genes using the non-fused version of crRNA and tracrRNA.[66] When Charpentier and Doudna published their work later that year, Zhang again tried his 2012 study, this time using Charpentier and Doudna's newly-discovered sgRNA — *i.e.*, with fused crRNA and tracrRNA.[67] In so doing, Zhang found that this modified sgRNA worked poorly

[58] Bichell, *supra* note 28.

[59] *See* Lander, *supra* note 27, at 18, 24.

[60] Prior to May 2012, all the technological advancements within the CRISPR-Cas9 field were the product of experimentation on single-celled organisms. *See id*. at 18. Although the research on simple organisms served as critical foundation, the technology's fullest scientific and commercial potential rested on the ability to use the CRISPR-Cas9 complex in eukaryotic cells. *Id*.

[61] *See* Susan Young Rojahn, *Broad Institute Gets Patent on Revolutionary Gene-Editing Method*, MIT TECH. REV. (Apr. 16, 2014), http://www.technologyreview.com/view/526726/broadinstitute-gets-patent-on-revolutionary-gene-editing-method/ [https://perma.cc/33UN-XZZW].

[62] *See* Lander, *supra* note 27, at 25. In addition to Zhang's role in the CRISPR story, he also co-discovered another groundbreaking genetic technology known as optogenetics, whereby a light-dependent channel protein can induce a neuron to emit visible light when firing an electrical stimulus-response pulse known as an action potential. *Id*.

[63] TALENs are transcription activator-like effector nucleases—enzymes that can be programmed to cleave specific, targeted DNA sequences. *See id*.

[64] Jeffrey C. Miller et al., *A TALE Nuclease Architecture for Efficient Genome Editing*, 29 NATURE. BIOTECHNOLOGY 143, 143, 147 (2011); Feng Zhang et al., *Efficient Construction of Sequence-Specific TAL Effectors for Modulating Mammalian Transcription*, 29 NATURE. BIOTECHNOLOGY 149, 149, 152 (2011).

[65] Lander, *supra* note 27, at 25.

[66] Le Cong, et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCIENCE 819, 819-20 (2013); *see also* Zhang Patent, *infra* note 94.

[67] Lander, *supra* note 27, at 24-25 (quoting Cong et al., *supra* note 66).

in vivo in mammalian cells.[68] But, more importantly, Zhang discovered a different version of sgRNA which worked *in vivo* within other, non-mammalian eukaryotic cells.[69] This distinction, between Doudna and Charpentier's sgRNA and Zhang's sgRNA, was the primary point of contention during the forthcoming battle over CRISPR's underlying intellectual property.[70]

In a remarkably short time span, scientists successfully repurposed a naturally occurring, prokaryotic gene repair system into a potentially revolutionary technology — a method for editing the genomes of mammals and other eukaryotic organisms *in vivo*.[71] Within a year of these seminal publications, the scientific, commercial, and ethical communities began responding. In the scientific realm, investigators successfully tested CRISPR in multiple eukaryotic organisms.[72] Ethics committees formed worldwide to determine how to regulate the highly-controversial technology.[73] Simultaneously, patent applications were being filed, and patents were granted and licensed by start-up ventures and established companies alike.[74]

II. THE FIGHT FOR CRISPR'S INTELLECTUAL PROPERTY RIGHTS: THE BROAD INSTITUTE V. U.C. BERKELEY.

In 2011, Congress passed the Leahy-Smith America Invents Act ("America Invents Act"), and in doing so, changed the U.S. patent system from a first-to-invent system to a first-to-file system.[75] Under the first-to-invent system, patent

[68] *Id*.

[69] *Id*.

[70] *See* Rojahn, *supra* note 61.

[71] Lander, *supra* note 27, at 18, 24.

[72] Such organisms included yeast, nematodes, fruit flies, zebrafish, mice, and non-human primates. Lander, *supra* note 27, at 26. For thorough review on the topic, see generally Rodolphe Barrangou & Luciano A. Marraffini, *CRISPR-Cas systems: Prokaryotes Upgrade to Adaptive Immunity*, 54 MOLECULAR CELL 234 (2014); Patrick D. Hsu et al., *Development and Applications of CRISPR-Cas9 for Genome Engineering*, 157 CELL 1262 (2014); Wenyan Jiang & Luciano A. Marraffini, *CRISPR-Cas: New Tools for Genetic Manipulations from Bacterial Immunity Systems*, 69 ANN. REV. MICROBIOLOGY 209 (2015); Jeffry D. Sander & J. Keith Joung, *CRISPR-Cas Systems for Editing, Regulating and Targeting Genomes*, 32 NATURE BIOTECHNOLOGY 347 (2014); Samuel H. Sternberg & Jennifer A. Doudna, *Expanding the Biologist's Toolkit with CRISPR-Cas9*, 58 MOLECULAR CELL 568 (2015); John van der Oost et al., *Unravelling the Structural and Mechanistic Basis of CRISPR-Cas Systems*, 12 NATURE REVS.: MICROBIOLOGY 479 (2014); Addison V. Wright et al., *Biology and Applications of CRISPR Systems: Harnessing Nature's Toolbox for Genome Engineering*, 164 CELL 29 (2016).

[73] John Travis, *Germline Editing Dominates DNA Summit*, 350 SCIENCE 1299, 1299–300 (2015).

[74] *See, e.g.*, Sherkow, *supra* note 37, at 256-57.

[75] Leahy-Smith America Invents Act, Pub L. No. 112-29, 125 Stat. 284 (2011) (codified as amended at 35 U.S.C. §§ 102-103). Under a "first to invent" system, patent novelty turns on an individual's having been the first to invent the design or utility that a patent embodies,

novelty turned on an individual's having been the first to invent the design or utility that a patent embodies.[76] While such a system was well intentioned in that it sought to protect unsophisticated inventors who might have been unfamiliar with the United States Patent and Trademark Office ("USPTO") filing process,[77] it also had key disadvantages that made the first-to-file system more appealing: heightened secrecy among inventors, unnecessary administrative burdens, and rules that were incongruous with the rest of the world. The new first-to-file system sought to remedy these key issues and increase innovation by incentivizing the free flow of information, reducing administrative burdens at the USPTO, and creating uniformity with the majority of other patent systems worldwide.

First, heightened secrecy resulted from the first-to-invent system — a result of inventors keeping new inventions out of the public domain until the concept had developed to a point of patentability. This secrecy hampered the free flow of information that lies at the heart of the patent system, thereby reducing the pace of innovation.[78] By contrast, the new first-to-file system incentivizes early disclosure through grace periods; a party may file a patent application up to a year following the public disclosure[79] of a technology.[80]

Second, the first-to-invent system caused the USPTO to incur unnecessary administrative burdens as a result of both patent review and patent dispute resolution.[81] Determining who invented a technology first was often difficult and unwieldy, and took ample amounts of valuable time and resources. The first-to-

whereas under a "first to file" system, patent novelty turns on, *inter alia*, an individual's having been the first to file a patent application. U.S. PAT. & TRADEMARK OFFICE, FIRST-INVENTOR-TO-FILE STATUTORY FRAMEWORK 1-2 (2016), https://www.uspto.gov/sites/default/files/aia_implementation/FITF_card.pdf [https://perma.cc/4UGE-26BD].

[76] *See* 35 U.S.C. § 102(g) (2006); Michael F. Martin, *The End of the First-To-Invent Rule: A Concise History of its Origin*, 49 IDEA 435, 456-59 (2009); U.S. PAT. & TRADEMARK OFFICE, *supra* note 75, at 1-2.

[77] Andrew L. Sharp, *Misguided Patent Reform: The Questionable Constitutionality of First-to-File*, 84 U. COLO. L. REV. 1227, 1236 (2013). In other words, the first-to-invent system rewarded the first individual inventor to discover the new technology, instead of the fastest individual or entity to file a patent application. *Id*.

[78] *Id*. at 1242-43. This is because under the first-to-invent system, a new undisclosed technology would not become part of the public domain (*i.e*., the "prior art"), and thus an inventor would not have incentive to disclose their invention absent the ability to commercialize it themselves. *See id*.

[79] Examples of public disclosure include: discussing the technology in an abstract at a scientific conference, publishing a paper, and, in some instances, even giving a slideshow presentation *See* In re Klopfenstein, 380 F.3d 1345, 1351-52 (Fed. Cir. 2004); Sean B. Seymore, *The "Printed Publication" Bar After Klopfenstein: Has the Federal Circuit Changed the Way Professors Should Talk About Science?*, 40 AKRON L. REV. 493, 504-05 (2007) (citing Norian Corp v. Stryker Corp., 252 F.Supp.2d 945, 954 (N.D.Cal. 2002)).

[80] 35 U.S.C. § 102(b)(1)(A) (2012); U.S. PAT. & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2153.01 (2014); Sharp, *supra* note 77, at 1241.

[81] Sharp, *supra* note 77, at 1241.

file system relieved the USPTO of these burdens by making "interference proceedings," lengthy and expensive hearings to determine which party was the technology's true inventor,[82] unnecessary.[83] Thus a patent examiner now needs only consider whether a party filed (1) first;[84] and (2) within a year of the "priority date," *i.e.*, the date on which a technology was publicly disclosed in advance of a timely application.[85]

Finally, the first-to-invent system rendered the U.S. out-of-date in the global patent landscape. As of 2011, only the U.S. and the Philippines had first-to-invent patent systems, which made it difficult for individuals to uniformly protect their inventions worldwide.[86] The America Invents Act thus sought to (1) increase innovation through incentivizing the free flow of information; (2) address the extensive backlog of pending patent applications at the USPTO by increasing efficiency and lowering administrative costs; and (3) remedy the lack of uniformity in global patent systems.[87]

These changes would prove significant in the dispute over patent rights to CRISPR. On March 15, 2013, Charpentier and Doudna filed a U.S. patent application for the CRISPR-Cas9 methodology (the "Berkeley patent").[88] The Berkeley patent application included 155 claims to the CRISPR methodology as described in Charpentier and Doudna's 2012 paper,[89] and claimed a priority date of May 25, 2012.[90] However, despite being the first publication disclosing the novel use of the CRISPR system, that paper only described CRISPR's use *in*

[82] *Id.* at 1242. In addition to the cost and lengthy duration of interference proceedings, a first-to-invent system also forced courts to address issues of deception. *See, e.g.*, Coleman v. Dines, 754 F.2d 353, 359 (Fed. Cir. 1985).

[83] Sharp, *supra* note 77, at 1243. Under the first-to-file system an inventor may file a patent application up to year following public disclosure of a given technology.

[84] While one party may not literally be the first filer at the USPTO, that party may be considered "first-to-file" if their public disclosure both (1) occurred before the other party's public disclosure; and (2) the subsequent application was timely filed. *See id.* at 1241-42. Further, in the event that an application is not timely filed following public disclosure, the disclosure will be considered part of the prior art, and the inventor may no longer may claim patent rights in the invention. *Id.* Therefore, in a first-to-file system a patent examiner need only consider the priority dates of conflicting applications, giving the patent rights to the application with the earliest date. *Id.* at 1242.

[85] *Id.* at 1241.

[86] *See* Martin, *supra* note 76, at 439 n.16. Even the Philippine system, however, was not *truly* first-to-invent system. *See* Sharp, *supra* note 77, at 1229 n.9.

[87] Sharp, *supra* note 77, at 1241-42.

[88] U.C. Berkeley was Doudna's employer. *See* U.S. Patent Application No. 13/842,859 (filed Mar. 15, 2013) [hereinafter the Berkeley Patent].

[89] *Id.*; *see generally* Jinek et al., *supra* note 27.

[90] Berkeley Patent, *supra* note 88; Deborah Netburn, *UC Berkeley Suffers Big loss in CRISPR Patent Fight: What's Next for the Powerful Gene-Editing Technology?*, L.A. TIMES (Feb. 15, 2017, 8:00 PM), http://www.latimes.com/science/sciencenow/la-sci-sn-crispr-patent-decision-20170215-story.html [**https://perma.cc/UXV2-45TX**].

vitro in a non-cellular environment and did not describe CRISPR's use in eukaryotic cells.[91] Accordingly, the Berkeley application did not "refer to a particular cell type or environment."[92] As of 2019, this Berkeley patent had not issued.[93]

On October 15, 2013, the Eli and Edythe L. Broad Institute of MIT and Harvard (the "Broad Institute") filed a second competing set of claims on behalf of Feng Zhang (the "Zhang Patent").[94] This patent included only twenty claims, all of which concerned the method of using CRISPR on eukaryotic cells as described in Zhang's 2013 paper.[95] Notably, the Zhang patent claimed a priority date of December 12, 2012, which is approximately seven months later than the Berkeley patent's priority date.[96] Unlike the Berkeley patent, however, the Zhang patent issued on April 15, 2014, shortly after its filing, most likely as a result of its comparably smaller number of claims and accelerated review process.[97]

While the Zhang patent issued first, it does not enjoy priority over the Berkeley patent.[98] Because the Berkeley group was both the first to invent CRISPR and the first to file a patent application on the technology,[99] the Berkeley patent would have priority over all Zhang patent claims which interfere, or overlap, with the pending Berkeley patent's claims — both before and after the American Invents Act.[100] However, the Berkeley patent application was lengthy and it was drafted quite broadly.[101] In contrast, the relatively short and direct Zhang patent only claimed application of CRISPR to modify the genes of mammalian eukaryotic cells,[102] which holds the most promise for improving human health and the greatest commercial significance.[103]

In a 2016 effort to gain exclusive patent rights to CRISPR regardless of cell type, the Berkeley group challenged the approval of the Zhang patent before the USPTO's Patent Trials and Appeals Board ("PTAB").[104] The dispute centered

[91] Regents of the Univ. of Cal. v. Broad Inst., Inc., 903 F.3d 1286, 1289 (Fed. Cir. 2018); *see generally* Jinek et al., *supra* note 27.

[92] *Regents of the Univ. of Cal.*, 903 F.3d at 1289; Berkeley Patent, *supra* note 88.

[93] Netburn, *supra* note 90.

[94] U.S. Patent No. 8,697,359 B1 (filed Oct. 15, 2013) (issued Apr. 15, 2014) [hereinafter the Zhang Patent].

[95] See *id.*; Cong et al., *supra* note 66.

[96] Zhang Patent, *supra* note 94.

[97] Netburn, *supra* note 90.

[98] *See supra* notes 75-87 and accompanying text.

[99] *See* Berkeley Patent, *supra* note 88. *See also* Jinek, et al., *supra* note 27, at 820.

[100] Sherkow, *supra* note 37, at 256.

[101] *See* Berkeley Patent, *supra* note 88. *See also* Sherkow, *supra* note 37, at 256.

[102] *See* Zhang Patent, *supra* note 94.

[103] 12 patents granted, 1 application pending as of Sept. 2018. *See* Regents of the Univ. of Cal. v. Broad Inst., Inc., 903 F.3d 1286, 1289 (Fed. Cir. 2018); *see also* Netburn, *supra* note 90.

[104] The Broad Inst., Inc. v. The Regents of the Univ. of Calif., No. 106,048 (DK), at 2 (P.T.A.B. Feb. 15, 2017); Alessandra Potenza, *UC Berkeley Challenges Decision that*

around the requirement of patentability known as "non-obviousness," whereby a claimed invention must contain an inventive step that is substantially unique from any application of an existing technology that would be obvious to a person having ordinary skill in the art.[105] At the interference proceeding, the Berkeley group argued that, after the publication of Doudna and Charpentier's 2012 paper, anyone with ordinary skill in the art could have extended CRISPR's application from prokaryotic to eukaryotic cells.[106] The Broad Institute disagreed, alleging that the Zhang claims amounted to a significant inventive leap and were deserving of patent rights,[107] because, *inter alia*, Doudna had previously acknowledged that the Berkeley group was having substantial difficulty applying the CRISPR-Cas9 method to eukaryotic cells.[108]

Ultimately, the PTAB agreed with the Broad Institute and entered a judgment of no interference-in-fact on February 15, 2017.[109] Pursuant to this judgement, (1) the Zhang patent remains valid; (2) no claims of the either party were cancelled or finally refused; and (3) the Berkeley patent application, which was put on hold when Berkeley requested the interference, would be fully evaluated by the USPTO, independent of the PTAB's judgment.[110] Unsatisfied, in September of 2018 the Berkeley group appealed the PTAB's decision to the U.S. Court of Appeals for the Federal Circuit, who affirmed the judgment of the PTAB.[111]

The ramifications of this decision are substantial. Although a party may appeal any decision arising from a federal court of appeals to the U.S. Supreme

CRISPR Patents Belong to Broad Institute, THE VERGE (Apr. 13, 2017, 9:16 AM), http://www.theverge.com/2017/4/13/15278478/crispr-gene-editing-tool-patent-dispute-appeal-ucb-mit-broad [https://perma.cc/Z92L-JZPD]. *See also* 35 U.S.C. § 135(a)-(b) (2012) (explaining the basics of a derivation proceeding).

[105] Under the "non-obviousness" requirement, an invention is only eligible for patent protection where it would not be obvious a person having ordinary skill in the art. 35 U.S.C. § 103 (2012). Where aspects of the invention exist in multiple prior art references, it must be the result of an "inventive step" that is substantially unique from any application of an existing technology. *See, e.g.*, KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 399 (2007).

[106] *The Broad Inst., Inc.*, No. 106,048 (DK), at 11 (P.T.A.B. Feb. 15, 2017); Potenza, *supra* note 104.

[107] Potenza, *supra* note 104.

[108] Netburn, *supra* note 90. Zhang's group likewise found that use of the Berkeley group's sgRNA on eukaryotic cells was ineffective. *See* Lander, *supra* note 68 and accompanying text.

[109] *The Broad Inst., Inc.*, No. 106,048 (DK), at 11 (P.T.A.B. Feb. 15, 2017).

[110] *Id.*; Netburn, *supra* note 90.

[111] *See* Regents of the Univ. of Cal. v. Broad Inst., Inc., 903 F.3d 1286, 1289 (Fed. Cir. 2018). Before the Federal Circuit, Berkeley argued "that the Board: (1) improperly adopted a rigid test for obviousness that required the prior art contain specific instructions, and (2) erred in dismissing evidence of simultaneous invention as irrelevant." *Id.* at 1291. In response, the Federal Circuit stated that "substantial evidence support[ed] the [PTAB]'s finding that there was not a reasonable expectation of success, and the Board did not err in its determination that there is no interference-in-fact." *Id.* at 1296.

Court, such review is not guaranteed. Furthermore, the Federal Circuit even hinted that the Berkeley group may not wish to expend additional resources on the further appeal as the court had "considered UC's remaining arguments and [found] them unpersuasive."[112] While the Berkeley group may have failed to persuade the Federal Circuit, the same is not true of all patent granting entities. In a parallel challenge before the European Patent Organization ("EPO"), the Berkeley group was successful in securing CRISPR's patent rights, regardless of the cell type to which it is applied.[113] The Broad Institute will likely contest the EPO's decisions, which would render this dispute both ongoing and international.[114] That said, science does not wait for final adjudication on intellectual property rights to continue to innovate, and nor should the government wait to regulate such technologies.[115]

III. BIOETHICAL AND SOCIETAL CONCERNS REGARDING THE USE OF CRISPR TO MODIFY THE HUMAN GERMLINE.

CRISPR's scientific, commercial, and therapeutic potential has, in recent years, garnered global attention.[116] For example, the scientific journal *Nature Methods* awarded genome editing, a general term referring to a variety of techniques for modifying DNA, "Method of the Year" in 2011[117] and *Science* magazine named CRISPR its "Breakthrough of the Year" for 2015.[118] However, this attention has not been uniformly positive. Some have raised questions centered on the possibility that CRISPR could have "unwanted effects" both physiological, through errors in application, and ethical, where the technology could be used for non-essential purposes.[119] Such ethical quandaries are more than simply theoretical; they are looming and must be addressed now. As evidence of this urgency, Chinese researchers have already begun clinical trials using the

[112] *Id*. at 1289.

[113] Jon Cohen, *Europe Says University of California Deserves Broad Patent for CRISPR*, SCIENCE (March 27, 2017, 6:15 PM), http://www.sciencemag.org/news/2017/03/europe-says-university-california-deserves-broad-patent-crispr [http://perma.cc/NB3Z-L7N5].

[114] *Id*.

[115] *See* NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at xi.

[116] 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/8PMH-K76U].

[117] Monya Baker, *Gene-Editing Nucleases*, 9 NATURE METHODS 23, 23 (2012) (each year, *Nature Methods* selects a "Method of the Year" that the publication deems most revolutionary and influential).

[118] John Travis, *Making the Cut: CRISPR Genome-Editing Technology Shows Its Power*, 350 SCIENCE 1456, 1456 (2015).

[119] NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at xi (evidencing concern regarding the "technical aspects of achieving desired results while avoiding unwanted effects, and about a range of uses that may include not only healing the sick, but also preventing disease in this and future generations, or even altering traits unrelated to health needs.")

CRISPR-Cas9 method of genome editing on human somatic cells, and such trials are poised to begin elsewhere, including in the U.S.[120]

Biotechnology has a history of responding to ethical questions via successful self-regulation, which promotes both technological advancement and discourse within the scientific community.[121] For example, in 1975, a group of recombinant DNA technology[122] researchers organized the Asilomar Conference in response to a 1974 National Academy of Sciences committee decision that, absent an international consensus, scientists should halt their research into the technology.[123] The Asilomar Conference successfully met its goal of creating voluntary guidelines for the use of recombinant DNA technology and, in doing so, allowed experiments employing the technology to resume.[124] Perhaps more importantly the conference set the stage for development of informed scientific policy through group discussion and consensus. Indeed, widespread use of the Asilomar guidelines allowed recombinant DNA technology to become a dominant force in biotechnology research.[125]

Like recombinant DNA technology, CRISPR — a novel technology with high public health utility — raises complex ethical issues.[126] Aside from potentially

[120] *See id.*; *see also* Diana Kwon, *CRISPR to Debut in Clinical Trials*, THE SCIENTIST (Dec. 14, 2017), https://www.the-scientist.com/?articles.view/articleNo/51174/title/CRISPR-to-Debut-in-Clinical-Trials/ [https://perma.cc/YN56-LBS8] (note that the upcoming U.S. clinical trials planned by CRISPR Therapeutics, the company co-founded by Charpentier, are not simply editing human cells *in vitro*, but rather will remove mutated cells from human subjects, modify the mutated cells in the laboratory using CRISPR-Cas9, and then return the modified cells to the human donor); Emily Mullin, *CRISPR in 2018: Coming to a Human Near You*, MIT TECH. REV. (Dec. 18, 2017), https://www.technologyreview.com/s/609722/crispr-in-2018-coming-to-a-human-near-you/ [https://perma.cc/R6VM-PBSC].

[121] *See, e.g.*, Paul Berg & Maxine Singer, *The Recombinant DNA Controversy: Twenty Years Later*, 92 PROCEEDINGS OF NAT'L ACAD. SCI. U.S.A 9011, 9011-13 (1995); Paul Berg et al., *Summary Statement of the Asilomar Conference on Recombinant DNA Molecules*, 72 PROCEEDINGS OF NAT'L ACAD. SCI. U.S.A 1981, 1981-84 (1975). *See also* Amalia M. Issa, *Ethical Considerations in Clinical Pharmacogenomics Research*, 21 VIEWPOINT 247, 247–49 (2000).

[122] Recombinant DNA technology refers to the combining of DNA from different organisms and inserting that DNA into a host organism. Anthony J.F. Griffiths, *Recombinant DNA technology*, ENCYC. BRITANNICA (Dec. 7, 2018), https://www.britannica.com/science/recombinant-DNA-technology [https://perma.cc/N87Z-PTJL].

[123] *See* Berg et al., *supra* note 121, at 1981.

[124] *Id.* at 1982.

[125] Berg & Singer, *supra* note 121, at 9013.

[126] *See* Issa, *supra* note 121. The pharmaceutical industry represents an additional example, as drug manufacturers have responded to ethical concerns regarding astronomical drug prices by claiming that those prices are the result of high costs and economic interests, and thus cannot be lowered. *See* Preet Patel, *The Moral Argument of Drug Availability: Capitalism vs. Ethics*, TEAM KENAN AT THE KENAN INST. FOR ETHICS, https://archive.kenan.ethics.duke.edu/teamkenan/encompass/current-issue/the-moral-argument-of-drug-availability/ [https://perma.cc/66N9-QPYS] (last visited Oct. 29, 2018).

being extremely costly, CRISPR has the potential to, in theory, allow one to remove entire genetic traits from the human genome.[127] Although removal of undesirable, or even lethal, genetic abnormalities may sound desirable in the case of an unwanted disease, the process begs a question: how much control should a select group of humans have over the genetic makeup of the entirety of the human population?[128]

Much of that calculus turns on the intent of that "select group." Their intent, however, and indeed even their identity, remains a mystery.[129] The scientists, innovators, and market actors all may serve as possible culprits. That said, while those individuals have intellectual control, they may act only insomuch as legislators — who have the power to regulate clinical genetic editing (and are contemplating using that power) — will permit them to. Given this dynamic, the need for immediate, informed, and intellectually sound governmental guidance on the topic of clinical genetic editing is abundantly clear.

In fact, the U.S. government is making an effort to address this need for guidance. In an interesting parallel to the Asilomar Conference, the National Academy of Sciences hosted an International Summit on Human Gene Editing in 2015 (the "Summit").[130] Nearly 500 scientists, legal experts, ethicists, and advocacy groups from more than twenty countries convened at the Summit to discuss human germline modifications, and to produce guidelines for clinical genetic editing.[131] A member of Congress even weighed in; speaking at the Summit, Representative Bill Foster (D–IL), a physicist and one of the few members of Congress with an advanced degree in the sciences,[132] noted that "CRISPR and related technologies have the potential to revolutionize the treatment of diseases but could be used in many ways not beneficial to society."[133]

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[127] *See* Netburn, *supra* note 90.

[128] *See* Niklaus H. Evitt, Shamik Mascharak & Russ Altman, *Human Germline CRISPR-Cas Modification: Toward a Regulatory Framework*, 15 AM. J. BIOETHICS 25, 25–29 (2015). Some have analogized CRISPR to eugenics — *i.e.*, regardless of the degree to which one might believe a change to be "rational," interference with natural biological makeup of less educated, elite, and/or healthy members of society is still "the end of the simplest notion of each of us being 'endowed by our Creator with certain inalienable rights.'" Robert Pollack, *Eugenics lurks in the shadow of CRISPR*, 348 SCIENCE 871, 871 (2015).

[129] *See id.*

[130] *See* Sara Reardon, *Global Summit Reveals Divergent Views on Human Gene Editing*, 528 NATURE 173, 173 (2015).

[131] *Id.*

[132] *See* Maggie Fox, *Science was a big winner in Tuesday's vote*, NBC NEWS (Nov. 7, 2018, 7:00 PM), https://www.nbcnews.com/health/health-news/science-was-big-winner-tuesday-s-vote-n933761 [https://perma.cc/7UMF-ZBPM].

[133] Travis, *supra* note 73, at 1299. Such statement is noteworthy, as the topic of clinical genetic editing is often politically, religiously, and ethically charged, particularly in the U.S. *See, e.g.*, Andrew Joseph, *Gene-editing, religion and one scientist's quest to reconcile the two*, PBS NEWS HOUR (Oct. 14, 2016, 10:56 AM), https://www.pbs.org/newshour/science/gene-editing-religion-scientist [https://perma.cc/WW6T-HATC].

Indeed, CRISPR's proponents argue that use of the technology to, for example, modify embryos created during assisted reproduction treatments — which, unlike traditional reproduction, need not be a "genetic lottery"[134] — is merely society balancing two norms: (1) fulfilling its duty to rectify known genetic errors and avoid unnecessary suffering; while (2) affording everyone the opportunity to procreate.[135] Participating at the Summit as a panelist, one supporter of this view, Philosopher John Harris, argued that "there is nothing sacred about the germline" and that all forms of assisted reproduction affect future generations.[136] In Harris' argument CRISPR is no different than *in-vitro* fertilization ("IVF") because both technologies affect future generations in their own way, and thus it cannot be more morally problematic than IVF.[137]

Others, like Hille Haker, a Catholic theologian at Loyola University Chicago, believe just the opposite.[138] They argue that selection of "good" traits and removal of "bad" traits can result in negative effects on humanity,[139] and that there is no "right to have healthy children."[140] They thus believe that all human germline modification should be prohibited, including research conducted on somatic cells.[141]

As Harris suggests, one might characterize IVF itself as a method of germline modification. All IVF embryos are genetically screened prior to implantation in the womb, and, in many instances, parents will choose to implant only "healthy" embryos while "editing out" — *i.e.*, discarding — embryos with genetic anomalies.[142] Alternatively, some parents select for embryos with genetic abnormalities, so that the resulting children express the parents' genetic traits. For example, a deaf couple from the United Kingdom made headlines when they selected for embryos with congenital hearing loss so as to ensure that they had an all-deaf family.[143]

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[134] The concept arises out of the idea that breeding asexually would be akin to buying a large quantity of tickets to the national lottery, but giving them all the same number, while breeding sexually would give each ticket its own number. GEORGE C. WILLIAMS, SEX AND EVOLUTION 15–17, 37 (1975).

[135] Joseph, *supra* note 133; Travis, *supra* note 73, at 1300.

[136] Travis, *supra* note 73, at 1300. *See also* Jim Kozubek, *How Gene Editing Could Ruin Human Evolution*, TIME (Jan. 9, 2017), http://time.com/4626571/crispr-gene-modification-evolution/ [https://perma.cc/P5UE-DE4B].

[137] *See* Travis, *supra* note 73, at 1300.

[138] Id. *See also* Joseph, *supra* note 133.

[139] Kozubek, *supra* note 136; Pollack, *supra* note 128, at 871 ("Rational eugenics is still eugenics.").

[140] Joseph, *supra* note 133; Travis, *supra* note 73, at 1300.

[141] *Id*.

[142] Jim Eckman, *The Ethical Dilemmas Associated with Frozen Embryos*, ISSUES IN PERSP. (May 30, 2015), https://graceuniversity.edu/iip/2015/05/the-ethical-dilemmas-associated-with-frozen-embryos/ [https://perma.cc/CX79-333N]; Travis, *supra* note 73, at 1300.

[143] The U.K. legislature blocked the couple from doing so. *See* Gaby Hinsliff & Robin McKie, *This Couple Want a Deaf Child. Should We Try to Stop Them?*, GUARDIAN (Mar. 9,

If parents commonly and without approbation edit their familial germline by affirmatively selecting only "healthy" embryos, why should society balk when parents opt to edit their familial germline by selecting embryos exhibiting a manageable and non-fatal, yet irregular, trait such as hereditary deafness? Further, cases exist where, but for germline-editing, there would be a high-likelihood that the resulting child will have genetic abnormalities,[144] and germline-editing would present a solution that might lead to the birth of a healthy child without the "discarding" of numerous embryos. As Dr. David Baltimore, a scientist at the California Institute of Technology, asked: "Is it more ethical to edit embryos or screen a lot of embryos and throw many away?"[145] Genetic modification of the embryo before implantation in the womb, if successful, could potentially lead to the birth of a child who does not exhibit the disease phenotype. If the technique developed to the point of high reliability and accuracy, would germline editing not be the more ethical of the two scenarios presented by Dr. Baltimore?

These and other difficult questions led the twelve-person Summit panel, representing the array of professionals in attendance, to take a cautious approach — recommending that DNA-editing techniques should be used for basic research only, rather than for therapeutic clinical practice.[146] Although the panel's experts did not explicitly rule out germline editing, they strongly recommended against using DNA modification techniques to produce pregnancies from modified embryos, calling it "irresponsible" from a safety perspective and citing a lack of societal consensus.[147]

This caution may be appropriate. Some believe that, as a result of the ethical and safety-related concerns regarding research on reproductive cells, allowing even basic DNA-editing research on somatic, *i.e.*, non-reproductive, cells may have potentially negative effects on the field as a whole.[148] Many experts also

2008, 5:54 AM), https://www.theguardian.com/science/2008/mar/09/genetics.medicalresearch [https://perma.cc/LTG3-A4S8].

[144] This would be there case where both parents carry an autosomal recessive genetic mutation, meaning that any embryo created will carry the same trait. Travis, *supra* note 73 at 1300 ("For example, if both parents have cystic fibrosis, an autosomal recessive disorder, any offspring would carry double mutations."). *See also* Helen Thomson, *Baby Born with Cystic Fibrosis After IVF Screening Blunder*, FORBES (Dec. 14, 2017, 2:03 PM), https://www.forbes.com/sites/helenthomson/2017/12/14/baby-born-with-cystic-fibrosis-after-ivf-screening-blunder/#7af7b3481a5c [https://perma.cc/KT5G-VW56].

[145] Travis, *supra* note 73, at 1300.

[146] *Id*. at 1299. *See also* Edward Lanphier et al., Comment, *Don't Edit the Human Germ Line*, 519 NATURE 410, 410-11 (2015).

[147] Travis, *supra* note 73, at 1299.

[148] Lanphier et al., *supra* note 146, at 410 ("In our view, genome editing in human embryos using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable. Such research could be exploited for non-therapeutic modifications. We are concerned that a public outcry about such an ethical breach could

point to CRISPR's technological imperfections that, as of now, might produce inconsistent results when editing embryonic DNA.[149] Even absent concerns as to inconsistent results in embryonic DNA, controlling the quantity of cells that CRISPR modifies will be difficult, and there remains a high likelihood that untargeted cells would be affected.[150] While this potential problem will only exist so long as the field has not made sufficient technological advancements to meet necessary standards of precision, and while, if the past several years are any indication, innovation will soon reduce the error rate,[151] the concern nonetheless remains valid as a contemporary matter.

IV. MODIFYING HUMAN DNA & THE EXISTING REGULATORY LANDSCAPE.

According to Barbara Evans, of the University of Houston Law Center in Texas, "the 'science' of regulation is more precarious and uncertain than the science of gene editing."[152] While this paper focuses on CRISPR, there are several other germline modification techniques that have developed over the years.[153] As the technology progressed from theoretical to possible to actual, the associated safety and bioethical concerns grew accordingly.[154] Countries, especially those with strong technological industries, took notice.[155] Today, CRISPR-Cas9 leads a field of highly promising germline modification techniques that face varying degrees of regulation.[156]

One manner through which a jurisdiction might regulate human germline editing is by restricting the use of human embryonic tissue in clinical research — absent which the efficacy of germline editing techniques on human DNA is by

hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited.").

[149] *Id*. at 411.

[150] *Id*.

[151] *Id*.

[152] Travis, *supra* note 73, at 1300.

[153] *See, e.g.*, Kelly E. Ormond et al., *Human Germline Genome Editing*, 101 AM. J. HUM. GENETICS 167, 168 (2017).

[154] *See infra* Part III.

[155] The United States, for example, regulates a procedure called ooplasmic transfer that has successfully resulted in more than thirty childbirths. FOOD & DRUG ADMIN., BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMM., OOPLASM TRANSFER AS METHOD TO TREAT FEMALE INFERTILITY 1 (2002), https://web.archive.org/web/20030729044243/http://www.fda.gov:80/OHRMS/DOCKETS/ac/02/briefing/3855B1_01.pdf. In this process, a small amount of material ("ooplasm") from the healthy egg of a fertile woman in injected into the eggs of women with abnormal fertility. *Id*. The Food and Drug Administration cited this process, ooplasmic transfer, as a potential health risk to progeny. *Id*. at 4.

[156] *See* Motoko Araki & Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing Into In Vitro Fertilization*, REPROD. BIOLOGY & ENDOCRINOLOGY, 2014, at 1, 1-2, 8, 10.

definition unascertainable.[157] Despite the numerous ways to collect embryonic tissue,[158] for ethical reasons, many countries and some U.S. jurisdictions strictly regulate both the use and *in vitro* culture of human embryonic tissue specifically for research purposes.[159] Some jurisdictions ban the practice outright, while others allow researchers to utilize embryonic tissue where the tissue was (1) donated in accordance with the regulatory guidelines; or (2) was created for other purposes.[160]

Alternatively, a jurisdiction might regulate human germline editing through statute, administrative regulation, and government-issued guidelines.[161] Researchers Motoko Araki and Tatsuya Ishii surveyed the international regulatory landscape as it applies to regulating human germline editing, examining the pertinent laws of thirty-nine countries.[162] Of those countries, twenty-nine banned human germline gene modification outright[163] — four of which employed loosely structured guidelines that do not have the binding effect of formal laws,[164] and ten of which were ambiguous as to the legal status of germline modifications.[165]

In the U.S. specifically, individual states take predictably divergent approaches to regulating germline research. Some, like California, Connecticut,

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[157] *See id*. at 1-5.

[158] These methods include: voluntary donation following the elective termination of pregnancy; voluntary donation of fertilized, but not yet implanted, IVF embryos; and through small tissue samples that are then cultured *in vitro*. *See* Dianne Gerrelli et al., *Enabling Research with Human Embryonic and Fetal Tissue Resources*, 142 DEVELOPMENT 3073, 3073-76 (Sept. 15, 2015); NAT'L INST. OF HEALTH, DEP'T HEALTH & HUM. SERVS., STEM CELLS: SCIENTIFIC PROGRESS AND FUTURE RESEARCH DIRECTIONS ch. 3 (2001) (ebook), https://stemcells.nih.gov/info/2001report/chapter3.htm [https://perma.cc/S8VN-DKF2].

[159] Tetsuya Ishii et al., *Ethical and Legal Issues Arising in Research on Inducing Human Germ Cells from Pluripotent Stem Cells*, 13 CELL STEM CELL 145, 145-48 (2013). Araki & Ishii, *supra* note 156, at 8.

[160] An embryo created for *in vitro* fertilization, for example, that was left unfertilized and unimplanted. Researchers using embryos created for this and similar purposes would always be required to proceed with informed consent of the parents. Araki & Ishii, *supra* note 156, at 8.

[161] Ledford, *supra* note 14, at 311 ("[M]any researchers long for international guidelines").

[162] *Id*. at 310.

[163] *Id*. at 310-11 (the countries include Mexico, Canada, Brazil, China, India, Australia, New Zealand, and Japan; most, but not all, of Europe also bans modification). *See also id*. at 310 ("'The truth is, we have guidelines but some people never follow them,' said Qi Zhou, a developmental biologist at the Chinese Academy of Sciences Institute of Zoology in Beijing.").

[164] Those countries are China, India, Ireland, and Japan. Araki & Ishii, *supra* note 156, at 8.

[165] Those countries include Russia, Argentina, and the U.S. *Id*. ("When the safety of genome editing-mediated germline gene correction is enhanced, [China, India, Ireland, Japan] and the USA might permit it.").

Illinois, Iowa, Maryland, Massachusetts, New Jersey, and New York, have statutes in place that encourage embryonic stem cell research.[166] On the other hand, some states, like South Dakota, ban the use of embryos outright.[167] Still others, like Hawaii and Alaska, have no laws in place.[168] The variability of the state-by-state approaches to regulating reproductive technology, be it stem cells, germline modification, or otherwise, is confusing and unwieldy. A cohesive federal regulatory system could alleviate some of this variability, especially if constructed such that federal laws relating to germline modification will preempt conflicting state law.[169]

At a federal level, the Food and Drug Administration ("FDA") and the National Institutes of Health ("NIH") currently regulate germline modification, albeit indirectly.[170] The FDA, for example, regulates clinical trials, including not only how trials are conducted, but also which scientific inquiries are allowed to progress to trials involving human subjects or tissue.[171] The NIH, on the other hand, restricts the available applications of germline editing technology through its control of research funding.[172] Though President Obama lifted, in a 2009 executive order, several regulations that limited the use of embryonic stem cells in

[166] *Embryonic and Fetal Research Laws*, NAT'L CONFERENCE OF STATE LEGISLATURES (Jan. 1, 2016), http://www.ncsl.org/research/health/embryonic-and-fetal-research-laws.aspx [http://perma.cc/XE3Q-N6PQ]. There are reasons to encourage such research — most plausibly, its economic benefits. States with favorable laws will both attract new associated enterprise and will incentivize existing enterprise to continue to do business within the state. For instance, California's Proposition 71 allocated $3 billion for stem cell research in 2004 — the result being over a billion dollars in spending on "on six new research facilities, grants, and the recruitment of scientists" as well as at least one recorded instance of a company relocating to the state "to take advantage of the state's funding for hESC research." Ceara O'Brien, *California Proposition 71, Stem Cell Research (2004)*, EMBRYO PROJECT ENCYC., (Apr. 3, 2014), https://embryo.asu.edu/pages/california-proposition-71-2004 [https://perma.cc/M73S-UGAP].

[167] NAT'L CONFERENCE OF STATE LEGISLATURES, *supra* note 166. Notably, in the states with statutes in place, the regulatory efforts seek to restrict activities like human reproductive cloning — wherein an embryo is cloned from a donor's genetic material, and then implanted into a uterine environment for gestation — or transactions involving fetal tissue. *See* NAT'L ACADEMIES OF SCIENCES, ENG'G & MED., HUMAN REPRODUCTIVE CLONING: PROPOSED ACTIVITIES AND REGULATORY CONTEXT 84-85 (2002), (ebook) https://www.ncbi.nlm.nih.gov/books/NBK223951 [http://perma.cc/Z787-YFFP]; NAT'L CONFERENCE OF STATE LEGISLATURES, *supra* note 166.

[168] NAT'L CONFERENCE OF STATE LEGISLATURES, *supra* note 166.

[169] U.S. CONST. art. VI, cl. 2.

[170] *See* NAT'L ACADEMIES OF SCIENCES, ENG'G & MED., *supra* note 22, at 264.

[171] *See, e.g.*, U.S. FOOD & DRUG ASS'N, *Clinical Trials and Human Subject Protection*, https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm [http://perma.cc/6YSA-9TV9] (last updated Oct. 11, 2018).

[172] Araki & Ishii, *supra* note 156, at 8.

the research setting, many remain in effect.[173] For example, under the 'Dickey-Wicker Amendment,' funds appropriated to the Department of Health and Human Services in 2009 may not be used to create human embryos for research purposes and for "research in which . . . human . . . embryos are destroyed, discarded, or knowingly subjected to risk of injury or death."[174]

Shortly after President Obama issued the executive order, two stem cell researchers brought suit, arguing that research on human embryonic stem cells harms embryos, and therefore should not receive funding pursuant to the Dickey-Wicker Act.[175] After "a tortuous legal process that resembled . . . a game of chutes and ladders,"[176] the Court of Appeals for the District of Columbia Circuit upheld the district court's decision to grant summary judgment in favor of the government's position.[177]

President Obama's executive order and the *Sherley* case illustrate the contentious and ever-changing environment pervading the use of human embryonic tissue in a clinical setting. While the U.S. does not currently levy a formal ban on the use of germline editing techniques on human tissue in clinical research settings, existing federal regulations still pose significant and ongoing hurdles to the technology's development.

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[173] Exec. Order No. 13,505, 3 C.F.R.§ 13505 (2009); *Obama Overturns Bush Policy on Stem Cells*, CNN (Mar. 9, 2009, 12:43 PM), http://www.cnn.com/2009/POLITICS/03/09/obama.stem.cells/index.html [http://perma.cc/428G-Y8S5].

[174] Omnibus Appropriations Act, Pub. L. No. 111-8, § 509(a), 123 Stat. 524, 803 (2009).

[175] Sherley v. Sebelius, 704 F. Supp. 2d 63, 63, 66 (D.D.C. 2010), *vacated*, 644 F.3d 388 (D.C. Cir. 2011). Shockingly, the district court also issued a preliminary injunction that suspended federal funding for research involving human embryonic stem cells. *Id*. This injunction was later suspended by the appellate court until the case was resolved. *See* Meredith Wadman, *High Court Ensures Continued US Funding of Human Embryonic-Stem-Cell Research*, NATURE (Jan. 7, 2013), https://www.nature.com/news/high-court-ensures-continued-us-funding-of-human-embryonic-stem-cell-research-1.12171 [http://perma.cc/W67X-BD27]; *Sherley v. Sebelius Background and Timeline,* LAW OF LIFE PROJECT, http://www.lawoflifeproject.org/SherleyvSebelius [http://perma.cc/EWL8-GC3T] (last visited Nov. 29, 2018).

[176] Dena S. Davis, *Not with a Bang, but a Whimper: Sherley v. Sebelius*, HASTINGS CTR. REPORT January-February 2013, at 17, 17. Following the District Court's aforementioned preliminary injunction, the Secretary of Health and Human Services, defendant in the case, appealed. Sherley v. Sebelius, 689 F.3d 776, 778 (D.C. Cir. 2012), *cert. denied*, 568 U.S. 1087 (2013). The Court of Appeals vacated the injunction and remanded the case to the District Court. *Id*. On remand, the District Court granted the Defendant summary judgment, and the Plaintiffs appealed. *Id*.

[177] *Sherley*, 689 F.3d at 785.

V. RESULTS & RECOMMENDATIONS: THE U.S. NATIONAL ACADEMIES OF SCIENCES AND MEDICINE'S 2017 COMMITTEE ON HUMAN GENE EDITING.

In 2017, the U.S. National Academies of Sciences and Medicine convened the Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations (the "Committee") for the purpose of conducting a study on the uses of genome editing techniques in humans.[178] While the Committee considered several genome editing techniques, CRISPR received comparably more attention because it can effectuate human germline modifications more economically and efficiently than its peers.[179] More broadly, the Committee considered three categories of genome editing use: (1) basic research;[180] (2) somatic interventions to modify non-reproductive cells; and (3) germline interventions to modify reproductive cells that may affect future offspring.[181]

Basic research is foundational, rather than clinical, in nature. Accordingly, absent privacy or safety concerns, the federal government does not subject individuals conducting basic research to onerous regulations concerning human subjects.[182] Because of this, basic research can include, and, in the case of CRISPR, often does include experiments on germline — *i.e.*, reproductive[183] — cells.[184] So, the Committee concerned itself with basic research on germline cells, specifically the collection and use of such cells.[185] It concluded that the existing

[178] *See* NAT'L ACADEMIES OF SCIENCES, ENG'G & MED., *supra* note 22, at xi. More specifically, the Committee was tasked with analyzing, "the state of the science in genome editing, possible clinical applications of these technologies, potential risks and benefits, whether standards can be established for quantifying unintended effects, whether current regulatory frameworks provide adequate oversight, and what overarching principles should guide the regulation of genome editing in humans." *Id.* at 2.

[179] *See id.*

[180] Basic research refers to research that "'is performed without thought of practical ends'" in that it isn't aimed a specific disease or condition. *See* NAT'L SCI. FOUND., THIRD ANNUAL REPORT OF THE NATIONAL SCIENCE FOUNDATION 38 (1953), http://www.nsf.gov/pubs/1953/annualreports/ar_1953_sec6.pdf [https://perma.cc/3HZV-M4BY].

[181] *See* NAT'L ACADEMIES OF SCIENCES, ENG'G & MED., *supra* note 22, at 3.

[182] 45 C.F.R. 46 (2017); *see* NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 3.

[183] NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 3 (explaining that germline cells can be "early-stage human embryos, eggs, sperm, and the cells that give rise to eggs and sperm").

[184] *See generally, e.g.*, Chengzu Long et al., *Prevention of Muscular Dystrophy in Mice by CRISPR/Cas9-Mediated Editing of Germline DNA*, 345 SCIENCE 1184 (2014)

[185] NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 3; Richard Pérez-Peña, *Anti-Abortion Activists Charged in Planned Parenthood Video Case*, N.Y. TIMES (Mar. 29, 2017), https://www.nytimes.com/2017/03/29/us/planned-parenthood-video-charges.html?_r=0 [https://perma.cc/3AX6-SHP4]; *see generally* Chengzu Long et al., *supra* note 184 (presenting the findings of an experiment aimed to correct a mutation in the germ line of mdx mice.).

regulatory infrastructure among the various scientific disciplines already adequately and thoroughly addresses associated issues — including the lawful use of human gametes and embryos in laboratory research.[186]

Conversely, clinical research involves direct contact with human subjects and is highly regulated in the U.S.[187] Any medical advances that will ultimately be used in a clinical setting must first go through at least one, and often several, strictly regulated and carefully vetted clinical experimentation phase before becoming available for public use.[188] The Committee addressed concerns regarding two branches of clinical research: (1) genome modification that only affects a treated individual — *i.e.*, that individual's somatic cells ("clinical somatic genetic editing"); and (2) genome modification that potentially affects both treated individuals and their offspring — *i.e.*, their reproductive cells ("clinical germline modification").[189]

The first, clinical somatic genetic editing, is subject to existing regulations and ethical norms developed in response to older gene therapy treatments.[190] And, because clinical somatic gene editing involves only a single person's genome, the Committee concluded that any scientific or technical issues arising during the process were readily addressable through ongoing improvements of efficiency and accuracy. Ethical and regulatory hurdles would factor into the existing regulatory framework insomuch as that framework calls for balancing "anticipated risks and benefits to a patient."[191] Nevertheless, the breadth of somatic genome editing poses some challenge to implementing a cohesive regulatory standard.[192] The Committee further suggested that "regulators will need to consider the technical context of the genome-editing system as well as the proposed clinical application in weighing anticipated risks and benefits."[193]

The second, clinical germline modification, investigates heritable changes that will affect future offspring, and consequently raises more cause for concern.[194] Indeed, in the U.S., clinical germline modification can be a highly politicized topic. In 2016, for example, Congress passed legislation requiring the FDA to reject all requests to allow "research in which a human embryo is intentionally created or modified to include a heritable genetic modification."[195] The underlying reasoning seems clear: the U.S. government does not want taxpayer

[186] NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 4-5.

[187] 6 C.F.R. § 46.104 (2018); NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 3.

[188] NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 3.

[189] *Id*. at 5.

[190] *Id*.

[191] *Id*. at 6.

[192] *Id*.

[193] *Id*.

[194] *Id*.

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

funds to go to the creation or manipulation of intentionally diseased or deformed human life. Likewise, its effect on the development of CRISPR is clear: the federal ban on mere consideration of such proposals means that CRISPR, despite its need for clinical trials, is highly suspect. The suspicion and concern surrounding clinical germline modification is unfortunate, however, because this potential CRISPR use may well encompass the greatest utility in terms of public health — the ability for all humans to have children without the fear of passing on a debilitating, genetically heritable disease.[196]

Given the potential utility associated with clinical germline modification, the Committee did not find that existing federal regulations[197] are sufficient, but rather provided a recommendation for future studies that attempted to balance the myriad of "technical and social" issues at play.[198] This recommendation stressed that if clinical trials of germline modification commence, they should proceed with the utmost caution and with the thoughtful consideration of public opinion at each step.[199] Specifically, the Committee outlined the following recommendations for a regulatory framework that might one day oversee such future clinical trials, instructing that such trials should only proceed under the following conditions and criteria:

- absence of reasonable alternatives;
- restriction to preventing a serious disease or condition;
- restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition;
- restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects;
- availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures;
- ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of the research participants;
- comprehensive plans for long-term, multigenerational follow-up that still respect personal autonomy;
- maximum transparency consistent with patient privacy;

[196] NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 6. This is because clinical germline modifications could be transmissible, *i.e.*, elimination of a genetically heritable disease could prevent a carrier's offspring from inheriting the genetic mutation responsible for that disease. *See id.*

[197] *See, e.g.*, 45 C.F.R. § 46 (2017).

[198] NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 7.

[199] *Id.*

- continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public; and
- reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.[200]

Even with these comprehensive guidelines in mind, the Committee acknowledged the contentiousness of the issue. Any reader of the recommendations might think them either too strict or too broad, depending on their personal perspective.[201]

Finally, the Committee considered the "trendier" issue of using clinical genetic editing for "enhancement" — *i.e.*, modifications "that go beyond treatment or prevention of disease or disability" — which could theoretically involve either somatic or germline cells.[202] The Committee was careful in its treatment of the term "enhancement," specifically hypothetical enhancement in relation to what might be considered "normal," or desirable.[203] Treatments that may be deemed restorative in one sense may easily be considered enhancements in another. For example, curing a muscular weakness through treatment could, in one sense, be considered restorative. In another sense, this same restorative treatment may easily be considered an enhancement if used to sculpt a typical physique into a musclebound superhuman.[204]

This balance, between using genome-editing techniques to alleviate undesirable disease phenotypes and using these techniques to enhance, incites ample amounts of "public discomfort."[205] There is fear that their use might exacerbate wealth and other social inequalities, and that people might feel pressure to engage in practices that they may not have otherwise considered.[206] Since there is a great public interest in this particular aspect of genome editing, the Committee found it imperative that ongoing public discussion[207] — addressing, *inter alia*, the real and anticipated social impacts of clinical genetic editing for "enhancement" purposes — precede any formal decisions on "whether or how to pursue

[200] *Id*. at 7-8.

[201] *See id*. at 8.

[202] *Id*. at 8-9. *See also* Belluck, *supra* note 20.

[203] NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 8-9.

[204] *Id*. ("[U]sing genome editing to improve musculature for patients with muscular dystrophy would be considered a restorative treatment, whereas doing so for individuals with no known pathology and average capabilities just to make them stronger but still within the 'normal' range might be considered enhancement. And using the technology to increase someone's muscle strength to the extreme end of human capacity (or beyond) would almost certainly be considered enhancement.")

[205] *Id*. *See supra* Part V.

[206] *See* NAT'L ACADEM. OF SCIENCES, ENG'G, & MED., *supra* note 22, at 9.

[207] The Committee encouraged "broad participation and input by the public and ongoing reassessment of both health and societal benefits and risks." *See id*. at 9-10.

clinical trials of such applications."[208] After all of these considerations, the Committee recommended that "genome editing for purposes other than treatment or prevention of disease and disability should not proceed at this time."[209]

VI. LEGISLATIVE RECOMMENDATION FOR THE UNITED STATES.

There are a number of possible approaches to crafting a regulatory regime which addresses the complex issues associated with clinical genetic editing: statutes, regulations, funding mechanisms, incentive programs, and guidelines, among others. For example, a regulation that effectively controls research through federal funding logically might not exert the same control over an independently-funded commercial enterprise — even if the same technology is being used in both cases. Moreover, as mentioned above, clinical trials, an intermediate step in the progression from lab-based research to commercial enterprises, pose another regulatory hurdle. This article's findings are illustrative of the fact that, given the many relevant challenges and considerations one must consider when regulating this field, any such regulation is unlikely to be "one size fits all" — no matter how thoughtful and complete.

That said, in many respects, the existing framework for scientific research is adequate to address most of the potential ethical concerns. The government essentially retains control at two points: (1) via NIH limitations on federal funding at the research's outset; and (2) through the FDA's power to regulate clinical trials after research moves from animal to human testing.[210] Thus these two federal bodies — both of which already regulate CRISPR to some degree — act as gatekeepers, but in different ways. The NIH has control over federal funding, but does not reach privately-funded research.[211] The FDA, on the other hand,

[208] *Id*. at 9-10.

[209] *Id*. at 9.

[210] *See, e.g*., *Is Gene Therapy Safe?*, GENETICS HOME REFERENCE (Nov. 6, 2018) https://ghr.nlm.nih.gov/primer/therapy/safety [https://perma.cc/8LK4-VK93]. Note that any scientific animal testing is generally controlled by the United States Department of Agriculture. *See generally* Animal Welfare Act of 1966, 7 U.S.C. § 2131 (2012).

[211] Though some commercial enterprises offer research grant funding, the NIH serves as the primary funding mechanism for scientific research in the United States. *See, e.g*. *Budget*, NAT'L INST. OF HEALTH https://www.nih.gov/about-nih/what-we-do/budget [https://perma.cc/B4SQ-G5GL] (last updated Apr. 11, 2018). Significantly, as the U.S. legal response to clinical genetic editing continues to develop, both the NIH and private actors continue to allocate millions of dollars to advance germline editing technology. Legislative solutions that render those allocations illegal would effectively waste those substantial financial investments. *See* Office of Strategic Coordination - The Common Fund, *Somatic Cell Genome Editing: Funded Research*, NAT'L INST. OF HEALTH (Feb. 11, 2019), https://commonfund.nih.gov/editing/fundedresearch [https://perma.cc/YF7B-UPQT] (listing funded studies). *See also* Ben Adams, *CRISPR Therapeutics adds $38M to Series B pot, but lags behind Parker*, FIERCEBIOTECH (June 24, 2016. 7:40 AM), https://www.fiercebiotech.com/biotech/crispr-therapeutics-adds-38m-to-series-b-pot-but-lags-behind-parker [https://perma.cc/R278-SKGJ]; *NIH Commits $190M to Somatic Gene-Editing Tools/Tech*

can exercise control over scientific for-profit enterprises. Through its regulation of clinical trials, it can refuse permission for any research, regardless of the funding source, provided that the results of the research are to be used in humans.[212]

The government is thus generally capable of regulating the bulk of scientific research. Despite this capability, there is room for improvement. First and foremost, one might validly question whether the current domestic regulatory model, exercise of power through the administrative state, is proper. Such a model reaches only those seeking federal funding and clinical trial approval — and is thus not the equivalent of binding all who hope to engage in research via statutory law. Further, as research into clinical genetic editing progresses, testing on increasingly advanced organisms — including, in all likelihood, on human volunteers for the purpose of modifying the human germline — will become necessary.[213] While the FDA currently acts as the regulatory body overseeing such trials, the complex societal and ethical issues at play may demand a change. Future legislative efforts might consider whether the FDA is the appropriate entity for this task, or alternatively, if vesting that power in elected officials, or even the community-at-large might be more apt.

Moreover, some advocate for limiting the scope of permissible research to only the genetic editing of monogenic diseases — diseases caused by a mutation in a single gene.[214] If the mutated gene could be successfully edited, or modified, so as not to include the mutation, the monogenic disease would no longer be present. Proponents of this limitation advocate research on only monogenic diseases, to the exclusion of all other potential utilities of CRISPR. While a more developed version of CRISPR could *theoretically* eradicate monogenic diseases,[215] this notion of limiting research to eliminating monogenic diseases is itself flawed and would have the effect of more rigorously regulating such scientific research — which would be a grave mistake.

Research, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Jan. 24, 2018), https://www.genengnews.com/topics/translational-medicine/nih-commits-190m-to-somatic-gene-editing-tools-tech-research/ [https://perma.cc/HFD3-WLXJ].

[212] *IRB Review of Studies Utilizing Drugs, Biologics and Devices,* PITT. INSTITUTIONAL REV. BD., https://www.irb.pitt.edu/content/chapter-16-considerations-fda-regulated-research [https://perma.cc/4VC9-ZSEN] (last visited Jan. 25, 2019).

[213] *See What are the Phases of Clinical Trials?*, AM. CANCER SOC'Y, https://www.cancer.org/treatment/treatments-and-side-effects/clinical-trials/what-you-need-to-know/phases-of-clinical-trials.html (last updated Feb. 7, 2017) [https://perma.cc/CL8M-9V5W].

[214] Sickle cell disease and cystic fibrosis are both examples of monogenic diseases. *See Frequently Asked Questions About Genetic Disorders*, NAT'L HUMAN GENOME RES. INST. (Nov. 10, 2015), https://www.genome.gov/19016930/faq-about-genetic-disorders/ [https://perma.cc/5RDA-MH6P].

[215] Chengzu Long et al., *Genome Editing of Monogenic Neuromuscular Diseases: A Systematic Review*, 73 J. AM. MEDICAL ASS'N: NEUROLOGY 1349, 1349 (2016) ("To date, more than 780 monogenic neuromuscular diseases, linked to 417 different genes, have been identified in humans. Genome-editing methods, especially the CRISPR–Cas9 system, hold clinical potential for curing many monogenic disorders").

Scientific discovery should not be constrained to a simple paradigm where a pre-formed hypothesis perfectly solves an identified problem. There are many instances, for example, where we owe the identification of useful, novel therapies — including CRISPR — to chance.[216] Just a decade ago, the idea that a genetic immune response system of algae would be the topic of intense debate concerning human ethics would have been unthinkable. Therefore, scientific research should be allowed to proceed with as much freedom as is safely and pragmatically possible, and should not be limited by performance-based outcomes relating to specific diseases.[217]

Finally, the U.S. has an opportunity to regulate germline modification technology through laws surrounding commercial enterprise and intellectual property. Depending on the future efficacy of these techniques, we must address questions of equity and large-scale access to ensure that more than just privileged portions of the population have access to their benefits. For example, intellectual property rights might enable licensees or patent holding entities to charge premium rates for the use of germline modification techniques. If such a system is allowed to progress without thoughtful modifications, the possibility exists that a health-based caste system might emerge, or that existing inequality might become more acute.[218] The government then, arguably, has an obligation to ensure equal access to this promising technology when it becomes commercially available for human use.

The following five recommendations emerge from the foregoing considerations:

1. Convene focus groups from various disciplines to produce lists of concerns and proposals that might not be evident to those working strictly in the scientific and medical communities. This might include, for example, religious, ethical, environmental, legal, regulatory, governmental, or financial groups. A cohesive perspective, including that of the scientists,[219] is necessary to address the

[216] *See supra* Part I.

[217] Contrary to my suggested pragmatism, some authors suggest conditioning further germline modification research on its inclusion of a "reversal mechanism." Though errors are always possible, expending taxpayer money to figure out how to "reverse" a gene edit when the editing process itself is not yet in reliable use seems counterproductive. *See, e.g.*, Evitt, Mascharak, & Altman, *supra* note 128, at 26 ("Until we develop the technology to remove deleterious edits, we should not accelerate the pace at which edits can spread. It follows that the use of gene drives in conjunction with germline CRISPR should be prohibited in any project that lacks a validated reversal strategy.").

[218] *See, e.g.*, David King, *Editing the Human Genome Brings Us One Step Closer to Consumer Eugenics*, GUARDIAN (Aug. 4, 2017, 7:02 EDT) https://www.theguardian.com/commentisfree/2017/aug/04/editing-human-genome-consumer-eugenics-designer-babies [https://perma.cc/ERY5-WENZ?type=image].

[219] *See infra* Part V, recommendation 4.

complexity of the issues surrounding germline modification technologies.

2. Continue to tightly regulate domestic research into germline modification in humans[220] until the various concerns that the aforementioned focus groups identify have been either (1) cohesively integrated into a national strategy; or (2) addressed satisfactorily through other means.
3. Organize and participate in international meetings with the purpose of creating a cohesive and inclusive agreement that individual countries can modify without compromising the agreement's central, bargained-for tenets. Specifically, the international guidelines should focus on societal, environmental, ethical, and trade implications of this research.
4. Finally, listen to the scientists. Experts in this field are best able to assess the potential of this technology, as well as its limitations. Continue to allow research in the field that falls within acceptable boundaries. Do not let the desire for regulation overwhelm the pursuit of scientific discovery. This balance must be considered through any regulatory process, or else society will risk losing access to what could be major advances in human health.

CONCLUSION

Germline editing technologies, such as CRISPR-Cas9, offer enormous promise. However, their ultimate capabilities for human applications remain unknown as yet, and will only unfold over time through scientific inquiry. The U.S. should take immediate action to understand the capabilities of this technology, as well as the many impacts that may result from its use. Regulation, or legal intervention, should follow a thorough inquiry into both scientific and societal concerns. Finally, any regulation — be it existing or future — should be careful not to impede scientific research that could, if successful, have a profound and lasting positive impact on society as a whole.

[220] Not to be confused with research on excised or artificially created human tissue, which is subject to different oversight.