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Genome Editing and the Jurisprudence of Scientific Empiricism

Paul Enriquez

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Genome Editing and the Jurisprudence of Scientific Empiricism

Paul Enríquez*

ABSTRACT

Humankind has reached, in tow by the hand of a scientific breakthrough called CRISPR, the Rubicon of precise genetic manipulation first envisioned over fifty years ago. Despite CRISPR's renown in science and its power to transform the world, it remains virtually unaddressed in legal scholarship. In the absence of on-point law, the scientific community has attempted to reach some consensus to preempt antagonistic regulation and prescribe subjective standards of use under the guise of a priori scientific empiricism. Significant and complex legal issues concerning this technology are emerging, and the void in legal scholarship is no longer tolerable.

This Article shrinks the scholarly gap, and it is the first to introduce CRISPR to legal literature. By providing a resource for jurists, scholars, and practitioners, it challenges conventional notions concerning the false dichotomy frequently associated with mutually exclusive normative roles for science and law. The Article makes two independent contributions. First, it lays a robust and comprehensive epistemic foundation of genome editing suitable for legal audiences. This element is descriptive, but essential because a detailed and coherent understanding of the nuts and bolts of the science is requisite for a discussion of law and policy. Second, it advocates for a jurisprudence of scientific empiricism, namely, a normative legal framework that consolidates empiricism and technological—e.g., genome editing—applications into a uniform doctrinal structure unencumbered by common substantive impediments to constructive debate. These impediments consist of impractical and often

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sensationalist claims about issues raised by technological advances and are collectively characterized as “deceptive simplicity.” The proposed paradigm, which lays a blueprint for the legal community to combat the deleterious effects of scientific illiteracy, flows from the Supreme Court’s recent decision in Association for Molecular Pathology v. Myriad Genetics and is broadly adaptable to addressing questions of science in law.

Applying this framework, the Article reconsiders Buck v. Bell and argues that, contrary to long-held views, Buck is not a direct product of false science, but of unbridled deceptive simplicity. Lastly, the Article sets the stage for a series of forthcoming works that will analyze genome editing from regulatory, constitutional, international, egalitarian, ethical, and policy standpoints, which highlight pivotal synergistic roles for law, science, and public policy in the development of this remarkable nascent biotechnology.

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I. INTRODUCTION

The most significant technological breakthrough of this generation, namely, a genome editing tool called "CRISPR," has inconspicuously arrived. Only on rare occasions does a technology with such far-reaching implications lightly knock to announce its arrival while holding the power to forever change the world and humankind.

The world has heard that sporadic light knock before. Nearly eight decades ago, scientific inquiry conceptualized nuclear fission1 as a theoretical explanation for the recondite empirical evidence that $^{239}\text{U}$, an isotope of uranium produced by the neutronic irradiation of $^{238}\text{U}$, could have its nucleus split into highly radioactive fragments.2 That theory was ultimately supported by experimental observations showing the enormous release of ionization energy resulting from nuclear fragmentation,3 thereby confirming a decades-old relationship between mass and energy—$E = mc^2$—first formulated by Albert Einstein.4 With remarkable speed, the newfangled knowledge covertly

served as the basis for the Manhattan Project, the research program that ultimately developed the atomic bomb through nuclear fission.\(^5\)

The scientific breakthrough *modus operandi* is, to a certain extent, wholly universal. The genesis of modern computing had its principles neatly packaged in a seminal paper authored by the mathematician Alan Turing.\(^6\) The revolutionary notion that a machine could imitate computations performed by humans spawned the first "Turing-complete," programmable, general-purpose, Electronic Numerical Integrator and Computer (ENIAC).\(^7\) Unpredictably, the technology evolved into personal computers and smartphones, and enabled the ensuing development of the Internet.\(^8\)

Other fundamental discoveries over the past few centuries—in mathematics, physics, chemistry, and biology—have facilitated our ability to harness the power of natural phenomena in space travel, wireless communications, medicine, and a myriad other applications.

The technological breakthrough of this generation, unlike many of its predecessors, holds the power to alter humankind from

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5. For a historical account of the origins and development of the US atomic bomb program of World War II, see generally F.G. Gosling, THE MANHATTAN PROJECT: MAKING THE ATOMIC BOMB (U.S. Dep't of Energy ed. 1999).


Thus, the debate focuses on whether ENIAC's programmable and Turing-complete features qualify it as the precursor to modern computers. Ultimately, some dismiss the importance of whether the ABC, ENIAC, or other machines of the time constituted the "first" computer. Id. Others argue that the invention of the modern computer has ambiguous origins and involves contributions from scientists in at least three different countries. See Raúl Rojas, *Who Invented the Computer? The Debate from the Viewpoint of Computer Architecture*, in MATHEMATICS OF COMPUTATION 1943-1993: A HALF-CENTURY OF COMPUTATIONAL MATHEMATICS, 48 PROC. SYMPOSIA APPLIED MATHEMATICS 361, 364–65 (Walter Gautschi ed., 1993).

within. A quantum leap in genome editing\(^9\) capabilities has led us to the Rubicon of precise, endogenous, genetic manipulation—one originally envisioned decades ago, yet methodologically beyond reach for prior generations of scientists. The protagonist of this genome editing revolution is an atomic, programmable, macromolecular machine comprising a pair of precision scalpels that shear DNA molecules and has been colloquially baptized as “CRISPR,” an acronym for the system of Clustered, Regularly Interspaced, Short Palindromic Repeats (CRISPR) and CRISPR-associated (Cas) proteins.\(^{10}\)

In the last four years, CRISPR systems—and CRISPR-Cas9 in particular—have been adapted in laboratories across the globe at an exponential rate. Astoundingly, more than 2,500 scientific publications\(^{11}\) feature theory, empirical observations, and descriptions of applications for this budding biotechnology. Stratospheric expectations for CRISPR systems have already attracted more than $1 billion in venture capital\(^{12}\) in a brief period of time. One of a few CRISPR-based companies became the first to file the requisite paperwork for an initial public offering with the Securities and

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9. See definition infra Part II; see also infra notes 53–55 and accompanying text.
10. See discussion infra Section III.D.
Exchange Commission (SEC) recently, and rumors abound that other firms will follow suit in the near future.

Despite its renown in select scientific niches, CRISPR continues to be an arcane secret in the legal realm. Whereas scientific scholarship has produced thousands of publications on CRISPR, legal scholarship concerning this transformative biotechnology is virtually nonexistent. The gap is striking, notably on account of an ongoing, high-stakes, intellectual property battle over patent rights to CRISPR systems with multi-billion-dollar ramifications.

The neglect of CRISPR in legal scholarship poses grave uncertainty regarding how the law will treat this emerging technology going forward. Legal scholars have either largely ignored this field or kept a distance from it, presumably due, in part, to the challenges that complex scientific principles often pose to non-scientists in the legal


14. See, e.g., Chen, supra note 12. Between the time this Article was accepted for publication and its printing, other companies have filed for initial public offerings with the SEC. For instance, CRISPR Therapeutics AG filed for an initial public offering with the SEC on September 9, 2016. CRISPR Therapeutics AG, Form S-1 Registration Statement Under the Securities Act of 1933, U.S. SEC. & EXCHANGE COMMISSION (Sept. 9, 2016), http://www.nasdaq.com/markets/ipo/filing.ashx?filingid=11077159 [https://perma.cc/KM9L-9YEH].

15. CRISPR earned the 2015 “Breakthrough of the Year” accolade awarded by the prominent Science journal. Marcia McNutt, Breakthrough to Genome Editing, 350 SCIENCE 1445, 1456 (2015).

16. See supra note 11 and accompanying text.

17. An unfiltered search on the Westlaw database using the “CRISPR” acronym at the time this Article was completed in late 2015 returned zero hits for all primary—statutory and case law—sources, and only one hit for all legal scholarship journals. Westlaw Search for CRISPR, WESTLAW (search for all documents containing “CRISPR”) (last visited Feb. 1, 2016). The sole mention of CRISPR in all of legal scholarship was relegated to one sentence without explanation of what CRISPR is or even what it means. See Girard Kelly, Note, Choosing the Genetics of Our Children: Options for Framing Public Policy, 30 SANTA CLARA HIGH TECH. L.J. 303, 312 (2014).

18. A patent interference proceeding is underway, which challenges priority and validity of the first CRISPR patent. See Engineering and Optimization of Systems, Methods and Compositions for Sequence Manipulation with Functional Domains, U.S. Patent No. 8,993,233 (filed Dec. 12, 2013) (issued Mar. 31, 2015). In early 2016, the U.S. Patent and Trademark Office agreed to allow the interference proceedings to determine whether the Broad Institute of MIT and Harvard—on one side—or the University of California, Berkeley, the University of Vienna, and Emmanuelle Charpentier—on the opposite side—were first to invent CRISPR under US Patent Law. See Heidi Ledford, Bitter Fight over CRISPR Patent Heats up, 529 NATURE 265, 265 (2016), http://www.nature.com/polopoly_fs/1.179611/menu/main/topColumns/topLeftColumn/pdf/nature.2016.17961.pdf [https://perma.cc/6MGY-TLNA].
and legislative arenas. A recent concurring opinion by the late Justice Antonin Scalia famously illustrated the degree of scientific antipathy among some members of the legal community. Exercising great candor, Scalia conceded his lack of knowledge of relevant scientific details in a case before him. At the same time, he disturbingly remarked he did not even believe in scientific facts that have been well established for decades.

19. Consider, for example, the questions and commentary by Justices of the Supreme Court during oral argument in a recent case involving complex concepts in genetics and molecular biology. See generally Transcript of Oral Argument, Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013) (No. 12-398), http://www.supremecourt.gov/oral_arguments/argument_transcripts/12-398-amc7.pdf [https://perma.cc/8STG-PXJF].

"I thought that maybe the cDNA was kind of an economy class gene, was—it wasn’t.... That may be incorrect for the record, but that was my present understanding." Id. at 20:6 (Kennedy, J.).

I just didn’t understand, because I thought the... chromosome has the BRCA gene in the middle of it and it’s attached to two ends. But also in the body, perhaps because cells die, there is isolated DNA.... I probably misread it.

There’s a better chance that I’ve misread it. Id. at 38:2 (Breyer, J.) (BRCA appears without emphasis in the original transcript, though proper scientific nomenclature requires the gene to be italicized).

My understanding is that here,... what’s involved, is snipping. You’ve got the thing there and you snip—snip off the top and you snip off the bottom and there you’ve got it.... I still don’t understand what—in what sense it’s different than just snipping along—along the line.

Id. at 41:8, 42:22 (Roberts, C.J.).

To get back to your baseball bat example, which at least I—I can understand better than perhaps some of this biochemistry, I suppose that in... all of that time possibly someplace a branch has fallen off a tree and it’s fallen into the ocean and it’s been manipulated by the waves, and then something’s been washed up on the shore, and what do you know, it’s a baseball bat.

Id. at 48:4 (Alito, J.).

"[I]f I’ve read it correctly, that when you have an R—the messenger RNA does not have the same base pairs. There’s a U or something instead of an A or whatever it is." Id. at 18:5 (Breyer, J.).

20. See Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2120 (2013) (Scalia, J., concurring in part and concurring in the judgment) ("I join the judgment of the Court... except Part I-A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief.").

21. To some extent, Scalia’s admission is commendable from the perspective that a person in a position of great power should not be afraid to admit knowledge gaps. After all, no human holds absolute knowledge in any area. On the other hand, it is worrisome that a powerful person may be called to decide pivotal questions with broad societal implications when that person makes no effort whatsoever to close self-perceived knowledge gaps. Expressing disbelief in science is not sufficient. Those with power to delineate the contours of what constitutes the rule of law ought to educate themselves about matters before them.

22. Myriad, 133 S. Ct. at 2120.

23. See id.
That kind of scientific aversion has corrosive effects. It ultimately hinders the sort of interdisciplinary dialogue and insight required to fully understand and address significant problems in an increasingly interconnected world. In the near future, law- and policy-makers will be confronted with many questions related to CRISPR, and the legal community must proactively take steps to familiarize itself with this new technology. Given the rapid expansion of CRISPR-based applications, the void in legal scholarship concerning the technology is becoming increasingly problematic.

As a testament to this growing problem, Judge David Neuberger, President of the UK Supreme Court, recently published a commentary in Nature calling attention to the scientific community and arguing that scientific primers would be "hugely beneficial" for the legal community. Such primers, he contended, would save money and time, help assess the reliability of expert witnesses, and increase the proportion of cases that are settled without trial. Specifically, he singled out genetic engineering as an area in which a primer would be useful to jurists given that legal controversies in the field are likely to recur.

In the absence of on-point law, some in the scientific community are campaigning, in arguably self-serving ways, for a complete ban of germline genome editing. Notably, this commentary co-authored by Edward Lanphier, President and Chief Executive Officer of Sangamo BioSciences, highlights a meaningful need to elaborate on issues concerning competing financial interests. Sangamo BioSciences currently controls a vast intellectual property portfolio comprising twenty issued U.S. patents encompassing the foundational technology of design, selection, and application of an older generation of genome editing tools consisting of Zinc Finger proteins, nucleases, and transcription factors. See Sangamo BioSciences, Inc., Form 10-K Annual Report Under the Securities Act of 1933, U.S. SEC. & EXCHANGE COMMISSION (Dec. 31, 2014), https://www.sec.gov/Archives/edgar/data/1001233/000156459015000950/sgmo-10k_20141231.htm [[https://perma.cc/N68E-4X64]]. As of February 4, 2015, Sangamo has compiled "133 families of internally generated U.S. patent filings, including 120 U.S. and 437 foreign issued patents." Id. A few things are worth pointing out.

First, CRISPR-based biotechnologies may pose an economic threat to Sangamo's monopoly over genome editing using older Zinc Finger-based technologies. Although Sangamo has recently hopped on the CRISPR wagon, see, e.g., Screening Assays for Therapeutics for Parkinson's Disease, U.S. Patent Application No. 14/647,732 (filed Dec. 2, 2013), it lacks the commanding foundational intellectual property it enjoys in the Zinc Finger field. Second, many of Sangamo's gene editing biotechnologies, some of which are currently in clinical trials, see infra notes 179–
consensus to preempt antagonistic regulation and prescribe subjective standards of use under the misguided auspices of *a priori* scientific empiricism. This must give us pause. Einstein memorably remarked, "T]he man of science is a poor philosopher." Most scientists—by training—are unfamiliar with intricate legal principles, constitutional doctrine, regulatory processes, and policy making; likewise, most lawyers are oblivious to scientific theory, physico-chemical laws, and cellular and macromolecular processes. Given these vastly different realms of knowledge, it is understandable that many scientists and lawyers often pursue insularism by academic discipline. Surely, there is comfort in academic seclusion, but isolation is often dangerous to learning and the pursuit of knowledge. "People do not learn very much when they are surrounded only by the likes of themselves." Interdisciplinary colloquy, therefore, is the most sensible approach to bridge the current chasm between science and law surrounding this momentous biotechnology.

Broadly speaking, this Article seeks to shrink the scholarly gap vis-à-vis genome editing and CRISPR-based technologies in legal literature. It is the first of a series of forthcoming articles that, collectively, propose a normative structural legal framework; namely, they conceptualize a jurisprudence of scientific empiricism that is broadly adaptable to addressing questions of science in law. The scientific empiricism referred to in this Article specifically concerns the natural sciences—e.g., physics, chemistry, biology—and not the.

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81. are based on somatic cell, rather than germ cell, therapeutics. Correcting genomes in the germline is arguably more effective than that in somatic cells, given that germ cells are totipotent and give rise to all cell types. Accordingly, CRISPR-Cas9 germline editing could in theory, if proven safe, obviate resorting to a number of Sangamo’s therapeutic tools, which would dilapidate more than a decade of capital investments in research and development. Third, Lanphier and colleagues’ efforts to distinguish somatic and germline editing along with claims that germline therapeutic benefits are tenuous, and philosophically and ethically unjustifiable, see Lanphier et al., *supra*, at 411, inordinately approach the logical fallacy of a distinction without a difference, particularly given the commentary’s moral-arbiter tone. The authors avoid acknowledging that, as with any incipient biotechnology including Sangamo’s own Zinc Finger Nucleases at one time, safety and ethical concerns are always part of the calculus behind a cost-benefit analysis for clinical applications of a technology in its early developmental stages. For a more detailed discussion of Zinc Finger Nucleases and other older genome editing technologies based on protein-DNA interactions, see discussion *infra* Section III.C.

29. Albert Einstein, *Physics and Reality*, 221 J. FRANKLIN INST. 349, 349 (Jean Piccard trans., 1936). Whether his assessment is correct is, of course, beyond the scope of this Article.


social sciences—e.g., sociology, psychology, economics, political science, etc. This distinction is mainly due to discrete research methodologies and analytical tools endogenous to each discipline.\textsuperscript{32} The paradigm proposed here originates from the Supreme Court’s recent decision in Association for Molecular Pathology \textit{v.} Myriad Genetics, which this Article will refer to as \textit{Myriad}.\textsuperscript{33}

This Article introduces CRISPR and the next generation of genome editing tools to legal scholarship. By providing a resource for jurists, scholars, and practitioners alike, it challenges conventional views regarding the false dichotomy frequently associated with mutually exclusive normative roles for science and law—the proximate cause driving laissez-faire attitudes\textsuperscript{34} of deference to elude questions of “law in science and science in law.”\textsuperscript{35}

\textsuperscript{32.} In particular, this point revolves around the fact that, whereas the natural sciences rely extensively on quantitative methods, the social sciences depend, to a great extent, on qualitative research. The proposed framework in this Article is exclusively concerned with scientific empirical data that is reproducible and quantifiable. Hence, for example, a jurisprudence of scientific empiricism would seek to answer whether genome editing may lawfully be used to correct a genetic mutation associated with a monogenic disease as a consequence of a clinical trial, given the existence of empirical data demonstrating that such genetic corrections are feasible and reproducible (or not) under controlled experiments. The approach, however, would not apply to deciding the legal status by studying the decision making processes and attitudes toward genome editing of the patients undergoing treatment under the clinical trial. The primary empirical data acquired from social scientists in the former scenario would largely depend on interviews and other qualitative research that may be considered ontologically subjective.


\textsuperscript{33.} \textit{Ass’n for Molecular Pathology v. Myriad Genetics, Inc.}, 133 S. Ct. 2107 (2013).

\textsuperscript{34.} \textit{See, e.g., Craig v. Boren}, 429 U.S. 190, 204 (1976) (“There is no reason to belabor this line of analysis. It is unrealistic to expect either members of the judiciary or state officials to be well versed in the rigors of experimental or statistical technique.”); ROBIN FELDMAN, \textit{THE ROLE OF SCIENCE IN LAW 37–48} (2009) (discussing lawyers’ proclivities to defer to scientific expertise).

\textsuperscript{35.} This Article adopts this phrase from the title of an article penned by Oliver W. Holmes, Jr. over a century ago. See Oliver Wendell Holmes, \textit{Law in Science and Science in Law}, 12 HARV. L. REV. 443, 444 (1899). Ironically, the same Holmes authored the infamous \textit{Buck v. Bell} decision upholding the constitutionality of sexual sterilization for the mentally disabled relying on dubious science. \textit{See discussion infra Section V.C.}
Although legal scholars need not become “amateur scientists,”36 this Article insists that law- and policy-makers must become engaged and proactively strive to grasp the core elements of significant technologies like CRISPR, which hold the power to transform the world. The Article’s overarching goals are to (1) ignite a measured and scholarly conversation about the current and prospective uses of select biotechnologies, stripped of illusory conjectures, and (2) provide the legal community with a primer on genome editing to facilitate an interdisciplinary exchange of ideas. There is much the legal community can contribute to this field.

In furtherance of these goals, the Article makes two independent but synergistic contributions. First, it provides a robust and comprehensive epistemic foundation of the history and current state of the scientific literature in the field of genome editing. It is descriptive and technical, but is intended to be suitable for both legal and scientific audiences. This work is precisely the type of primer for which Judge David Neuberger recently advocated.37 Notably, it faithfully tracks and explains primary scientific sources, something generally absent from legal scholarship construing scientific themes. This prologue is essential because, without a detailed explanation and coherent understanding of the nuts and bolts of genome editing, the audience may extrapolate unfounded notions of the immediate, short-term, and long-term prospects and limitations of the technology.38 Simply put, a solid foundation of key genome editing scientific principles offers the structural scaffolding—an insurance policy, so to speak—for a fruitful dialogue grounded in reason rather than baseless conjecture.

The second contribution propounds positive claims for prospective applications of genome editing that are firmly grounded in empirical evidence.39 One substantial predicament about powerful technologies is that they are often prone to manipulation by speculative agents who—knowingly or not—spread misinformation and oversell what is technologically feasible. By anchoring prospective technological applications in a jurisprudence of scientific empiricism, this Article advocates for a normative approach that consolidates genome editing applications into a uniform doctrinal

37. See Neuberger, supra note 25, at 9.
38. See discussion infra Parts IV and V.
39. A revolution is well underway in genome editing science with the potential to fundamentally reshape the way we approach agriculture, synthetic biology, ecosystems, bioterrorism, gene therapy, and biomedicine through law and policy. See discussion infra Part IV.
structure unencumbered by common substantive impediments to constructive debate. These impediments consist of impractical and often sensationalist claims about issues raised by technological advances and are collectively characterized as "deceptive simplicity." This approach aims to cultivate and expand Myriad’s roots of scientific empiricism and is broadly applicable to other fields of law in which scientific inquiry may play important or dispositive roles.

The synergism between these two contributions underscores the importance of interdisciplinary efforts to prevent, mitigate, and resolve future "global problems" raised by technological progress. In essence, a jurisprudence of scientific empiricism is based on the notion that "[c]ritical thinking . . . cannot possibly be restricted to the examination of the concepts of [one's] own specific field."42

This Article is divided into four sections. Part II begins by proposing a genome editing definition,43 a necessity for any applicable regulatory or statutory scheme.44 It introduces the reader to the manipulation of genetic material, explains how this concept of biotechnology is well rooted in popular and scientific history, and describes the discovery of two critical elements that facilitated genome editing.

Part III rummages through the genome editing toolbox and examines the development of modern, cost-effective, powerful, programmable tools that are democratizing researchers’ access to genome editing technologies.

Part IV examines current applications of genome editing in a number of fields ranging from stem cell research and agriculture to

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40. Although this term has not been used in the context proposed in this Article, it has appeared in legal scholarship, at least as early as 1937. See The Availability of a Principal’s Defense to His Uncompensated Surety, 46 YALE L.J. 833, 839 (1937); see also, e.g., Brief for Respondent, Tan v. Phelan, 333 U.S. 6 (1948) (No. 370), 1947 WL 44413, at *12; Georg Schwarzenberger, The Inductive Approach to International Law, 60 HARV. L. REV. 539, 569 (1947); Frederick M. Rowe, Note, Price Discrimination, Competition, and Confusion: Another Look at Robinson-Patman, 60 YALE L.J. 929, 961 n.210 (1951); Note, State Law and Uniformity in Federal Taxation, 55 HARV. L. REV. 255, 255 (1941).


42. Einstein, supra note 29, at 349.

43. See also infra notes 53–55 and accompanying text.

44. The search for meaning in ambiguous statutory text lacking robust definitions has, in recent years, lead to increased use of dictionaries in judicial opinions. See, e.g., James J. Brudney & Lawrence Baum, Oasis or Mirage: The Supreme Court’s Thirst for Dictionaries in the Rehnquist and Roberts Eras, 55 WM. & MARY L. REV. 483 (2013) (pointing out that as many as one-third of statutory decisions in modern Supreme Court jurisprudence consult dictionaries in often highly subjective modes).
biofuels production and human pathophysiology. It meticulously acquaints the reader with prospective genome editing uses in each field, relying exclusively on primary scientific sources. Importantly, the Article deliberately contemplates genome editing from diverse viewpoints and recognizes that every technology endowed with awe-inspiring powers should be handled responsibly and with respect. This Part argues that, taken together, genome editing biotechnologies are not mere tools for basic research, but rather epitomize prolific mines for future significant medical and scientific breakthroughs. The goal is to engage the legal community in discussions about the technology's potential for good and bad, including what should or should not be done to legally promote or hinder it.

Finally, Part V concentrates on deceptive simplicity and implements the normative framework articulated in this preamble to delineate adequate contours for a discussion that avoids the squabbles frequently set forth by manufactured fears; the kerfuffle concerning “designer babies” is one example relevant to genome editing. To that end, it reconsiders *Buck v. Bell* and the indelible scar it left on

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45. Consider the advent of the atomic bomb. Some argue that the technology changed the world for the better as it brought an end to the bloodiest conflict the world has ever witnessed. MICHAEL KORT, THE COLUMBIA GUIDE TO HIROSHIMA AND THE BOMB 8, 46–49 (2007); Winston Churchill, Leader of the Opposition, Where Do We Stand?, (Aug. 16, 1945), in 11 VITAL SPEECHES DAY 738 (1945), http://www.ibiblio.org/pha/policy/1945/1945-08-16c.html (https://perma.cc/7RS7-C76R]. Others decry the bomb as an instrument that led to utter destruction in two cities, nearly a half-million deaths, and political instability for decades after World War II. GOSLING, supra note 5, at 51, 54, (stating that the bombs dropped on Japan eventually killed an estimated 340,000); KORT, supra, at 76–78, 81 (describing political instability); Martin J. Sherwin, The Atomic Bomb and the Origins of the Cold War: U.S. Atomic-Energy Policy and Diplomacy, 1941-45, 78 AM. HIST. REV. 945, 945 (1973). Computers and the Internet have changed—in both positive and negative ways—how humans communicate, access information, shop, and even perceive reality. See generally, e.g., Kaveri Subrahmanyam et al., The Impact of Home Computer Use on Children’s Activities and Development, 10 CHILD. & COMPUTER TECH. 123 (2000). Genome editing is no different in this sense. Although this Article highlights many potential benefits, it by no means argues that the biotechnology should be viewed as a panacea for all world problems.

46. To some extent, the scientific community has begun engaging in this debate. See, e.g., Scientists Debate Ethics of Human Gene Editing at International Summit, GUARDIAN (Dec. 1, 2015), https://www.theguardian.com/science/2015/dec/01/human-gene-editing-international-summit [https://perma.cc/FY62-EJCL]. However, the legal community has not assumed a leadership role to direct a pervasive discussion of legal issues framed by genome editing technologies.

47. See, e.g., Joan Mahoney, Genome Mapping and Designer Babies, 79 UMKC L. REV. 309, 313 (2010) (citing not a single primary scientific source for the proposition that new technology may presumably allow parents to decide eye color and sexual orientation of designed babies); discussion infra Section V.A.

American jurisprudence from a novel perspective—namely, to illustrate the dangers of unchecked deceptive simplicity.

Much has been written about *Buck* in legal scholarship and this Article will not belabor what has already been said about the case. The conventional view is that *Buck*'s holding is illegitimate because it rests on false, or pseudo, science and incorrect moral and ethical principles. This Article rejects that view and applies a jurisprudence of scientific empiricism to instead contend that *Buck* is a direct product, not of false science, but of rampant deceptive simplicity that permeated every aspect of elite circles at the time it was decided. The distinction between false science and deceptive simplicity is crucial. Whereas false, or pseudo, science refers to a system of theories and rules configured to give the appearance of being grounded in scientific methodology, deceptive simplicity strips logic beyond a bare minimum using vague intuition born out of second-hand, reductive explanations that diminish a scientific concept to a deceptively simple catchphrase. To support this proposition, the Article studies *Buck*'s substantively porous decision, which cited not a single scientific source for the Court's lending of credence to the notion that "heredity plays an important part in the transmission of insanity, imbecility, etc."

Lastly, this Part sets the stage for a series of upcoming articles that aim to analyze the prospective benefits and risks associated with the use of genome editing biotechnologies from statutory, regulatory, constitutional, international, ethical, egalitarian, scientific, and policy standpoints. In so doing, it encourages scholarly debate and highlights the pivotal synergistic roles that law, science, and public policy will play on the development of this truly exceptional and transformative emerging biotechnology.

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49. Pseudoscience is defined as “a system of theories, assumptions, and methods erroneously regarded as scientific.” *Pseudoscience*, MERRIAM-WEBSTER ONLINE DICTIONARY, http://www.merriam-webster.com/dictionary/pseudoscience [https://perma.cc/8FKP-4GVS] (last visited Feb. 23, 2017); see also discussion infra Section V.C.


51. See discussion infra notes 558–70 and accompanying text.

52. *Buck*, 274 U.S. at 206.
II. GENOME EDITING—A SYNOPSIS

Genome editing,\(^{53}\) as referred to in this Article, encompasses scientific technological advances that enable rational genetic engineering\(^{54}\)—at a local (gene) or global (genome) level—to facilitate precise insertion, removal, or substitution of fragments of Deoxyribonucleic acid (DNA) molecules, comprising one or more nucleotides—Adenine (A), Thymine (T), Cystosine (C), Guanine (G), and possibly others which may be synthetically derived\(^{55}\)—into the cell(s) of an organism’s genome. This process of manipulation of

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53. Different colloquial permutations of the term ‘genome editing’ exist including, but not limited to, ‘gene editing,’ ‘genetic editing,’ ‘genetic engineering,’ ‘gene engineering,’ ‘gene targeting,’ ‘gene splicing,’ and ‘genome surgery.’ Although the line between these terms is often blurred beyond discernible recognition, this Article proposes that genome engineering may be best interpreted as the rational design of genomes, while genome editing may describe the process of bringing the design to fruition. However, for purposes of this discussion, they are all used interchangeably to denote genome editing as an umbrella term with the definition provided. Notwithstanding, other definitions abound. For instance, Merriam-Webster Dictionary defines genetic engineering as “the group of applied techniques of genetics and biotechnology used to cut up and join together genetic material and especially DNA from one or more species of organism and to introduce the result into an organism in order to change one or more of its characteristics.” Genetic Engineering, MERRIAM-WEBSTER ONLINE DICTIONARY, http://www.merriam-webster.com/dictionary/genetic%20engineering [https://perma.cc/E3VG-KDMU] (last visited Feb. 23, 2017). Genome editing involves the precise modification of the nucleotide sequence of the genome. See, e.g., Matthew H. Porteus, Towards a New Era in Medicine: Therapeutic Genome Editing, 16 GENOME BIOLOGY 1 (2015); accord Ignazio Maggio & Manuel A.F.V. Gonçalves, Genome Editing at the Crossroads of Delivery, Specificity, and Fidelity, 33 TRENDS BIOTECHNOLOGY 280, 280 (2015); Nature Am., Inc., Method of the Year 2011, 9 NATURE METHODS 1, 1 (2012). The propounded definition in this Article is presented as a more robust and inclusive definition than that found in the current scientific literature.

54. The term genetic engineering was coined in the 1940s as the “purposive manipulation of genetic material.” BRIAN STABLEFORD, SCIENCE FACT AND SCIENCE FICTION: AN ENCYCLOPEDIA 207 (Routledge 2006). At the time, the term was meant to describe the molecular surgical cutting and stitching of chromosomes to remove or rearrange sets of genes. Id. Genetic engineering, eugenics, and selective breeding were main themes in Robert A. Heinlein’s novel Beyond This Horizon, which originally appeared as a two-part serial in the spring of 1942. Beyond This Horizon, WIKIPEDIA, https://en.wikipedia.org/wiki/Beyond_This_Horizon [https://perma.cc/N9B8-GCF9] (last updated Dec. 18, 2016). The term was also independently imported into science fiction by Jack Williamson in Dragon’s Island (1951). STABLEFORD, supra, at 207.

55. Synthetic, non-natural nucleotides to expand the natural four-letter (A, C, T, G) genetic alphabet or “code” have been reported in the scientific literature. See, e.g., Millie M. Georgiadis et al., Structural Basis for a Six Nucleotide Genetic Alphabet, 137 J. AM. CHEMICAL SOC’Y 6947 (2015); Denis A. Malyshhev et al., A Semi-Synthetic Organism with an Expanded Genetic Alphabet, 509 NATURE 385 (2014); Itaru Okamoto et al., High Fidelity, Efficiency and Functionalization of Ds-Px Unnatural Base Pairs in PCR Amplification for a Genetic Alphabet Expansion System, 5 ACS SYNTHETIC BIOLOGY 1220 (2016); Joseph A. Piccirilli et al., Enzymatic Incorporation of a New Base Pair into DNA and RNA Extends the Genetic Alphabet, 343 NATURE 33 (1990); Liqin Zhang et al., Evolution of Functional Six-Nucleotide DNA, 137 J. AM. CHEMICAL SOC’Y 6734 (2015).
endogenous nucleotide sequences constitutes the bedrock of modern biotechnology and molecular biology. It can be accomplished through a variety of methods using DNA-cutting nucleases (proteins that act as molecular scalpels), viral-based systems, chemistry-based DNA scission systems, and, most recently, Ribonucleic acid (RNA)-guided DNA nucleases.56

Despite the recent fervor surrounding genome editing in the last three years,57 the concept itself is not new. Following the discovery of genes by Gregor Mendel in 1866,58 DNA in 1869 by Friedrich Miescher,59 and the subsequent work of Nobel Laureate Thomas Morgan, who demonstrated that genes are carried on chromosomes and constitute the molecular basis of heredity,60 the notion of manipulating genetic material took root in the popular culture.61 A peculiar finding concerning reduced efficiency of viral infection in bacterial hosts—i.e., bacterial defensive mechanisms to viral infection—in the 1950s62 led to the hypothesis of the existence of "restriction and modification" systems, which functioned as effective

56. For a detailed discussion of these methods, see infra Sections III.A–D.
61. Numerous works in scientific romance and science fiction began to incorporate themes of biological engineering and genetic manipulation in creative ways during the 1910s, 1920s, and every decade thereafter. For a detailed list of such popular works in the 20th Century, see STABLEFORD, supra note 54, at 207–09.
62. S.E. Luria, Host-Induced Modifications of Viruses, 18 COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY 237, 237 (1953).
barriers to DNA uptake. And in 1970, the first “restriction enzyme” was characterized, thus offering proof-of-concept that a protein can trigger sequence-specific enzymatic cleavage of DNA molecules.

The restriction enzyme quantum leap underscored the requirement of DNA double-stranded breaks (DSBs) as the critical first step in genome editing. However, as time passed, it became apparent that these breaks in DNA were highly deleterious because they promoted genome instability, interfered with the pivotal processes of replication and transcription, led to chromosomal rearrangements—inversions and translocations—associated with cancers and other diseases, and often induced apoptosis (cell death). Due to the hazardous nature of DSBs to DNA stability,

64. Restriction enzymes, also known as restriction endonucleases, are proteins capable of cutting DNA at or near specific nucleotide sequences. See Richard J. Roberts & Kenneth Murray, *Restriction Endonucleases*, 4 CRITICAL REV. BIOCHEMISTRY 123, 123 (1976).
66. Structurally, DNA comprises two single-stranded molecules that come together via hydrogen bonds to form the famous DNA double helix. See James D. Watson & Francis H.C. Crick, *A Structure for Deoxyribose Nucleic Acid*, 171 NATURE 737, 737 (1953). Accordingly, introducing a double-stranded, rather than a single-stranded, break is necessary to complete full scission of DNA.
complex mechanisms associated with deployment of specialized macromolecules that trigger repair of an injured DNA site have evolved within cells.

To date, at least three DSB repair pathways have been characterized:

(1) Nonhomologous End Joining (NHEJ),
(2) Microhomology-Mediated End Joining (MMEJ),
(3) Homology-Directed Repair (HDR).

NHEJ is an error-prone DSB repair mechanism that can efficiently introduce small, random nucleotide mutations—insertions and deletions—capable of disrupting gene expression. MMEJ is also an error-prone pathway, but uses microhomologous sequences—short homology sequences of a few nucleotides flanking the initial DSB site—to anneal and ligate broken DNA ends. MMEJ DSB repair often leads to deletion mutations that play a role in cancers involving chromosomal translocation and telomere fusions. Unlike NHEJ and MMEJ, HDR is significantly more precise, but requires the presence of an undamaged, homologous, donor template for repair. This is the case in Homologous Recombination (HR), the most common form of HDR, where the requirement of longer sequence homology between the donor and acceptor DNA ensures highly accurate rates of DSB.
repair. Together, these mechanisms of DNA repair constitute the second critical element required to facilitate genome editing.

A. The Rise of Recombinant DNA

The discovery of restriction enzymes capable of inducing DNA double-stranded breaks prone for repair marked the genesis of modern molecular medicine and biotechnology and gave rise to the era of recombinant DNA technology. As the list of restriction enzymes grew, the rational manipulation of genes and DNA sequences to study function yielded important research with pharmaceutical applications such as the large-scale production of insulin,80 other hormones,81 and vaccines.82 The fundamental knowledge derived from the research fueled innovation in genetic engineering,83 gave rise to new intellectual property,84 and spawned a multi-billion-dollar biotechnology industry. At the same time, scientific fears of the repercussions of gene editing technologies began to percolate through popular discourse.85

The concept of genome editing is well rooted in history. Scientists have long recognized the value of developing methods to

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82. E.g., Cladd E. Stevens et al., Hepatitis B Vaccine: Immune Responses in Haemodialysis Patients, 316 Lancet 1211 (1980).
induce DNA breaks and modify nucleotide sequences.  

However, recent additions to the technological toolbox of genome editing have overruled long-held views of what is technologically feasible. Remarkable, cost-effective, easy-to-use, programmable tools developed in the last few years finally allow researchers to precisely engineer genomes in ways originally envisioned decades ago, yet methodologically beyond reach to prior generations of scientists.

The next Section surveys the transformative technologies of modern day genome editing that have revolutionized, and are revolutionizing, molecular biotechnology and biomedicine. Together, these biotechnologies offer potential promising applications for agriculture, synthetic biology, gene therapy, and eradication of diseases.

III. THE GENOME EDITING TOOLBOX

Armed with the bipartite insights of restriction enzyme-mediated DSBs and DNA repair, scientists began to explore genome engineering apace. As of this writing, the genome editing toolbox consists of systems that fit four categories: chemistry-based synthetic DNA scission, viral-based editing, nucleases that rely on protein-DNA interactions for targeting, and a revolutionary RNA-guided DNA nuclease system.

A. Chemistry-Based Synthetic DNA Scission

Early methods of chemical-mediated DNA scission involved the use of oligonucleotides—short DNA or RNA molecules—coupled to chemical reagents. These complexes successfully induced site-specific cleavage of DNA and activated DNA repair in yeast and

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86. Stewart Scherer & Ronald W. Davis, Replacement of Chromosome Segments with Altered DNA Sequences Constructed in Vitro, 76 PROC. NAT'L ACAD. SCI. U.S. 4951 (1979); see also supra notes 65, 80–84 and accompanying text.

87. See discussion infra Part III.


mammalian cells without the use of nucleases. Alternative DSB approaches also emerged involving Peptide Nucleic Acids (PNA)\textsuperscript{92} that associate with nucleases\textsuperscript{93} and synthetic polyamides that bind DNA's minor groove.\textsuperscript{94} Reports that the element Cerium\textsuperscript{95} Ce(IV) species is highly stable and capable of cutting DNA via hydrolysis\textsuperscript{96} paved the way for more sophisticated artificial DNA-cutting methods involving complexation of Ce(IV) with the chelating reagent Ethylenediaminetetraacetic acid (EDTA).\textsuperscript{97} In recent years, a research team conceived a novel chemistry-based artificial restriction DNA cutter strategy featuring pseudo-complementary PNA and the metal complex Ce(IV)EDTA for targeting and cleavage.\textsuperscript{98} Although these synthetic scission platforms—with or without the use of nucleases—have not been widely adopted, they demonstrate the value of chemistry-based cutting tools for genome editing.

### B. Viral-Based Editing

A nuclease-free, viral-based system consisting of vectors using adeno-associated viruses\textsuperscript{99} (AAV) has proven able to introduce specific

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\textsuperscript{91}. A. Fawad Faruqi et al., *Recombination Induced by Triple-Helix-Targeted DNA Damage in Mammalian Cells*, 16 MOLECULAR CELL BIOLOGY 6820, 6820 (1996).

\textsuperscript{92}. PNA is an artificial molecule that resembles DNA or RNA, but has a protein-like, rather than a sugar phosphate, backbone. Peter E. Nielsen et al., *Sequence-Selective Recognition of DNA by Strand Displacement with a Thymine-Substituted Polyamide*, 254 SCIENCE 1497, 1498 fig.1 (1991).

\textsuperscript{93}. Vadim Demidov et al., *Sequence Selective Double Strand DNA Cleavage by Peptide Nucleic Acid (PNA) Targeting Using Nuclease S1*, 21 NUCLEIC ACIDS RES. 2103, 2103 (1993).

\textsuperscript{94}. Joel M. Gottesfeld et al., *Regulation of Gene Expression by Small Molecules*, 387 NATURE 202, 202 (1997).

\textsuperscript{95}. Cerium is the fifty-eighth element on the Periodic Table. It is an iron-gray, malleable, lustrous metal that is susceptible to rapid oxidation at room temperature. C.R. HAMMOND, *THE ELEMENTS* 4–7 (n.d.), http://www-d0.fnal.gov/hardware/cal/lvps_info/engineering/elements.pdf [https://perma.cc/986X-Z2LA].

\textsuperscript{96}. Makoto Komiyama et al., *Catalytically Active Species for CeCl\textsubscript{3}-Induced DNA Hydrolysis*, 115 J. BIOCHEMISTRY 809, 809 (1994).

\textsuperscript{97}. Wen Chen & Makoto Komiyama, *Site-Selective DNA Hydrolysis by CeIV–EDTA with the Use of One Oligonucleotide Additive Bearing Two Monophosphates*, 6 CHEMBIOCHEM 1825, 1825 (2005); Jia-Ming Yan et al., (Ethylenediaminetetraacetic Acid)cerium(IV) [CeIV(EDTA)] Complexes with Dual Hydrophobic Binding Sites as Highly Efficient Catalysts for the Hydrolysis of Phosphodiesters, 85 HELVETICA CHIMICA ACTA 1496, 1496 (2002).

\textsuperscript{98}. Makoto Komiyama et al., *Artificial Restriction DNA Cutter for Site-Selective Scission of Double-Stranded DNA with Tunable Scission Site and Specificity*, 3 NATURE PROTOCOLS 655, 655 (2008).

genetic modifications at high frequencies. With this approach, engineered recombinant AAV vectors can replace some or all of the viral genes with packaged foreign DNA sequences of interest for efficient cellular delivery. Subsequent cargo release into the nucleus mediates HR at selected loci, which demonstrates promising therapeutic gene targeting applications. Because they have proven to be safe and effective, commercialization of AAV vectors and testing in clinical trials are underway. Despite a modest commercial performance, likely due to the platform’s labor-intensive manufacturing and costs, preliminary results from clinical testing show significant improvement of patients with an incurable, inherited retinal disease.

C. Nuclease Genome Editing Based on Protein-DNA Interactions

1. Meganucleases

Meganucleases, also known as Homing Endonucleases, are naturally occurring DSB nucleases that target relatively long DNA

100. David W. Russell & Roli K. Hirata, Human Gene Targeting by Viral Vectors, 18 NATURE GENETICS 325, 325 (1998). The term “high frequencies” used by the authors is ambiguous without an explanation. A closer look at the study reveals that high frequencies relate to gene-targeting events in cell populations and stem directly from a comparative analysis of gene-targeting frequencies between AAV-transduction ($10^{-3}$) and other methods ($10^{-5}$ to $10^{-8}$). Id. at 328.


106. The term “homing” refers to a gene conversion process, whereby a mobile sequence is copied and inserted into a new cognate site lacking the sequence. Maria J. Marcaida et al., Homing Endonucleases: From Basics to Therapeutic Applications, 67 Cellular & Molecular Life Sci. 727, 727 (2010).
sequences ranging from twelve to forty base pairs.\textsuperscript{107} Meganucleases have been instrumental in the study of DSB repair.\textsuperscript{108} They were initially identified as potential site-specific DNA nucleases for genome editing from the use of self-splicing\textsuperscript{109} introns\textsuperscript{110} and became the first type of nucleases with demonstrable ability to modify the mammalian genome with precision.\textsuperscript{111} Long recognition sequences intrinsic to meganucleases confer high target specificity, but often render them futile because lengthy target sequences in particular arrangements occur rarely in a whole genome.\textsuperscript{112} The problem, therefore, is that a researcher might have a very specific nuclease at her disposal for a DNA sequence she has no interest in targeting. Complex protein engineering strategies to alter DNA preference of the meganuclease can ameliorate this predicament.\textsuperscript{113} However, due to inherent intricacies of protein engineering, and the fact that meganuclease DNA binding and cleavage functions are interlaced in a single domain,\textsuperscript{114} this platform for genome editing has found it challenging to progress into translational medicine.

\textsuperscript{107} Id.
\textsuperscript{108} Tamas Lukacsovich et al., Repair of a Specific Double-Strand Break Generated Within a Mammalian Chromosome by Yeast Endonuclease I-Sce1, 22 NUCLEIC ACIDS RES. 5649, 5650 (1994).
\textsuperscript{110} An intron is a noncoding piece of RNA transcript, or the DNA encoding it, that is removed before translation into a protein. See Intron, SCITABLE, http://www.nature.com/scitable/definition/intron-introns-67 [https://perma.cc/RZH2-DBNA] (last visited Feb. 25, 2017).
\textsuperscript{111} See, e.g., Philippe Rouet et al., Expression of a Site-Specific Endonuclease Stimulates Homologous Recombination in Mammalian Cells, 91 PROC. NAT'L ACAD. SCI. U.S. 6064 (1994); R. Geoffrey Sargent et al., Repair of Site-Specific Double-Strand Breaks in a Mammalian Chromosome by Homologous and Illegitimate Recombination, 17 MOLECULAR & CELLULAR BIOLOGY 267 (1997); Jian Yang et al., Efficient Integration of an Intron RNA into Double-Stranded DNA by Reverse Splicing, 381 NATURE 332 (1996).
\textsuperscript{112} Marcaida et al., supra note 106, at 727.
\textsuperscript{114} Julianne Smith et al., A Combinatorial Approach to Create Artificial Homing Endonucleases Cleaving Chosen Sequences, 32 NUCLEIC ACIDS RES. e149, 2, 6−7 (2006).
2. Zinc Finger Nucleases

A study of transcription in the African clawed frog first revealed that zinc-binding domains, potentially looped into finger-like arrangements, were required for transcription factor-mediated gene regulation. These modules rely on interactions between Cysteine and Histidine residues with a zinc ion ligand, which together form three-dimensional structures where one zinc finger recognizes three contiguous nucleotides of DNA. Scientists quickly realized that the modular DNA recognition of each zinc finger motif could be exploited by coupling it to the nuclease domain of FokI—a restriction endonuclease known at the time—to engineer artificial fusion proteins called Zinc Finger Nucleases (ZFNs).

Combining a non-specific nuclease like FokI to zinc fingers capable of recognizing specific sequences of DNA provided a solution to the barriers posed by meganucleases. Thus, ZFNs became the first method to demonstrate the practicability of genome editing in human cells and animals in vivo. A decade later, ZFNs entered clinical trials amid high expectations. However, as critical as ZFNs have been to promote the progress of genome editing technologies, their widespread use has been limited by the high technical expertise needed to engineer them—due primarily to context-dependent
specificity—and extensive screening processes to validate them.\textsuperscript{124} Adoption has lagged even despite frequent reporting of strategies designed to simplify and update engineering challenges associated with ZFNs.\textsuperscript{125}

3. TALENs

For a number of years, ZFNs and meganucleases dominated the genome editing landscape despite their technical shortcomings. Then, in 2007, two research teams independently discovered that a particular bacterial strain, pathogenic to certain crop plants, secretes effector (transcription activator-like effector—TALE) proteins capable of specific DNA binding by mimicking transcription factors.\textsuperscript{126} The mechanism and code responsible for DNA recognition was promptly deciphered.\textsuperscript{127} And borrowing from its ZFN predecessor, versions of TALE proteins fused to the FokI nuclease domain led to the creation of TALE nucleases (TALENs).\textsuperscript{128}

TALENs and ZFNs share similar architectural features, most prominently the fusion of the FokI nuclease domain to the DNA recognition domain.\textsuperscript{129} However, TALENs exhibit greater simplicity of design because a single TALE recognizes one nucleotide, in contrast to

\textsuperscript{124} Scot A. Wolfe et al., DNA Recognition by Cys2His2 Zinc Finger Proteins, 29 ANN. REV. BIOPHYSICS & BIOMOLECULAR STRUCTURE 183, 199–201, 203–05 (2000); see also infra note 126 (reporting various ways to address challenges inherently associated with ZFNs.).


\textsuperscript{126} Sabine Kay et al., A Bacterial Effector Acts as a Plant Transcription Factor and Induces a Cell Size Regulator, 318 SCIENCE 648, 650 (2007); Patrick Römer et al., Plant Pathogen Recognition Mediated by Promoter Activation of the Pepper Bs3 Resistance Gene, 318 SCIENCE 645, 646 (2007).


\textsuperscript{128} See, e.g., Michelle Christian et al., Targeting DNA Double-Strand Breaks with TAL Effector Nucleases, 186 GENETICS 757 (2010); Ting Li et al., TAL Nucleases (TALENs): Hybrid Proteins Composed of TAL Effectors and FokI DNA-Cleavage Domain, 39 NUCLEIC ACIDS RES. 359 (2011); Magdy M. Mahfuuz et al., De Novo-Engineered Transcription Activator-Like Effector (TALE) Hybrid Nuclease with Novel DNA Binding Specificity Creates Double-Strand Breaks, 108 PROC. NAT’L ACADEM. SCI. U.S. 2623 (2011); Jeffrey C. Miller et al., A TALE Nuclease Architecture for Efficient Genome Editing, 29 NATURE BIOTECHNOLOGY 143 (2011).

\textsuperscript{129} Id.
zinc fingers, which recognize three nucleotides. Engineering of TALE arrays is therefore less onerous than zinc finger arrays, and TALENs lead to decreased toxicity thanks to higher specificity for cognate DNA targets. Simplicity has contributed to a relatively healthy expansion of TALENs in recent years, surpassing even ZFNs. Indeed, TALENs have successfully been used to modify cells as well as plant and animal genomes. Nonetheless, TALENs are not without limitations. The size and highly repetitive nature of TALEN-coding sequences pose great challenges for delivery using standard viral vectors. Construction of TALENs is also costly and can require up to four times the materials needed for comparable ZFN constructs.

D. Programmable, RNA-guided, DNA Nuclease Genome Editing

The latest and most remarkable additions to the genome editing toolbox are programmable, RNA-guided, DNA nucleases. Of these, the best-known and characterized system is the Clustered, Regularly Interspaced, Short Palindromic Repeat (CRISPR) and CRISPR-associated (Cas) proteins. Unlike the nuclease genome editing methods based on protein-DNA interactions discussed above, RNA-guided, DNA nucleases circumvent the intricate and often cumbersome requirement of protein engineering to target DNA.
sequences. Instead, RNA-guided, DNA nucleases harness nature’s principles of Watson-Crick base-pairing of nucleic acids to mediate DNA recognition.

The origins of CRISPR can be traced back nearly three decades when a team of Japanese researchers published findings of a mysterious repeat cluster of unknown function in the bacterium *Escherichia coli* (*E. coli*). The accumulation of sequenced bacterial genomes in public databases by the turn of the millennium revealed that such particular clusters are pervasive in numerous bacterial and archaeal strains.

Soon after, scientists coined the term CRISPR and identified a group of Cas genes encoding proteins involved in catalyzing biochemical reactions using nucleic acids as substrates. These findings sparked a great deal of interest in the scientific community for CRISPR systems. Then in 2007, two decades after their discovery, key experiments performed at Danisco presented the first empirical evidence that CRISPR was, in fact, an adaptive immunity system used by bacteria and archaea, a mnemonic—so to speak—designed to provide immunological memory against viral infection.

As research into CRISPR systems has accelerated, so too has our knowledge of the mechanistic details of this adaptive immunity phenomenon. To date, five CRISPR types and sixteen subtypes have been classified on the basis of phylogenetic analyses, with more likely awaiting characterization. Among CRISPR systems, CRISPR-Cas9 has emerged as the foremost genome editing platform, partly due to being the first RNA-guided, DNA nuclease discovered. However, other

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139. See discussion supra Section III.C.
140. Watson-Crick base pairing refers to the principle through which DNA bases—Adenine-Thymine and Guanine-Cytosine—pair up with each other via hydrogen bonds to allow DNA to maintain its double-helical structure. See Watson & Crick, supra note 66, at 738.
142. 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 (2000).
143. In standard genetic scientific nomenclature, gene names are generally italicized. In contrast, gene products such as proteins are designated using the same gene name, but in non-italicized font.
144. Jansen et al., supra note 138, at 1568–69. Helicase—unwinding of double-helical nucleic acids—and nuclease activities are two such biochemical reactions.
CRISPR systems,\textsuperscript{147} such as CRISPR-Cpfl,\textsuperscript{148} have very recently been identified and are likely to offer valuable alternatives for DNA targeting.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{X-Ray, three-dimensional structure of the CRISPR-Cas9 endonuclease (gray) from \textit{Streptococcus pyogenes} in complex with a sgRNA (blue) and double-stranded DNA (red) primed for target DNA cleavage. Yellow spheres represent the two active site residues indispensable for enzyme catalysis (Aspartate 10, bottom; Histidine 840, top). The figure appears in color in the online version of this Article.\textsuperscript{150}}
\end{figure}


\textsuperscript{148} Bernd Zetsche et al., \textit{Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System}, 163 \textit{CELL} 759, 760 (2015).

\textsuperscript{149} The model was built using the atomic coordinates deposited in the Protein Data Bank, accession code 5F9R (2016), http://www.rcsb.org/pdb/explore/explore.do?structureId=5F9R [https://perma.cc/F5TB-7T9P].

\textsuperscript{150} The online version can be accessed at the Journal's website, JETLaw.org, by clicking on the "Journal Archives" tab, Volume 19, Issue 3. [https://perma.cc/6BKD-D5DQ].
From a genome editing standpoint, CRISPR-Cas9 has garnered worldwide attention largely because the Cas9 enzyme is part of the CRISPR type II system, which requires only a single protein (Cas9) for RNA-guided, DNA cleavage.\textsuperscript{151} DNA targeting and formation of DSBs by the CRISPR-Cas9 complex require three essential components: (1) a short CRISPR RNA (crRNA) that recognizes the target DNA; (2) a short trans-activating crRNA (tracrRNA) that hybridizes with crRNA and helps recruit the nuclease;\textsuperscript{152} and (3) Cas9, the enzyme that cuts DNA.\textsuperscript{153} When assembled into a complex, this machinery seeks, detects, and cuts the target DNA a few nucleotides away from a protospacer adjacent motif (PAM) site.\textsuperscript{154}

A defining moment for the future of genome editing came in 2012 when an article published in \textit{Science} revealed that Cas9 is an RNA-guided, DNA endonuclease and the two small RNAs it associates with can be fused together into a synthetic, single-guide RNA (sgRNA) that could be engineered to direct Cas9 to any target DNA sequence of interest.\textsuperscript{155} This finding earned two scientists—a biochemist and a microbiologist—$3$ million each and the \textit{Breakthrough Prize}.\textsuperscript{156}

Thus, the landscape of genome editing changed. Scientists are no longer confined to the tedious process of protein design inherent in other nuclease-based tools. Today, any researcher armed with an active Cas9\textsuperscript{157} needs merely to design and order an inexpensive...
sgRNA, wait for it to be delivered to the lab, and—voilà!—edit her favorite genome for less than one hundred dollars. Even more striking, to edit additional sites, the researcher may use the same Cas9 with another made-to-order sgRNA. The inexpensive, accurate, and easy-to-use essence of CRISPR-Cas9 has changed the rules of the genome editing game; to such an extent, it has been hailed as a tool for the democratization of genome editing.

Widespread use of a biotechnology may not occur for years after it is first introduced to the scientific community. However, unlike its predecessor technologies, CRISPR-Cas9 has been adopted by laboratories around the world with unprecedented speed. Within months of the Science publication, reports of genome editing in human cancer cells and pluripotent stem cells surfaced. And soon after, a flurry of publications followed detailing genome editing studies on various organisms including mice, nematodes, fruit flies, zebrafish, frogs, rabbits, pigs, goats, cattle, rice, wheat, tobacco, thale cress, sorghum, and others. In just

158. At a cost of as little as $10. See Wadhwa, supra note 57.
159. Id.
161. See Prashant Mali et al., RNA-Guided Human Genome Engineering via Cas9, 339 SCIENCE 823 (2013).
162. E.g., id.; Martin Jinek et al., RNA-Programmed Genome Editing in Human Cells, 2 ELIFE e00471 (2013)
164. See generally Ari E. Friedland, Heritable Genome Editing in C. elegans via a CRISPR-Cas9 System, 10 NATURE METHODS 741 (2013).
165. See generally Zhongsheng Yu et al., Highly Efficient Genome Modifications Mediated by CRISPR/Cas9 in Drosophila, 195 GENETICS 289 (2013).
166. See generally Li-En Jao et al., Efficient Multiplex Biallelic Zebrafish Genome Editing Using a CRISPR Nuclease System, 110 PROC. NAT’L ACADEMY OF SCI. U.S. 13904 (2013).
168. See generally Dongshan Yang et al., Effective Gene Targeting in Rabbits Using RNA-Guided Cas9 Nucleases, 6 J. MOLECULAR CELL BIOLOGY 97 (2014).
170. Id.
171. Id.
173. See generally id.; Qiwei Shan et al., Targeted Genome Modification of Crop Plants Using a CRISPR-Cas System, 31 NATURE BIOTECHNOLOGY 686 (2013).
174. See generally Jiang et al., supra note 172.
over three years, more than 2,500 papers\(^1\) referring to this nascent biotechnology have been published. CRISPR systems have had a major impact on genome editing and will likely soon be applied for translational applications in agriculture, synthetic biology, biomedicine, and human therapeutics.

This Article next presents a comprehensive survey of the current applications of genome editing technologies in general, but with particular emphasis on CRISPR-derived advances. It further propounds positive claims for prospective applications of genome editing that are firmly grounded in empirical evidence.

IV. CURRENT AND PROSPECTIVE APPLICATIONS OF GENOME EDITING

A. Editing to Target Somatic Cells and Stem Cells

Genome editing technologies have already shown great promise in the treatment of human diseases. Editing of somatic cells\(^2\)—that is, differentiated cells, not including germline or undifferentiated stem cells—for example, is revolutionizing therapeutic approaches to HIV and AIDS.

A rationale for genome editing-based HIV treatment first appeared after an article in *Cell* reported that some individuals' resistance to HIV-1, the most commonly transmitted strain of HIV, had a genetic basis.\(^3\) To enter its host cells, the HIV virus requires a CD4 receptor and a chemokine coreceptor, predominantly the cell-surface protein called C-C Chemokine Receptor Type 5 (CCR5).\(^4\) Approximately 1% of Caucasians carry a 32-nucleotide deletion in the *CCR5* gene that renders the coreceptor unable to detect the HIV virus.\(^5\) The effect of this mutation is that individuals who are

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\(^1\) Id.

\(^2\) Id.

\(^3\) A search on the PubMed scientific database using the “CRISPR” acronym filtered by title and abstract returned 2,565 hits. PubMed.gov Search Results for CRISPR, PUBMED.GOV, http://www.ncbi.nlm.nih.gov/pubmed/?term=CRISPR[Title/Abstract] [https://perma.cc/7PC2-BNN8] (last visited Feb. 10, 2016) (search for CRISPR filtered by title and abstract by using the language “CRISPR[Title/Abstract]”). Note that the search does not include papers that refer to CRISPR in the body of the paper, which may return more hits.


\(^7\) Id.
homozygous—those who inherit the deletion from both parents—are virtually immune to HIV.\textsuperscript{182}

The potential for interrogating CCR5 was later clinically validated when Timothy Brown,\textsuperscript{183} an HIV-infected patient, received a bone marrow transplant from a donor who had the CCR5 deletion.\textsuperscript{184} The procedure led to restoration of normal CD4\textsuperscript{+} T-cell counts and undetectable levels of HIV in Brown's body, even two years post-transplantation.\textsuperscript{185} This remarkable study, and its long-lasting effects, confirmed that conversion of a patient's genome—although not through genome editing—could potentially lead to a cure for HIV and AIDS.

Inspired by the critical role of CCR5 in HIV infection, scientists at Sangamo, the California-based biopharmaceutical company, in collaboration with academic researchers, tested whether genome editing could be used to trim out a piece of the CCR5 gene in human T-cells and a mouse model of HIV infection.\textsuperscript{186} Using ZFNs, they demonstrated the feasibility of this approach as a strategy to confer robust protection against HIV.\textsuperscript{187}

A recent phase I clinical trial featuring this principle sought to remove CD4\textsuperscript{+} T-cells from HIV patients, edit them with ZFNs targeting the CCR5 locus, and transplant the edited cells back into the patients.\textsuperscript{188} Remarkably, results show that infusion of autologously modified CD4\textsuperscript{+} T-cells in which the CCR5 receptor had been rendered dysfunctional by ZFN targeting is safe,\textsuperscript{189} thereby paving the path for a phase II trial\textsuperscript{190} and potential cure in the near future. Furthermore, scientists have now used the CRISPR platform not only to target T-cells, but also to successfully disrupt expression of latently integrated

\begin{thebibliography}{100}
\bibitem{182} Id.
\bibitem{184} Hütter et al., supra note 180, at 692.
\bibitem{185} Id.
\bibitem{186} Elena E. Perez et al., \textit{Establishment of HIV-1 Resistance in CD4\textsuperscript{+} T Cells by Genome Editing Using Zinc-Finger Nucleases}, 26 NATURE BIOTECHNOLOGY 808, 808 (2008).
\bibitem{187} Id.
\bibitem{189} Pablo Tebas et al., \textit{Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV}, 370 NEW ENG. J. MED. 901, 908 (2014).
\end{thebibliography}
HIV-1 provirus and excise it from the host genome altogether in T-cells,\(^ {191}\) microglial cells,\(^ {192}\) promonocytic cells,\(^ {193}\) and human-induced pluripotent stem cells.\(^ {194}\) These studies are a vivid testament to the power of genome editing technologies to provide long-term, adaptive immunity against viral infections by introducing a disease-resistant allele—in the case of \(CCR5\)—or to completely deracinate a virus from its host genome. The implications of this research go far beyond HIV and could apply to other acquired diseases.

Progress has not been confined to one disease. Genome editing has successfully corrected a mutation associated with hereditary tyrosinemia type I (HTI), a fatal genetic disorder, in the liver cells of a mouse model of the disease.\(^ {195}\) Cystic Fibrosis (CF), a debilitating disease in which viscous mucus accumulates in the pulmonary and gastrointestinal tracts of patients—leading to a life expectancy of approximately forty years\(^ {196}\)—appears to be vulnerable to genome editing as well. CRISPR-Cas9 editing of the Cystic Fibrosis Transmembrane Conductor Receptor (CFTR or CFTR) protein in cultured intestinal stem cells isolated from CF patients corrected a one-amino-acid deletion mutation associated with the most common form of the disease.\(^ {197}\)

Furthermore, a mutation in the Leucine-Rich Repeat Kinase 2 (\(LRRK2\)) gene associated with a hereditary form of Parkinson’s Disease was rectified in induced pluripotent stem cells derived from patients afflicted with the disease, resulting in functional phenotypic rescue of differentiated neurons.\(^ {198}\) Correction of an \(IL2RG\)\(^ {199}\) gene mutation in hematopoietic stem cells (HSCs) derived from patients suffering from X-linked Severe Combined Immunodeficiency

\(^{191}\) E.g., Hirotaka Ebina et al., Harnessing the CRISPR/Cas9 System to Disrupt Latent HIV-1 Provirus, 3 SCI. REP. 2510 (2013).

\(^{192}\) E.g., Wenhui Hu et al., RNA-Directed Gene Editing Specifically Eradicates Latent and Prevents New HIV-1 Infection, 111 PROC. NAT’L ACAD. SCI. U.S. 11461, 11462 (2014).

\(^{193}\) Id.

\(^{194}\) E.g., Hsin-Kai Liao et al., Use of the CRISPR/Cas9 System as an Intracellular Defense Against HIV-1 Infection in Human Cells, 6 NATURE COMM. 6413 (2015).

\(^{195}\) Hao Yin et al., Genome Editing with Cas9 in Adult Mice Corrects a Disease Mutation and Phenotype, 32 NATURE BIOTECHNOLOGY 551, 551 (2014).

\(^{196}\) Gerald Schwank et al., Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients, 13 CELL STEM CELL 653, 655 (2013).

\(^{197}\) Id. at 653.

\(^{198}\) Peter Reinhardt et al., Genetic Correction of a LRRK2 Mutation in Human iPSCs Links Parkinsonian Neurodegeneration to ERK-Dependent Changes in Gene Expression, 12 CELL STEM CELL 354, 354 (2013).

\(^{199}\) Interleukin 2 Receptor Subunit Gamma, also known as Cytokine Receptor Common Subunit Gamma.
Syndrome (SCID-X1) gave rise to functional lymphoid cells. Editing of HSCs is of particular significance given that they differentiate into all hematopoietic cell types and can be autologously transplanted. Thus, genome editing using HSCs could open treatment avenues for many genetic blood disorders.

Efforts are underway to develop treatments for other types of monogenic diseases. For instance, an allele-specific editing strategy to combat Meesmann’s Epithelial Corneal Dystrophy (MECD) demonstrates that a faulty allele can be ablated without affecting the healthy allele in a heterozygous disease. Promising applications of genome editing could soon change therapeutic approaches in a multitude of hereditary diseases including Huntington’s disease, where a single mutation repeat causes a devastating neurodegenerative disorder; Achondroplasia, where one of two mutations leads to dwarfism; Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig’s disease, in which point mutations trigger death of neurons; Nicolaides-Baraitser syndrome (NBS), where mutations in a chromatin-remodeling gene lead to severe intellectual disability; or Tay-Sachs disease, where deleterious mutations prompt deterioration of nerve cells that render a child dead by age four.

Finally, it bears noting that although monogenic diseases are likely to be the focus of early genome editing therapies, in the long-run, genome editing biotechnologies will likely tackle more complex,

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201. See generally R. Aggarwal et al., Hematopoietic Stem Cells: Transcriptional Regulation, ex Vivo Expansion and Clinical Application, 12 CURRENT MOLECULAR MED. 34 (2012).


203. Mahru C. An et al., Genetic Correction of Huntington’s Disease Phenotypes in Induced Pluripotent Stem Cells, 11 CELL STEM CELL 253, 253 (2012).


208. The probable focus on monogenic diseases is likely due to the perception that targeting a single gene is inherently simpler than targeting multiple genes.
non-monogenic diseases as well—think cancer\textsuperscript{209} and even aging. Indeed, recent evidence in HSCs shows CRISPR-Cas9 can target noncoding regions—sections of chromosomal DNA without genes—of the genome to interrogate the \textit{BCL11A}\textsuperscript{210} erythroid enhancer\textsuperscript{211} involved in regulation of hemoglobin disorders.\textsuperscript{212} This proof-of-concept suggests viable, alternative therapeutic strategies to treat sickle-cell disease and thalassemias. Likewise, genome editing offers an opportunity to tackle other complex pathologies like Alzheimer’s Disease,\textsuperscript{213} HIV,\textsuperscript{214} cardiovascular disease,\textsuperscript{215} and Acute Lymphoblastic Leukemia\textsuperscript{216} by conferring protective mutations as treatment for affected patients or as prophylactic measures for those unaffected. These and other examples demonstrate both the feasibility and inevitability of applying genome editing technologies to rid society of congenital disorders—whether recessive or dominantly inherited—and acquired diseases.

\begin{itemize}
\item \textsuperscript{209} See, e.g., B. Berdien et al., \textit{TALEN-Mediated Editing of Endogenous T-Cell Receptors Facilitates Efficient Reprogramming of T Lymphocytes by Lentiviral Gene Transfer}, 21 \textit{GENE THERAPY} 539 (2014); Elena Provasi et al., \textit{Editing T Cell Specificity Towards Leukemia by Zinc Finger Nucleases and Lentiviral Gene Transfer}, 18 \textit{NATURE MED.} 807 (2012).
\item \textsuperscript{212} \textit{Id.} at 196.
\item \textsuperscript{213} Thorlakur Jonsson et al., \textit{A Mutation in APP Protects Against Alzheimer’s Disease and Age-Related Cognitive Decline}, 488 \textit{NATURE} 96, 96 (2012).
\item \textsuperscript{214} See discussion supra notes 179–94 and accompanying text.
\item \textsuperscript{215} Jonathan Cohen et al., \textit{Low LDL Cholesterol in Individuals of African Descent Resulting from Frequent Nonsense Mutations in PCSK9}, 37 \textit{NATURE GENETICS} 161, 162 (2005) (identifying two \textit{PCSK9} mutations having a protective effect against hypercholesterolemia); The TG and HDL Working Group of the Exome Sequencing Project, \textit{National Heart, Lung, and Blood Institute, Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease}, 371 \textit{NEW ENG. J. MED.} 22, 23 (2014) (identifying rare \textit{APOC3} mutations associated with a lower risk of heart disease).
\item \textsuperscript{216} Shannon L. Maude et al., \textit{Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia}, 371 \textit{NEW ENG. J. MED.} 1507, 1512 (2014).
\end{itemize}
B. Gene Drives

In what might seem like a concept straight out of a sci-fi script, reshaping entire populations of wild organisms with relatively short lifespans is now within technological reach thanks to a method coupling genome editing technology with old-fashioned sexual reproduction. This method, called a gene drive, encompasses the alteration of traits in wild populations via self-propagating, synthetic, genetic constructs that can artificially disseminate—a gene modification through an organism’s progeny with unprecedented speed.

The notion of gene drives dates back to the late 1960s, when a theoretical comment published in *Nature* proposed the hypothetical utility of chromosomal translocations as a way to control insect pest populations. At the time, that possibility was merely hypothetical because the technology to test the hypothesis—namely, the tools and knowledge required for triggering translocations via enzyme manipulation—simply did not exist. However, by the turn of the century, interest in gene drives resurfaced following insights that meganucleases could be used as drivers. The premise of targeting the fertility genes of vermin species provided a roadmap to carry out population-wide genetic engineering. And by 2011, the first validation of a meganuclease-based gene drive—aimed at controlling the human malaria vector—established proof-of-principle for the genetic manipulation of an entire population starting from only a few laboratory individuals.

It was not long before others realized that the same concept could be used to engineer drives by integrating genes encoding the more efficient Cas9 enzyme alongside specific sgRNAs. Less than two years ago, US scientists used the CRISPR-Cas9 system to develop the Mutagenic Chain Reaction (MCR). In contrast to classic laws of
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In the last few months, researchers have used CRISPR-Cas9-based gene drives to introduce genes that confer resistance to the malaria parasite, *Plasmodium falciparum*, into a South Asian mosquito species. An alternate approach to suppress a different species of mosquito vector for human malaria succeeded by targeting female mosquitoes that overwhelmingly—and helplessly—relinquished fertility by gene drive. The former strategy seeks to spare mosquitoes by making them malaria-resistant and incapable of spreading the disease, whereas the latter aims to drastically reduce—or even wipe out—mosquito populations from an ecosystem. Ultimately, both share the goal of suppressing a disease that places half the total world population at risk, particularly in low-income countries.

Yeast, fruit flies, and mosquito species—including the potent vector for the chikungunya, yellow fever, and dengue

225. Id. at 443.
226. Id.
229. The World Health Organization estimates that as of 2013, ninety-seven countries had ongoing malaria transmission and approximately 3.4 billion people were at risk of contracting malaria, 1.2 billion of whom were at a high risk. *Factsheet on the World Malaria Report 2013*, World Health Org. (Dec. 2013), http://www.who.int/malaria/media/world_malaria_report_2013/en/ [https://perma.cc/Z2XH-JLPN].
230. See DiCarlo et al., supra note 217, at 1250 (reporting gene drive systems in wild and laboratory strains of the yeast *Saccharomyces cerevisiae*).
231. See Gantz et al., supra note 227, at E6737 (testing a gene drive in *Drosophila melanogaster*).
viruses—have thus far been the subjects of CRISPR-mediated gene drive, or related, research. Though the technology remains enclosed within laboratory walls for now, some researchers have begun to study and model how releasing mosquitoes in the wild would spread certain engineered traits. Others have used mathematical and quantitative modeling to estimate the rate of fixation of a mutant allele and caution the release of gene drives in the wild.

Already, Oxitec, a British firm, has developed transgenic *Aedes aegypti* mosquitoes—through older technologies—and released them in field trials in Brazil, Malaysia, the Cayman Islands, and Panama with results showing up to a 90% reduction of insect populations. Trial successes led to Brazilian approval of the first genetically modified insect for commercial use. However, in the United States, Oxitec has faced intense criticism for releasing genetically modified moths in small outdoor trials in New York, and Florida rejected a proposal to permit Oxitec to release mosquitoes in the wild without federal approval.

Diametric public views concerning the apt use of genetically modified insects highlight the pivotal role that public opinion will play in the development of gene drive biotechnologies. Consider the recent threat to global human health posed by the Zika virus in the past year. Zika outbreaks have already been reported in more than fifty

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234. See Hammond et al., supra note 228, at 80 (demonstrating that alleles inserted at female-fertility loci can spread rapidly in mixed caged populations—of 600 mosquitoes per cage—with high gene drive activity).
countries. The World Health Organization declared a public health emergency of international concern as more than 4,000 microcephaly cases and neurological disorders have been documented in areas affected by the Zika virus. The first case of Zika-related microcephaly in a new born baby in the United States surfaced in January 2016, which prompted the Centers for Disease Control and Prevention to issue warnings for pregnant women to avoid traveling to countries with Zika outbreaks.

Fears were further augmented when studies revealed that, although mosquito bites are the main source of transmission, the virus can be spread through sexual intercourse and blood transfusions.

Throughout 2015 and 2016, Zika brought panic to many areas of the world. Babies born with microcephaly and intracranial calcification became a fixture in the news. Public support for the release of genetically modified insects as a method of population control in areas affected by Zika may be low at this point in time, particularly in the United States. However, the prospect of an epidemic at home coupled with laggard progress in research toward development of a vaccine could awaken the public’s appetite for drastic measures to prevent the spread of the virus. Groups that vehemently oppose genetic engineering under any circumstances might soon find themselves fighting a losing battle in the court of


246. See, e.g., Axford, supra note 239; Sarich, supra note 238.
public opinion. Such an outlook is not hypothetical; other countries confronting mosquito-related health crises have weighed the social and economic costs and benefits of releasing bioengineered insects into the environment and opted to avail themselves of biotechnology to allay the spread of disease.247

It is only a matter of time—and a brief one, at that—before the technological knack required for large-scale testing of a CRISPR gene drive is refined. Indeed, field trials could likely be ready to launch anytime now if a general consensus to support them formed and gave the green light to proceed.248

The stark imminence of these developments has prompted a debate about biosecurity and the benefits and harms of using gene drives for biological control of certain species, including how to safeguard gene drive testing in laboratory settings.249 In fact, scientists wary of the potential consequences of unintended release of species carrying gene drives into the environment have already designed and tested split-drives—to separate the pieces of a gene drive—and reversal-drives—to overwrite changes of the original gene drive—as molecular confinement insurance strategies to guard against inadvertent escape of mutant organisms.250

The wondrous capacity to circumvent Mendelian genetics constraints to guarantee that a gene can fix itself in a population is unprecedented. Regardless of the future regulatory decisions made to promote, control, or curtail gene drives altogether, no one can deny the power of the technology. For better or worse, the ability to hack genomes in pests finally bestows upon the world a weapon with the potential to help eradicate a long list of vector-borne

247. See, e.g., supra notes 236–37 and accompanying text.
248. Carl Zimmer, A Call to Fight Malaria One Mosquito at a Time by Altering DNA, N.Y. TIMES (July 17, 2014), http://www.nytimes.com/2014/07/17/science/a-call-to-fight-malaria-one-mosquito-at-a-time-by-altering-dna.html?_r=0 [https://perma.cc/D27C-K2MS] (quoting George Church, senior author of one of the papers targeting malaria mosquito vectors, as stating: "In a year or two, we could be doing field trials if there was a general consensus this was a good idea.").
250. See DiCarlo et al., supra note 217, at 1252–53.
diseases—malaria, dengue, yellow fever, Zika, epidemic typhus, Lyme disease, Rocky Mountain spotted fever, etc.—as well as neglected tropical diseases\(^{251}\) (NTDs) caused by parasitic organisms—e.g., schistosomiasis, caused by helminth parasites of the genus *Schistosoma*, which has brought suffering to hundreds of millions of people worldwide.\(^{252}\) Science has produced a method that offers a meaningful opportunity to strike back at the mosquito, the deadliest animal in the world.\(^{253}\)

By the same token, science has produced a tool to reshape entire ecosystems. On one hand, given the reported success of gene drives to endow a species with anti-parasite resistance,\(^{254}\) one can imagine possible scenarios where an endangered species could be generously armed with a gene drive to help it cope with changes in its habitat, or become immunized against parasites and opportunistic organisms driving it into extinction. On the other hand, CRISPR-based gene drives could be used to deliver a coup de grâce to invasive and noxious species like the Asian carp in the Great Lakes,\(^{255}\)

\(^{251}\) NTDs are a group of parasitic and bacterial diseases affecting more than one billion people worldwide, predominantly in low-income countries. *Neglected Tropical Diseases*, CTRS. DISEASE CONTROL & PREVENTION, http://www.cdc.gov/globalhealth/ntd/ [https://perma.cc/TK9L-9LZ3] (last updated June 7, 2016). NTDs cause substantial illness and death, impair physical and cognitive development, and limit productivity in the workplace. *Id.* They are considered neglected because they are largely nonexistent in developed nations, but persist only in the poorest, most marginalized areas of low-income countries. *Id.* The list of common NTDs includes Buruli ulcers, Chagas disease, Cysticercosis, Dengue fever, Echinococcosis, Fascioliasis, Leprosy, Onchocerciasis, Rabies, Schistosomiasis, and others. See *Diseases*, CTRS. DISEASE CONTROL & PREVENTION, http://www.cdc.gov/globalhealth/ntd/diseases/index.html [https://perma.cc/BE7T-4HPN] (last updated Feb. 17, 2017), for a list and information about NTDs.


\(^{254}\) See Gantz et al., *supra* note 227 (using a gene drive to make the mosquito *Anopheles Stephensi* resistant to the malaria parasite).

Argentine cactus moth in the Southern United States and Mexico,\(^{256}\) cane toads in Australia,\(^{257}\) tropical fire ants in the Galápagos Islands,\(^{258}\) Giant African snails,\(^{259}\) zebra mussels,\(^{260}\) kudzu,\(^{261}\) soybean cyst nematode—afflicting soybean crops worldwide—\(^{262}\) and a miscellany of other aquatic\(^{263}\) and terrestrial\(^{264}\) invasive plant and animal species.

C. Transgenic Animals for Translational and Basic Research

Animals have long played an integral role in scientific inquiry. From Aristotle’s experiments on living animals\(^ {265}\) to Pasteur’s groundbreaking studies on rabbits and dogs,\(^ {266}\) scientists have always sought animal models to explore biomedical research. Well over 100 million animals have been used for scientific research in Europe and the United States alone since governmental agencies began tracking


\(^{265}\) Rachel Hajar, Animal Testing and Medicine, 12 HEART VIEWS 42, 42 (2011).

\(^{266}\) Kendall A. Smith, Louis Pasteur, the Father of Immunology?, 3 FRONTIERS IMMUNOLOGY, art. 68, 8 (2012).
animal studies. A long list of model organisms has helped to elucidate fundamental questions in science over many decades. Without question, animal experimentation has provided insights into anatomy, physiology, and medicine that have dramatically transformed our ability to cope with and ameliorate human suffering. It would be nearly impossible to establish safety measures and criteria prior to launching new treatments without the use of animal models of human disease.

1. Mouse Pre-Clinical Models of Disease

In recent years, genome editing has routinely been utilized to edit a multitude of animal genomes. Of these, the mouse has become the foremost mammalian model organism for genetic and biomedical pre-clinical research, thanks in part to physiological similarities between mice and humans. Indeed, genome editing studies in mice are instrumental for translational purposes and demonstrate great promise in forging a path toward human clinical applications. For instance, last month, three independent US teams published proof-of-concept studies showing how CRISPR-based gene editing can be used to improve skeletal muscle function in adult and neonatal mice models of Duchenne muscular dystrophy (DMD), a fatal genetic disease that causes muscle degeneration, loss of mobility, and premature death. One of the three teams had previously


269. For a works-in-collection featuring a thorough examination of the use of animal models for human disease in a wide array of fields ranging from ophthalmology and cardiology to genetics, behavior, cancer, and development, see ANIMAL MODELS FOR THE STUDY OF HUMAN DISEASE (P. Michael Conn ed., 2013).

270. See, e.g., Lars Dalgaard, Comparison of Minipig, Dog, Monkey and Human Drug Metabolism and Disposition, 74 J. PHARMACOLOGICAL & TOXICOLOGICAL METHODS 80 (2015).

271. See, e.g., supra notes 163–71; supra Sections IV.A & IV.B.


273. Chengzu Long et al., Postnatal Genome Editing Partially Restores Dystrophin Expression in a Mouse Model of Muscular Dystrophy, 351 SCIENCE 400, 400 (2016); Christopher E. Nelson et al., In Vivo Genome Editing Improves Muscle Function in a Mouse Model of Duchenne Muscular Dystrophy, 351 SCIENCE 403, 403 (2016); Mohammadsharif Tabeordbar et
demonstrated the feasibility of preventing the disease by editing the germline—an organism's sex cells (e.g., eggs and sperm) that pass on genes from one generation to the next during sexual reproduction—of mice models of DMD.

Researchers have also corrected a mutation in the Crygc gene responsible for cataracts by editing the germline of mice, leading to the birth of fertile pups that went on to pass the corrected allele to their progeny. A mouse model of mitochondrial disease demonstrated that germline genome editing can prevent transmission of faulty mitochondria—organelles that supply energy to cells—to mice offspring. CRISPR-mediated genome editing in postmitotic neurons of adult mice brain has been achieved in vivo. And a separate team showed that Cas9-mediated germline multiplexing—the simultaneous disruption of multiple genes by gene editing—can be accomplished by targeting genes into zygotes, thereby producing animals with desired mutations in various genes.

Despite the widespread use of mouse models of human disease, there are stark limitations associated with pre-clinical trials in rodents. First, the very characteristics that make mice useful models—relatively short life cycle compared to other mammals, physical size, short gestation periods, abundant progeny, etc.—may render them inadequate for validating the relevance of clinical findings. Second, metabolic and physiological differences between mice and humans lead to differences in species-specific susceptibility to disease and pharmacological responses. Third, mice models of

al., In Vivo Gene Editing in Dystrophic Mouse Muscle and Muscle Stem Cells, 351 SCIENCE 407, 407 (2016).


276. Yuxuan Wu et al., Correction of a Genetic Disease in Mouse via Use of CRISPR-Cas9, 13 CELL STEM CELL 659, 659, 662 (2013).


279. Lukasz Swiech et al., In Vivo Interrogation of Gene Function in the Mammalian Brain Using CRISPR-Cas9, 33 NATURE BIOTECHNOLOGY 102, 102 (2015).


281. Chung et al., supra note 272, at 201.

282. Id.; see also Dalgaard, supra note 270 (discussing comparative pharmacology and toxicology in humans and other large mammals).
disease often cannot recapitulate features associated with many human pathologies. A quintessential illustration of this phenomenon is the inability of mice to replicate the full panoply of neuropathologies—most notably, overt neurodegeneration in the human brain—that constitute the hallmark of many neurodegenerative diseases such as Parkinson's Disease, Huntington's Disease, and Alzheimer’s Disease. The same holds true for Cystic Fibrosis, Lesch-Nyhan syndrome, and many other conditions. The lack of accurate pathological reproducibility is problematic and may be linked to the meager impact these mouse models have had in clinical outcomes.

2. Large Animal Pre-Clinical Models on the Rise

As a result of the natural constraints imposed by mice models of human disease, large animal models have become an increasingly attractive alternative for clinical investigation. Indeed, as controversial as the research might be, dogs, cats, pigs, and many other conditions. The lack of accurate pathological reproducibility is problematic and may be linked to the meager impact these mouse models have had in clinical outcomes.

289. See e.g., Ashish R. Pinnapureddy et al., Large Animal Models of Rare Genetic Disorders: Sheep as Phenotypically Relevant Models of Human Genetic Disease, 10 ORPHANET J. RARE DISEASES 107 (2015).
292. Id.
sheep, rabbits, goats, horses, non-human primates, and other large animals have contributed greatly to our understanding of human pathologies. Advocates of research on large animals argue that using higher mammalian species offers a more rigorous and reliable system to validate the efficacy of pre-clinical trials in small rodents. Accordingly, a tide of experiments on large animals is surfing apace thanks to novel genome editing technologies that have turned the unimaginable into a reality.

In almost parallel studies, CRISPR systems have been effectively used to create muscular versions of pigs and beagle dogs, the canine breed most widely used in biomedical research, via engineering MSTN mutations. At least nine genes, some of which are associated with lipid metabolism and cardiovascular conditions, have been targeted and mutated in rabbits. Editing the vWF gene, responsible for von Willebrand Disease (vWD)—a bleeding disorder that prevents normal blood clotting—led to a striking phenotype in mutant pigs; the animals exhibited prolonged bleeding that lasted nearly fifteen times longer than that of non-mutant pigs. Because mice models cannot fully recapitulate the severe bleeding phenotype of

294. Pinnapureddy et al., supra note 289.
297. C.W. McIrwraith et al., The Horse as a Model of Naturally Occurring Osteoarthritis, 1 BONE & JOINT RES. 297 (2012).
299. Li & Li, supra note 284, at 157.
303. Myostatin, also known as growth differentiation factor-8 (GDF-8), is a gene involved in regulation of skeletal muscle growth that has been linked to muscle hypertrophy. See Alexandra C. McPherron et al., Regulation of Skeletal Muscle Mass in Mice by a New TGF-beta Superfamily Member, 387 NATURE 83 (1997).
304. Yang et al., supra note 168.
vWD, the ability of CRISPR-edited pigs to mimic human vWD is a major step toward developing a bona fide model to study the disease.

Similar phenotypic replication of pathologies that could not be realized in mouse models has been accomplished in sheep, pigs, and other large animals, lending credence to the hypothesis that large animal models constitute a more precise platform to study some human diseases. Now that CRISPR technologies and their use are starting to become routine, we should fully expect numerous reports in the coming months and years establishing new large animal models for clinical research.

On this point, perhaps the most salient examples of the potential of genome editing for translational applications are the recent publications vis-à-vis CRISPR-edited non-human primates. In a world first, Chinese scientists have recently used genome editing technologies to modify the embryos of cynomolgus and rhesus monkeys and implant them into surrogate mothers, who delivered transgenic infant monkeys after full-term pregnancies. Proof that non-human primates' genomes can, in fact, be modified at the embryonic stage to produce progeny with desired modifications turns the prospect of human germline modification from a forlorn aspiration into a feasible goal. Indeed, the race to produce monkeys with

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307. Id. at 372.
309. Compare, e.g., Bernhardt G. Zeiher et al., A Mouse Model for the ΔF508 Allele of Cystic Fibrosis, 96 J. CLINICAL INVESTIGATION 2051, 2062 (1996) (introducing the most common CF-associated mutation of CFTR into transgenic mice without accurately replicating the CF pathology), with Lynda S. Ostedgaard et al., The ΔF508 Mutation Causes CFTR Misprocessing and Cystic Fibrosis–Like Disease in Pigs, 3 SCI. TRANSLATIONAL MED. 74ra24 (2011) (engineering pigs carrying the same mutation—ΔF508—as was done in the mouse, but observing a range of human CF pathology), and Christopher S. Rogers et al., Disruption of the CFTR Gene Produces a Model of Cystic Fibrosis in Newborn Pigs, 321 SCIENCE 1837 (2008) (disrupting the CFTR gene in pigs led to development of human CF clinical manifestations). See also Huaqiang Yang et al., Species-Dependent Neuropathology in Transgenic SOD1 Pigs, 24 CELL RES. 464 (2014) (engineering transgenic pigs that showed nuclear accumulation and ubiquitinated nuclear aggregates in the brain, as seen in some human Amyotrophic lateral sclerosis (ALS) patient brains, but not in ALS mouse models).
310. See, e.g., Xingshen Sun et al., Disease Phenotype of a Ferret CFTR-Knockout Model of Cystic Fibrosis, 120 J. CLINICAL INVESTIGATION 3149 (2010).
targeted genome modifications for more accurately modeling human diseases is now on.\textsuperscript{313}

In the last year, the birth of monkeys with markedly depleted dystrophin and muscle degeneration seen in early human DMD has been reported.\textsuperscript{314} A one-step method demonstrated successful embryonic editing and delivery of live monkeys carrying homozygous mutations in the tumor suppressor \textit{p53} gene.\textsuperscript{315} Furthermore, scientists recently published an article describing the creation of transgenic monkeys that exhibit autism-like behaviors and, remarkably, showed successful germline transmission of the modified gene by bringing their progeny into this world.\textsuperscript{316} These findings demonstrate that, unlike mouse models lacking higher perceptual and cognitive function seen in primates,\textsuperscript{317} studies using non-human primate genome editing are better equipped to provide models to further our understanding—and ultimately lead to treatments—of the cognitive, behavioral, anatomical, and emotional symptoms associated with a long list of neurological—autism spectrum disorder; behavioral—Attention Deficit Hyperactivity Disorder (ADHD), drug abuse, and alcohol abuse; psychiatric—schizophrenia, obsessive compulsive disorder, and depression; and neurodegenerative disorders—Alzheimer’s and Parkinson’s Disease—that contribute to human suffering worldwide.

3. Xenotransplantation—A Case Study

Genome editing technologies can now be used to create useful animal models to interrogate the mechanisms of human diseases, which may lead to future diagnoses and treatments, as discussed above. However, other translational applications of animal genome editing are even closer on the horizon, and a prime example is the field of xenotransplantation.\textsuperscript{318}

\begin{itemize}
  \item \textsuperscript{313} See, e.g., infra notes 314–16 and accompanying text.
  \item \textsuperscript{314} Yongchang Chen et al., \textit{Functional Disruption of the Dystrophin Gene in Rhesus Monkey Using CRISPR/Cas9}, 24 HUM. MOLECULAR GENETICS 3764 (2015); Yongchang Chen et al., \textit{Germline Acquisition of Cas9/RNA-Mediated Gene Modifications in Monkeys}, 25 CELL RES. 262 (2015).
  \item \textsuperscript{315} Haifeng Wan et al., \textit{One-Step Generation of p53 Gene Biallelic Mutant Cynomolgus Monkey via the CRISPR/Cas System}, 25 CELL RES. 258 (2015).
  \item \textsuperscript{316} Zhen Liu et al., \textit{Autism-Like Behaviours and Germline Transmission in Transgenic Monkeys Overexpressing MeCP2}, 530 NATURE 98 (2016).
  \item \textsuperscript{317} Jon H. Kaas, \textit{The Evolution of Brains from Early Mammals to Humans}, 4 WILEY INTERDISC. REV. 33 (2013).
  \item \textsuperscript{318} Xenotransplantation refers to the process of transplanting living cells, tissues, or organs from one species to another. See Xenotransplantation, WORLD HEALTH ORG. (May 2, 2005), http://www.who.int/transplantation/xeno/en/ [https://perma.cc/V65A-FZW5].
\end{itemize}
Organ donation and transplantation is the best, and often sole, form of treatment for end-stage organ failure worldwide. In the United States alone, a shortage of organs for transplantation claims approximately twenty-two lives every day—over 8,000 annually. Similarly, massive shortages of organ donors in China and India lead to tens-of-thousands and hundreds-of-thousands of deaths, respectively, with worldwide death tolls likely reaching the millions.


322. Approximately 500,000 people die annually in India due to a shortage of organs for transplantation. Shruti Saxena, Organ Donation: Does India Lack Will?, INDILENS, (Aug. 7, 2014), http://indilena.com/57441-world-organ-donation-day-does-india-lack-will/ [https://perma.cc/LJM5-JPHV]. India has a rate of less than 0.2 donors per one million population.

323. It is difficult to determine exactly how many people on organ waiting lists die every year globally due to the lack of reporting mechanisms in most of the developing world. According to the International Registry in Organ Donation and Transplantation (IRODaT), only seventy-one countries currently report national data of donation and transplantation activity for database compilation on IRODaT. Final Numbers 2013, INT'L REGISTRY ORGAN DONATION & TRANSPLANTATION 2 (Dec. 2014), http://www.irodat.org/img/database/pdf/IRODaT%20Newsletter%202013%20.pdf [https://perma.cc/7Q2Y-C7A7]. The World Health Organization (WHO) reported 117,700 solid organ transplants in 2013. Map: Global Observatory on Donation and Transplantation, Global Transplantation Activities of Solid Organs, 2013, WORLD HEALTH ORG., (2015), http://www.transplant-observatory.org/report-2013/ [https://perma.cc/4MTP-BGCU]. In contrast, 29,532 individuals received organ transplants in 2014 in the United States, where over 123,000 people are currently on waiting lists for lifesaving organ transplants. U.S. DEPT HEALTH & HUM. SERVS., supra note 320; Facts and Myths, AM. TRANSPLANT FOUND., http://www.americantransplantfoundation.org/about-transplant/facts-and-myths/ [https://perma.cc/4WS7-TP22] (last visited Feb. 12, 2017). It is important to point out that organ transplant statistics do not include corneas, veins, heart valves, tendons, bones, skin, and other tissues. Facts and Myths, supra. For example, 40,000 corneal transplants—the most routinely transplanted tissue—are performed every year in the United States. Id.

An overwhelmingly conservative, low-end estimate of worldwide deaths attributable to organ shortages could, at the very least, be purportedly derived by looking at US statistics. If roughly 6.5% of people on waiting lists die every year (8,000 deaths per annum from a select population of 123,000), and approximately 24% of wait-listed individuals receive transplants (29,532 recipients of a 123,000 applicant pool), we can use the number of reported worldwide transplants (117,700) and US-derived statistical rates to arrive at a baseline putative worldwide organ transplant waitlist population—limited to less than half (seventy-one) of total countries—of nearly a half-million individuals (~491,000), of which ~32,000—or 6.5%—would die annually. Yet, even this figure likely grossly underestimates the actual number given that there are nearly 200 countries in the world, and most of the non-reporting countries house low-income, poverty-stricken populations with limited access to healthcare and education. Undoubtedly, in this context, current statistics on organ transplantation-related data excludes individuals in low-income regions of the world who are in dire need of access to lifesaving organ transplantation.
To mitigate the shortage of organs, scientists began to experiment, decades ago, with xenotransplantation to determine whether animals could provide a supply of organs to humans.\(^{324}\) Animal kidney, heart, and liver organs were first in line, with catastrophic results for patients as a result of severe infection, immune reactions, and rejection of the organs.\(^{325}\) However, after decades of research on xenotransplantation and the advent of genome editing technology, researchers may now be on the verge of breaking through the non-human organ donor glass ceiling.

Recent articles published encouraging results from xenotransplantation of hearts\(^ {326}\) and a life-supporting kidney graft\(^ {327}\)
from genetically modified pigs to baboons. Last fall, a group of researchers used CRISPR-Cas9 to simultaneously eradicate all sixty-two copies of a porcine endogenous retrovirus (PERV)—a type of pig virus that could be transmitted to humans—in a pig kidney cell line and prevented in vitro viral infection and transmission to human cells.\textsuperscript{328} The same group also reported a forthcoming publication involving the editing of more than twenty genes in pig embryos, including some known to trigger human immune responses or blood clotting.\textsuperscript{329}

These and other findings have spurred entrepreneurial interest in using synthetic biology and genome editing methods to generate ready-for-transplant, human-compatible pig organs.\textsuperscript{330} Backed by an infusion of venture capital, biotech companies aim to get pig lungs in human clinical trials by 2020,\textsuperscript{331} and academic researchers funded by the National Institutes of Health are working to carry out parallel studies that may bring clinical trials of pig kidney, heart, and liver transplantation in humans within the realm of possibility.\textsuperscript{332}
hopeful preview came last year when the Chinese Food and Drug Administration approved the sale of the world’s first bioengineered cornea derived from pig’s eyes. The first transplant was performed in an older patient suffering from a serious corneal ulcer with successful results. As genome editing technologies mature, we should expect further developments in xenotransplantation and other important fields of clinical relevance.

D. Agriculture

1. Crops and Biofuels

The United Nations projects the world population will rise from today’s 7.2 billion to 9.6 billion by the year 2050. This gargantuan increase will pose significant challenges to the world’s ability to foster food security and meet nutritional needs using limited arable land and water available for irrigation. As a result, sustainability and the contributions of rising agriculture-related pollution to climate change will become global problems. Analyses for global crop demand forecast an increase between 100% and 110% from current levels by 2050. Investment in biotechnologies aimed at increasing food yields and producing pest-resistant genetically modified (GM) crops have been proposed as a solution to the global food crisis.

Fervid, and at times intemperate, controversy exists over the use of GM crops—colloquially known as GMOs—with supporters


336. Elliot M. Berry et al., Food Security and Sustainability: Can One Exist Without the Other?, 18 PUB. HEALTH NUTRITION 2293, 2300 (2015).

337. Id.


340. The controversy surrounding GMOs—and GM food in particular—is the focus of a forthcoming publication. See Enríquez, supra note 31. In that article, I examine the underlying basis for GMO controversies, synthesize the scientific literature concerning the perceived GMO-related human health and environmental risks, analyze the GMO regulatory framework
and critics constantly sparring about the perceived risks and benefits of GM crops to human health, the environment, and food security. However, although a minor potential for adverse events exists, to date, no overt or deleterious consequences have yet been documented in the scientific, peer-reviewed literature for the more than two decades that bioengineered foods have been available to consumers, with the exception of a few isolated cases. See, e.g., Found. on Econ. Trends v. Heckler, 756 F.2d 143, 146 (D.C. Cir. 1985) (enjoining the University of California from conducting a “deliberate release experiment” to delay field testing of genetically altered bacteria on select crops); All. for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166, 181 (D.D.C. 2000) (rejecting a challenge, brought by a coalition group of scientists and religious leaders, to the Food and Drug Administration’s policy on genetically engineered foods). Compare Ming Zhang et al., Long-Term Toxicity Study on Transgenic Rice with Cry1Ac and Sck Genes, 63 FOOD & CHEMICAL TOXICOLOGY 76, 82 (2014) (concluding that insect-resistant GM rice consumption in rodents has no long-term, adverse health effects), with Gilles-Eric Séralini et al., Republished Study: Long-Term Toxicity of a Roundup Herbicide and a Roundup-Tolerant Genetically Modified Maize, 26 ENVTL. SCI. EUR. 14 (2014) (documenting a series of long-term deleterious effects, including severe hormone-dependent mammary, hepatic, and kidney disturbances, arising from consumption of GM maize treated with Roundup—the most widely used herbicide worldwide—in rodents). See also, e.g., E.C., A DECADE OF EU-FUNDED GMO RESEARCH 2001-2010, at 15-17 (2010) (compiling results from research studies on the safety of GM organisms funded by the European Union); Allison Kopicki, Strong Support for Labeling Modified Foods, N.Y. TIMES (July 27, 2013), http://www.nytimes.com/2013/07/28/science/strong-support-for-labeling-modified-foods.html?_r=1 [https://perma.cc/JE9Z-NJGL] (citing a New York Times poll that shows 93 percent of American respondents support labeling GM foods and 75 percent harbor concerns about eating GM foodstuff); Millions March Against GM Crops, GUARDIAN (May 25, 2013, 8:26 PM), http://www.theguardian.com/environment/2013/may/26/millions-march-against-monsanto [https://perma.cc/V9XR-HCAU] (reporting on protest rallies organized in the United States and globally against Monsanto); Lee R. Morisy, Report on the Council for Public Health: Biomedical Engineering, AM. MED. ASS’N (2012), https://web.archive.org/web/20120907023039/http://www.ama-assn.org/resources/doc/csaph/a12-csaph2-bioengineeredfoods.pdf [https://perma.cc/DM6U-BS2A] (recommending that mandatory labeling of GM foods is not consistent with the FDA’s science-based labeling policies despite strong consumer interest in labeling); Lynne Peeples, GMO Debate Heats up: Critics Say Biotech Industry Manipulating Genes, and Science, HUFFINGTON POST (Sept. 21, 2012, 8:30 PM), http://www.huffingtonpost.com/2012/09/21/gmo-proposition-37-study-funding-research_n_1904535.html [https://perma.cc/6U73-ZY8P] (commenting on California’s 2012 Proposition 37, which sought to require labeling of GM foods).}

342. Although an exposition of the benefits and risks of GOMs, as well as their legal status and policy recommendations are outside the scope of this Article, a discussion of genome editing for agricultural purposes at least warrants the inclusion of some background on the controversy surrounding public perceptions and scientific evidence for or against GOMs. See supra note 341 and accompanying text. For an exemplification of the scientific debate surrounding GOMs, see Zhang et al., supra note 341 (finding no evidence of harmful health effects from GM rice consumption by rodents), and Morisy, supra note 341, at 2–5 (filing a report with the American Medical Association House of Delegates that cites literature presenting no evidence of health consequences to humans from two decades of GM crop consumption). Cf. Gilles-Eric Séralini et al., RETRACTED: Long Term Toxicity of a Roundup Herbicide and a Roundup-Tolerant Genetically Modified Maize, 50 FOOD &
exception of one highly contentious study. This is not to say that the lack of current scientific evidence—even decades after introduction of GM crops—is *prima facie* evidence of a complete absence of risk. Conversely, at least some evidence suggests that adoption of GM crops reduces food insecurity, improves calorie consumption and dietary quality, and can be a key factor in a broader global food security strategy.

Reports of the first GM plants—petunia, tobacco, sunflower, and carrot—appeared in the literature thirty-three years ago. Within a decade, Calgene, a California-based firm, introduced FLAVR SAVR tomato, the first GM crop product to be approved by the US

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343. See Séralini et al., supra note 342 and accompanying text.


Food and Drug Administration (FDA) for human consumption and commercialization.\(^{346}\) Today, 190 GM crops ranging from fruits to grains and vegetables have been approved for human consumption in the United States and many more countries worldwide.\(^{347}\) In 2014, a total of 18 million farmers planted GM crops across 448 million acres of farmland in twenty-eight countries.\(^{348}\) GM crop arable land has swollen 10,000% since commercialization of GM crops commenced two decades ago.\(^{349}\)

Scientists state that the exponential increase in farmlands devoted to GM crop agriculture is contributing to the global food crisis.\(^{350}\) GM crop supporters point to these statistics to argue that GM crops and further development of biotechnologies are necessary to address population growth, climate change, and global demands for food and feed.\(^{351}\) In contrast, opponents argue that the impact of GM crops on human health and the environment is not well established and warrants more research.\(^{352}\) They perceive approval by regulatory agencies as a precocious exercise that sets dangerous precedents to the detriment of humankind.\(^{353}\)

Regulatory controversies notwithstanding, scientists have reported proof-of-concept experiments involving genome editing in many plants, including crops, since CRISPR systems became widely available to the scientific community a mere three years ago. Among the CRISPR-Cas9 modified plants are wheat,\(^{354}\) rice,\(^{355}\) thale cress,\(^{356}\) etc.
tobacco, sweet orange, sorghum, maize, barley, wild cabbage, tomato, soybean, liverwort, potato, and others.

Two particular studies illustrate well the prototypical uses of genome editing in crop cultivars. The first involves CRISPR-mediated endogenous disruption of the tomato \( RIN \) gene, which encodes a transcription factor that regulates fruit ripening. \( RIN \)-defective mutations result in peculiar phenotypes in tomatoes including not turning to red color, maintaining flesh firmness for several months, and inhibiting other changes associated with fruit ripening. \( RIN \)-defective tomato cultivars are routinely bred with other tomato plant varieties to create tomatoes with an extended shelf life. These mutations occur naturally and, thus, mutant tomatoes are not considered to be transgenic or GMOs.

In the study, the authors used CRISPR-Cas9 to introduce single or few nucleotide changes in select regions of the \( RIN \) locus, which led to a truncated, nonfunctional \( RIN \) protein that mirrored the


357. Li et al., supra note 356, at 688–89; Vladimir Nekrasov et al., Targeted Mutagenesis in the Model Plant Nicotiana benthamiana Using Cas9 RNA-Guided Endonuclease, 31 NATURE BIOTECHNOLOGY 691 (2013).


362. Id.

363. Christopher Brooks et al., Efficient Gene Editing in Tomato in the First Generation Using the CRISPR/Cas9 System, 166 PLANT PHYSIOLOGY 1292 (2014).


367. Yasuhiro Ito et al., CRISPR/Cas9-Mediated Mutagenesis of the RIN Locus That Regulates Tomato Fruit Ripening, 467 BIOCHEMICAL & BIOPHYSICAL RES. COMM. 76 (2015).

368. Id. at 77.

369. Id.
RATION-defective tomatoes. They also showed that the mutations could be passed on to the next generation of plants. Hence, this study shows the feasibility of extending the shelf-life of a tomato fruit via genome editing without the use of transgenic constructs or selectable markers. In other words, the mutant tomato lines created in the experiments are, for all practical purposes, the equivalent of naturally occurring cultivars.

The second study concerns wheat resistance to the fungus *Blumeria graminis* f. sp. *tritici*, one of the world’s most devastating plant pathogens and the culprit of powdery mildew disease. The authors showed that small, single or few nucleotide, CRISPR- and TALEN-induced mutations targeting all six alleles of the *MLO* gene in the hexaploid wheat genome are sufficient to knock out the function of the MLO protein. The mutations led to strong resistance to the powdery mildew fungal disease in wheat plants. The mutations conferring broad-spectrum resistance to the disease were also shown to be heritable, given that the genetic trait was stable in subsequent generations.

This remarkable study—the first of its kind—demonstrates the potential of genome editing technologies to address global problems in agriculture via biotechnologies. From a genetics standpoint, the *MLO* knock-out plants are indistinguishable from mutant plants derived via conventional mutation breeding. Moreover, the fact that plants could now acquire disease resistance without the need to introduce DNA from other species or selectable markers highlight the supersedure of traditional transgenesis methods with precision genomic targeting.

Fruit ripening and disease resistance are merely the tip of the iceberg. Academic-industry partnerships will ensure a steady supply of scientific breakthroughs with commercial applications. As more research unfolds, it may be possible to cultivate crops without the use of pesticides and herbicides altogether by making plants emit

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370. Id. at 79–80.
371. Id. at 80.
373. Mildew-resistance locus.
374. Wang et al., *supra* note 372, at 948.
375. Id. at 950.
376. Id. at 948–49.
endogenous, natural compounds that aren't toxic to humans, to protect themselves against pathogenic organisms.\textsuperscript{378}

Grain seeds needed to feed the world could be engineered to increase storage tolerance and avoid deterioration and premature spoiling,\textsuperscript{379} which may help to ameliorate the ever-increasing need for arable lands. Production of allergen-free peanuts and other foodstuffs may now be possible by targeting and disrupting genes that encode allergens and other toxic cyanogens, which threaten the lives of millions of people with food sensitivities worldwide.\textsuperscript{380} Salt-resistant crop plants could be introduced to permit seawater irrigation.\textsuperscript{381} Drought-resistant crops could help to allay turmoil in water-poor regions of the world.\textsuperscript{382}

Emergency biotechnological intervention could also be established to pioneer crop diversification efforts where needed, and could even save staple crops from extinction when deadly diseases threaten their existence. For instance, such intervention could be used to mitigate the threat to the Cavendish banana, which is currently in danger of extinction in some parts of the world due to the Tropical Race 4 fungus.\textsuperscript{383}

Even biofuel production is on the horizon. Oilseeds from the plant \textit{Camelina sativa}, and others, have in recent years been identified as promising sources of renewable biofuels, capable of reducing CO\textsubscript{2} emissions by 78.5% compared to petroleum diesel.\textsuperscript{384} In

\begin{itemize}
\item \textsuperscript{378} \textit{Cf.} Abdul Rashid War et al., \textit{Mechanisms of Plant Defense Against Insect Herbivores}, 7 \textit{PLANT SIGNALING & BEHAV.} 1306 (2012).
\item \textsuperscript{379} \textit{See, e.g.}, Lei Ma et al., \textit{TALEN-Based Mutagenesis of Lipoxygenase LOX3 Enhances the Storage Tolerance of Rice (Oryza sativa) Seeds}, 10 PLOS ONE e0143877 (2015).
\item \textsuperscript{380} \textit{Cf.} Maria Gallo & Richard Sayre, \textit{Removing Allergens and Reducing Toxins from Food Crops}, 20 \textit{CURRENT OPINION BIOTECHNOLOGY} 191 (2009) (suggesting use of earlier biotechnologies to remove or reduce allergens and toxic cyanogens from food crops); Lena Y.C. Soo et al., \textit{Using Genome-Enabled Technologies to Address Allergens in Seeds of Crop Plants: Legumes as a Case Study}, in \textit{SEED DEVELOPMENT: OMICS TECHNOLOGIES TOWARD IMPROVEMENT OF SEED QUALITY AND CROP YIELD} 503 (2012).
\item \textsuperscript{381} \textit{See, e.g.}, Edward P. Glenn et al., \textit{Salicornia igelovii} Torr.: An Oilseed Halophyte for Seawater Irrigation, 251 \textit{SCIENCE} 1065 (1991); Stuart J. Roy et al., \textit{Salt Resistant Crop Plants}, 26 \textit{CURRENT OPINION BIOTECHNOLOGY} 115 (2014).
\item \textsuperscript{382} \textit{See, e.g.}, Honghong Hu & Lizhong Xiong, \textit{Genetic Engineering and Breeding of Drought-Resistant Crops}, 65 \textit{ANN. REV. PLANT BIOLOGY} 715 (2014).
\item \textsuperscript{383} \textit{See} DAN KOEPPEL, \textit{BANANA: THE FATE OF THE FRUIT THAT CHANGED THE WORLD} xiv (2008) (chronicling the alarming destruction of banana plantations around the globe and current efforts to save the world's most beloved fruit); \textit{see also} Dan Charles, \textit{Our Favorite Banana May Be Doomed; Can New Varieties Replace It?}, NPR (Jan. 11, 2016), http://www.npr.org/sections/thatsalt/2016/01/11/462375558/our-favorite-banana-may-be-doomed-can-new-varieties-replace-it [https://perma.cc/H2KE-CRTK].
\item \textsuperscript{384} \textit{See, e.g.}, John Sheehan et al., \textit{Overview of Biodiesel and Petroleum Diesel Life Cycles} 18 (1998), http://www.nrel.gov/docs/legosti/fy98/24772.pdf [https://perma.cc/8MEG-L2KU]; A.
fact, the US Navy, US Air Force, and many private entities have successfully tested Camelina-based fuel and announced plans to increase the use of biofuels to meet their energy requirements.\textsuperscript{385} Renewable biofuels could not only benefit the domestic economy, but also help reduce US dependence of foreign petroleum, greenhouse gas emissions, and air pollution.\textsuperscript{386} Genome editing technologies may finally help to lower current barriers for production of renewable biofuels including yield requirements and commercial viability.

Unlike transgenic crops created from earlier techniques, all these new crop varieties derived via modern genome editing biotechnologies do not require the introduction of any foreign DNA, are genetically indistinguishable from crops developed by mutation breeding protocols over the past three millennia, and bear no genetic manipulation footprints in their progeny. Thus, genome editing represents a powerful tool to protect and enhance important and desirable agronomic traits with vast repercussions for crop agriculture.

2. Animals

To satisfy the predicted food demand by 2050, global food production must increase by at least 70 percent from current levels, which translates into an additional—and quite staggering—400 billion pounds of meat worldwide.\textsuperscript{387} In the United States alone, red meat\textsuperscript{388} production totaled 47.4 billion pounds in 2014.\textsuperscript{389} More than 140 million livestock were slaughtered, including cattle, hogs, sheep, and lambs.\textsuperscript{390} A total of 8.54 billion broiler chickens and nearly 100 billion

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386. Sheehan et al., supra note 384, at iii–iv.


389. \textit{Id.}

390. \textit{Id.} at 8.

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eggs were produced in the United States in 2014.391 Global agricultural activity, and livestock production in particular, is exerting a colossal impact on the environment and accounts for 22 percent of total greenhouse gas emissions—a greater percentage than the total contribution from the transportation sector (e.g., cars, trucks, airplanes).392

Aside from translational and basic research purposes,393 farm animals constitute an important source of commodities such as food nutrients,394 natural fiber,395 and labor.396 A strategy to mitigate the current unsustainable rate of meat consumption involves genome editing in farm animals. One illustration concerns the objective of increasing the muscle mass of livestock for lean meat production by interfering with the MSTN gene responsible for muscle growth inhibition.397

Cases of naturally occurring mutations in the MSTN locus have been widely reported in animals that exhibit doubling of skeletal muscle mass.398 Proof-of-concept MSTN-edited studies aiming to increase mass yield in farm animals have been successfully established, inter alia, in pigs,399 cattle,400 goats,401 and sheep.402 More importantly, these methods of editing MSTN in livestock occur at native sites of the genome and abrogate the need to insert any foreign nucleotides that are not already found naturally inside the animals'

393. See discussion supra Section IV.C.
394. T.F. Randolph et al., Role of Livestock in Human Nutrition and Health for Poverty Reduction in Developing Countries, 85 J. ANIMAL SCI. 2788 (2007).
396. See, e.g., LEWIS FALLEY ALLEN, AMERICAN CATTLE: THEIR HISTORY, BREEDING AND MANAGEMENT 56-58 (1868).
399. Wang et al., supra note 301, at 1.
400. Luo et al., supra note 397, at 1.
genomes. This type of genome editing without the use of transgenes stands in contrast to the recent approval of transgenic salmon—genetically modified to grow at accelerated rates—by the FDA, which, despite being labeled as safe for human consumption, has engendered controversy from anti-GMO groups.

Another priority in animal agriculture is the development of methods to improve disease resistance to pathogens that threaten animal and human health. Substantial progress toward this goal has been documented by two recent studies. One demonstrated that minimal changes to the CD163 gene confer immunity in pigs against Porcine Reproductive and Respiratory Syndrome Virus, the most economically significant swine disease in North America, Europe, and Asia. The other targeted the RELA gene, which has been associated with the African Swine Fever Virus that triggers a deadly immune reaction in pigs. Although the latter team has not yet exposed edited pigs to the virus, the study showed modern genome editing biotechnologies can adequately deliver live pigs without the use of older, often cumbersome, cloning technologies like Somatic Cell Nuclear Transfer.

These scientific advances open the door for new strategies to combat other pathogenic organisms that affect important animals in agriculture. For example, the SAL1 gene in chickens has been linked to resistance against certain Salmonella strains responsible for food-borne gastroenteritis in humans. Genome editing now provides an opportunity to exploit this naturally occurring resistance to immunize chickens and avert serious economic losses stemming from human transmission events.


404. See Andrew Pollack, Genetically Engineered Salmon Approved for Consumption, N.Y. TIMES, Nov. 20, 2015, at Al.

405. Cluster of differentiation 163.


408. Id.

409. Paul Wigley et al., In Vivo and in Vitro Studies of Genetic Resistance to Systemic Salmonellosis in the Chicken Encoded by the SAL1 Locus, 4 MICROBES & INFECTION 1111 (2002).

Lastly, other potential uses of genome editing for animal agriculture range from the production of textiles—e.g., by triggering modifications in the Shannbei cashmere goat FGF5\textsuperscript{411} gene that controls hair length\textsuperscript{412}—to the development of safer dairy products—e.g., by generating animals that secrete milk with natural antibacterial properties\textsuperscript{413}—and animal welfare—e.g., by creating hornless cattle breeds with naturally occurring mutations in the POLLED gene to avoid painful, costly, and inhumane dehorning of animals.\textsuperscript{414} Like every other field mentioned above, genome editing technologies are poised to revolutionize the optimization of livestock production to meet future demands for food and animal products that could affect human health, the environment, intellectual property,\textsuperscript{415} the economy, and animal welfare.

\textbf{E. Human Germline Editing}

In 2015, a group of researchers launched humanity into uncharted territory. For the first time in the history of planet Earth and civilization, the human germline—gamete cells (sperm or eggs), zygotes, and embryos—underwent endogenous genetic manipulation by the macromolecular CRISPR-Cas9 system.\textsuperscript{416} Genome editing in human germ cells was largely predictable in light of the successes of germline editing in a plethora of animal and plant species over the last four years.\textsuperscript{417} Yet, predictability did not allay the global shockwaves created by the research.

In principle, manipulation of the human germline is not much different than germline manipulation in other species. Although
humans are biologically more complex than other organisms, the process of CRISPR-mediated genome editing is virtually the same: concoct a lab recipe that combines specific types of all three major bioorganic polymers—a target DNA, a sgRNA designed to hybridize with the DNA, and the Cas9 protein to trigger cuts in the DNA; allow the mix to form a complex inside the germ cells; and let science run its course. A group of Chinese researchers followed that precise formula and used the CRISPR system to interrogate the feasibility and efficiency of genome editing coupled to DNA repair mechanisms in the human germline.418

To establish proof-of-concept for human germline manipulation, the group chose to target the human β-globin (HBB) gene, the mutated form of which is linked to β-thalassemia, a debilitating and sometimes fatal blood disorder.419 A total of eighty-six non-viable human zygotes—the first cell formed upon a fertilization event—were injected with the CRISPR-Cas9 complex.420 Seventy-one of those zygotes survived the microinjection process and fifty-four were tested to confirm correct editing.421

Results revealed that only twenty-eight zygotes had their genome cleaved by the Cas9 enzyme, and a meager four zygotes (14%) had been successfully edited at the HBB locus using the template supplied by the scientists.422 From the outset, the team preemptively clarified that the zygotes used were triponuclear, that is, zygotes that carry an extra set of chromosomes due to fertilization of a single egg by two sperm.423 This property renders subsequent embryos non-viable, as the zygotes progress through the first stages of cell divisions in vitro, but become arrested in development and cannot result in a live birth.424

Three significant findings were identified in the experiment: (1) the editing and repair efficiency was dismally low (only 14% of embryos were successfully edited); (2) off-target mutations formed by cut-and-repair events in unintended DNA sites were detected, which resembled off-target events that typically occur in human cancer cells; and (3) the edited embryos were mosaic—i.e., some of the embryo cells

418. Liang et al., supra note 416, at 363.
419. Id. at 364.
420. Id. at 366–67.
421. Id.
422. Id.
423. The process of In Vitro Fertilization (IVF) typically leads to formation of approximately 5% triponuclear zygotes from the total zygote pool. Id. at 364. Because they cannot become viable embryos, the zygotes are usually discarded in IVF clinics, although they could be used to study human development where it is lawful. Id.
424. Id.
had the desired mutations while others did not. The landmark study showed that CRISPR-Cas9 can mediate DSB and DNA repair via HR in human embryos, but is replete with failures in terms of efficiency, specificity, and fidelity of the CRISPR-Cas9 system. More importantly, the data presented automatically preclude clinical use of CRISPR-Cas9 in the reported form and demonstrate that human germline editing is not yet ready for primetime.

To be clear, the paper represents a somewhat outdated snapshot of the state of the art at the time of its publication. Other published research around the time had already shown some improvements on efficiency and specificity, and the Chinese team’s results were consistent with already months-to-years-old CRISPR technology. Scientists at the forefront of genome editing technology were unimpressed with the results of the Protein & Cell paper—primarily because the research did not use the latest version of CRISPR-Cas9 technology—and called the attempt to edit human germ cells premature. Furthermore, it appears that some of the lackluster results could be attributable to inexperience with using CRISPR protocols. Palpably, the first try at human germline editing has gotten off to a rocky start. But tweaks and improvements in the field are occurring at an astounding speed.

From a scientific standpoint, the report did not contribute any novel understanding of the CRISPR system. Indeed, the authors pointed out that similar efficiencies had been reported in other organisms, including mice. In effect, the paper was merely a clone

425. Id. at 368.
426. See id. at 364.
427. Id. at 368.
428. Compare, e.g., Benjamin P. Kleinstiver et al., Engineered CRISPR-Cas9 Nucleases with Altered PAM Specificities, 523 NATURE 481 (2015) (improving DNA target specificity by a variant Cas9 that reduces off-target effects), with Yanfang Fu et al., High-Frequency Off-Target Mutagenesis Induced by CRISPR-Cas Nucleases in Human Cells, 31 NATURE BIOTECHNOLOGY 822 (2013) (reporting high frequency of off-target mutations using an older version of the CRISPR system).
430. Id. Not a single study coming out of Junjiu Huang’s laboratory in Sun Yat-sen University, Guangzhou, China describes the use of CRISPR-Cas9 predating the tripronuclear zygote study published in Protein & Cell, suggesting the investigation marked the first time the laboratory had worked with CRISPR-Cas9. See Junjiu Huang, PUBMED.GOV, http://www.ncbi.nlm.nih.gov/pubmed/?term=junjiu+huang[author] [https://perma.cc/5HNF-3MFE] (last visited Feb. 13, 2017).
431. See, e.g., Jean-Baptiste Renaud et al., Improved Genome Editing Efficiency and Flexibility Using Modified Oligonucleotides with TALEN and CRISPR-Cas9 Nucleases, 14 CELL REP. 1 (2016).
432. Liang et al., supra note 416, at 364–66.
of the same studies performed on other organisms. However, this time, the experiments were notable because they were conducted in human germ cells. The paper had first been submitted to Nature and Science, but was rejected by both journals in part because of ethical concerns. Notwithstanding the article's scientific shortcomings, the true nuances of this momentous report lie in the ethical implications of the research and the subsequent consternation it spawned.

Rumors that Chinese scientists had performed experiments to edit the human germline, purportedly circulated by reviewers or parties privy to the manuscript's content at one or both of the journals to which it was initially submitted, reverberated with a loud echo among scientific circles. Alarmed scientists rushed to publish commentaries in response to the leak in both Nature and Science to criticize the experiments and preemptively call for either a ban or an outright moratorium on facets of human germline editing research.

The situation was reminiscent of some bygone controversies. Not since the days of In Vitro Fertilization (IVF) and the birth of Dolly the sheep, the first animal cloned from an adult cell, had clamor been so thunderous concerning an emerging technology. A stentorian tone began to permeate news and media outlets within days of the published commentaries with several groups, including the Center for Genetics and Society in Berkeley, California, the Society for Developmental Biology in Bethesda, Maryland, and the International Society for Stem Cell Research echoing calls to halt...

433. Kaiser & Normile, supra note 429, at 486. Neither Nature nor Science confirmed the review or rejection of the manuscript. Id. at 487.

434. See id.

435. Lanphier et al., supra note 28.


441. Kaiser & Normile, supra note 429, at 486.

human germline editing research.\textsuperscript{443} Declarations of an urgent need to organize meetings about the appropriateness of using CRISPR-like biotechnologies for human germline research have led to meetings such as the International Summit on Human Gene Editing, which took place in December 2015 in Washington, D.C.\textsuperscript{444}

Just months earlier in September 2015, British scientists had promptly applied to the UK Human Fertilization and Embryology Authority (HFEA) for a license to edit genes in human embryos.\textsuperscript{445} The license was granted in February 2016. It allows biologists at the Francis Crick Institute in London to commence research on \textit{healthy} human embryos younger than seven days, pending approval by a local research ethics board.\textsuperscript{446}

The HFEA approval marks the first time a national regulatory agency condones investigations based on research involving human germline editing.\textsuperscript{447} It is also an important step toward elucidating more knowledge regarding CRISPR systems and their roles in genome editing within a more rigorous and developed framework than that of the research performed by the Chinese scientists, which involved non-viable human embryos and outdated versions of the CRISPR system. Findings derived from this forthcoming and unprecedented UK research will not only have an immediate impact on current reproductive technologies and human development, but may provide clues that will be useful for future clinical applications of genome editing.\textsuperscript{448}

Genome editing technologies involving the human germline have far greater prospects for human health and welfare than somatic or stem cell gene editing therapies. In addition to tackling acquired diseases, as well as monogenic and polygenic—dominant or recessive—congenital disorders in a particular individual,\textsuperscript{449} correcting gene errors or conferring prophylactic protection to diseases in the germline means the changes can be inherited in a firm and self-perpetuating configuration to subsequent generations. In essence, human germline editing is truly the holy grail of modern-day medicine.

\textsuperscript{443} Id.
\textsuperscript{445} Ewen Callaway, \textit{Embryo Editing Gets Green Light}, 530 NATURE 18 (2016).
\textsuperscript{446} Id.
\textsuperscript{447} Id.
\textsuperscript{448} Id.
\textsuperscript{449} See discussion \textit{supra} Sections IV.A and IV.C.
The potential benefits are infinite. Further maturation and tweaking of genome editing biotechnologies in combination with other foundational biotechnologies like genome sequencing and induced pluripotent stem cell (iPSC) biology may, sooner rather than later, enable us to ablate, mitigate, counteract, or safeguard against an extensive array of complex human ailments discussed earlier, including neurodegenerative disorders, congenital diseases, cognitive and behavioral anomalies, HIV and other viruses, obesity, cardiovascular disease, cancers, and more.

Contemplate, for a moment, the well-publicized dilemma of actress and director Angelina Jolie. In back-to-back op-eds in The New York Times, she shared with the world her decision to endure a preventive double mastectomy to remove her breasts and a laparoscopic bilateral salpingo-oophorectomy to remove her ovaries and fallopian tubes. Her decisions to undergo the procedures came following genetic testing via a blood test, which revealed she carried common mutations in the BRCA1 gene that placed her at an 87% risk of developing breast cancer and a 50% risk of ovarian cancer. Jolie lost her grandmother, aunt, and mother to cancer, making her family history a cautionary tale that could likely have foreshadowed her own destiny. In the span of two years, she took a surgical plunge any woman would dread. Her journey rendered her a menopausal woman well before her natural time. However, she also stands strong by her life-altering decision because she feels her children will no longer have to face losing their mother prematurely, as she did.

Jolie's remarkable story mirrors those of millions of women worldwide facing the deadly threat of cancer. The same can be said of men choosing to part ways with their prostates or testes, and millions of men and women all over the world facing tough decisions.


Id.

Id.

See Jolie, supra note 450, at A25.

Id. The World Health Organization estimates that breast cancer alone kills nearly 458,000 people each year, mainly in low- and middle-income countries. Id.


because of various forms of pervasive cancer diseases. But what if such drastic choices could be avoided? In Jolie’s case, the cancer risk was accentuated based on a familial history of cancer and mutations in the BRCA1 gene. Had genome editing been safe and readily available to her, her decision to extirpate her breasts and ovaries would not even have been considered.

In the future, humans may be able to identify quantitative-trait loci linked to a genetic basis or predisposition to disease and proactively correct deleterious mutations that could pose grave threats to human life. Genome editing finally brings into the realm of reality clinical applications that had been unreachable for decades. It is quite likely that the next generation of children and grandchildren may grow up in a CRISPR world, where they will no longer have to make Jolie-type choices due to cancers and numerous other human diseases. Even more remarkable is the notion that by correcting those mistakes in the germline DNA, new generations of would-be disease-prone mutation carriers may never have to witness the death of mothers, aunts, and grandmothers at the hands of the same killer.

Despite the vast potential for good by the use of genome editing biotechnologies, to some the notion of human germline modification—no matter what the purpose—conjures up the insidious spirit of eugenics and other potential societal harms. Frivolous enhancement of human traits, rising inequality, and a multitude of “designer babies” are commonly cited as major threats stemming from the use of genome editing biotechnologies. Others have chosen to either favorably cherry-pick or denounce certain applications of genome editing, as they worry that widespread opposition to the technology may curtail uses from which they stand to profit. This

458. Cancers are among the leading causes of morbidity and mortality worldwide. Cancer: Fact Sheet No. 297, WORLD HEALTH ORG. (Feb. 2015), http://www.who.int/mediacentre/factsheets/fs297/en/ [https://perma.cc/A6J3-KLQD]. In 2012, approximately 14 million new cases of cancer and 8.2 million cancer-related deaths were reported worldwide. Id. New cancer cases are expected to increase by 70% in the next twenty years. Id.

459. See, e.g., Cook, supra note 439 (commenting on the media’s perception that cloning research might give rise to “armies of Adolf Hitlers”); Robert Pollack, Eugenics Lurk in the Shadow of CRISPR, 348 SCIENCE 871 (2015) (analogizing the introduction of germline modification with a return to an agenda of eugenics that aims to select “good” traits and weed out “bad” ones).


461. See, e.g., Lanphier et al, supra note 28, at 410 (providing a pulpit to Sangamo BioSciences executives from which to argue that germline, but not somatic, genome editing should be banned). Sangamo BioSciences holds key patents in ZFN technology directed at somatic cell editing. Newer CRISPR-based technologies could negatively impact Sangamo’s business strategies. Id.
Article sets the stage to explore some of these themes arising from human germline editing in forthcoming genome editing-related scholarship.

* * *

The applications of genome editing biotechnologies described above constitute the first comprehensive—yet non-exhaustive—representation of the potential uses of this budding biotechnology to appear in legal literature. It is important to note that other uses of genome editing and CRISPR-based biotechnologies currently exist, including development of new antibiotics and antimicrobials, drug target discovery, systematic identification of gene and drug combinations, targeted epigenome editing, live imaging to study conformational and cellular dynamics, cell lineage tracing, whole genome screening and labeling, and others. However, it would be


463. See, e.g., Junwei Shi et al., Discovery of Cancer Drug Targets by CRISPR-Cas9 Screening of Protein Domains, 33 NATURE BIOTECHNOLOGY 661 (2015).


467. Aaron McKenna et al., Whole Organism Lineage Tracing by Combinatorial and Cumulative Genome Editing, 353 SCIENCE aaf7907 (2016).

468. Andrew B. Lane et al., Enzymatically Generated CRISPR Libraries for Genome Labeling and Screening, 34 DEVELOPMENTAL CELL 373 (2015).

469. See, e.g., Lukas E. Dow et al., Inducible in Vivo Genome Editing with CRISPR-Cas9, 33 NATURE BIOTECHNOLOGY 590 (2015) (describing a tool for inducible genome editing); Luke A. Gilbert et al., CRISPR-Mediated Modular RNA-Guided Regulation of Transcription in
impractical to list them all within the context of a law journal article, particularly given the astounding rate at which new applications continue to emerge.

Next, this Article weaves the genome editing scientific empiricism articulated above with jurisprudence to advocate for a normative approach that will lay a foundation for future examinations of the synergistic roles that law, science, and public policy will play in the development of this truly exceptional and transformative incipient biotechnology.

V. SCIENTIFIC EMPIRICISM AS A BEDROCK FOR GENOME EDITING JURISPRUDENCE

The pervasive reach of genome editing harbingers that the technology will continue to be a source of controversy in legal and policy arenas. Already, signs of impending controversy are coming into focus. However, the current legal landscape lacks a structural framework to systematically address questions of science in law. This Article proposes a normative framework to consolidate scientific empiricism and jurisprudence and argues that Myriad marks a turning point that facilitates the path to link these disciplines. The interdisciplinary approach set forth in this Article can be avidly applied to combat seeds of deceptive simplicity—namely, preposterous, impractical, or sensationalist claims that so often take root in dialogues concerning issues raised by technological advances.

This Article identifies the specter of “designer babies” as one of many quintessential examples of deceptive simplicity that law and policy makers should beware of as they deliberate on the future of genome editing. The doctrinal approach advocated here demonstrates

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Eukaryotes, 154 CELL 442 (2013) (introducing a platform to regulate transcriptional activation or repression in cells); Andrew A. Horwitz et al., Efficient Multiplexed Integration of Synergistic Alleles and Metabolic Pathways in Yeasts via CRISPR-Cas, 1 CELL SYS. 88 (2015) (explaining a technique to promote identification of biosynthetic pathways); Silvana Konermann et al., Optical Control of Mammalian Endogenous Transcription and Epigenetic States, 500 NATURE 472 (2013) (establishing a method for the optogenetic control of epigenetic chromatin modifications); Morgan L. Maeder et al., Targeted DNA Demethylation and Activation of Endogenous Genes Using Programmable TALE-TET1 Fusion Proteins, 31 NATURE BIOTECHNOLOGY 1137 (2013) (exploring targeted demethylation and its functional significance in cells); Lei S. Qi et al., Repurposing CRISPR as an RNA-Guided Platform for Sequence-Specific Control of Gene Expression, 152 CELL 1173 (2013) (introducing a platform to regulate transcriptional activation or repression in cells); Owen W. Ryan et al., Selection of Chromosomal DNA Libraries Using a Multiplex CRISPR System, 3 ELIFE 03703 (2014) (developing a CRISPR-based approach to facilitate directed evolution of biomolecules); Yuexin Zhou et al., High-Throughput Screening of a CRISPR/Cas9 Library for Functional Genomics in Human Cells, 509 NATURE 487 (2014) (unveiling a large-scale genetic library screen for functional genomics).

470. See, e.g., discussion supra notes 435–44 and accompanying text.
the efficacy of adopting a jurisprudence of scientific empiricism as a proverbial herbicide against rapidly spreading deceptive simplicity weeds. In addition, the Article reconsiders the illegitimacy of Buck v. Bell to argue that, contrary to the current prevailing wisdom, Buck relied not on false science, but on rampant deceptive simplicity instead.

A. The Exorcism of Designer Baby’s Specter

Nearly a quarter-century ago, advances in assisted reproductive technology pioneered the emergence of an unusual set of human pregnancies.471 Scientists had figured out an innovative approach to couple IVF and a novel way of screening fertilized embryos derived from couples at risk of transmitting genetic diseases to their offspring.472 The revolutionary method, called pre-implantation genetic diagnosis (PGD), involved screening for the presence of the Y chromosome in cells biopsied from fertilized embryos.473 Embryos carrying the Y chromosome are male and, thus, susceptible to inheriting recessive X-linked diseases such as X-linked mental retardation, Lesch-Nyhan syndrome, and DMD.474 PGD proved scientists could successfully screen embryos from these X-linked disease-carrier parents on the basis of gender and, consequently, it was presented as an alternative to abortion for couples whose only path to becoming parents to a healthy child had been to get pregnant, wait to find out the sex of the fetus—or do prenatal testing—and then decide to terminate the pregnancy if the fetus turned out to be genetically “defective” or male.475

It was not long before a debate on the social and ethical implications of PGD commenced. Some immediate concerns regarding PGD technologies initially focused on eliminating certain genetic

471. The first human pregnancies derived from this approach were reported in 1990. See A.H. Handyside et al., Pregnancies from Biopsied Human Preimplantation Embryos Sexed by Y-Specific DNA Amplification, 344 Nature 768, 768 (1990).
472. See id.
473. Id. at 769.
474. Id.; Whitney Akchurin & Ryan Kartzke, The Ethics of Gender Selection, in THE ETHICAL IMPERATIVE IN THE CONTEXT OF EVOLVING TECHNOLOGIES 33 (Dan McIntosh et al. eds., 1996), http://www.ethicapublishing.com/3CH2.htm [https://perma.cc/Z4U3-6NNM] (wildtype human embryos are diploid and inherit one sex-determining chromosome from each parent; embryos carrying X and Y chromosomes are male, while those carrying two sets of X chromosomes are female).
475. Handyside et al., supra note 471, at 768.
476. Id.
diseases, family balancing,\textsuperscript{477} and the prospect of gender
discrimination arising from embryonic sex selection,\textsuperscript{478} all of which
were actual considerations raised by the technology at the time.
However, other more dubious concerns—such as commercialization
of children, dehumanization of childbirth, and “playing
god”—piggybacked on the discussion.\textsuperscript{479}

Unfounded claims predicted the inevitable use of PGD to
essentially make people “smarter” or increase brain capacity,
“eventually lead[ing] to the entire human race becoming increasingly
intelligent.”\textsuperscript{480} Allegations that PGD was the first step in the creation
of a “designer baby” as a way to “use money and technology to fulfill
superficial desires” began to circulate.\textsuperscript{481} Alluring declarations that
parents could choose to endow their children with beautiful features
and athletic prowess became normalized.\textsuperscript{482} Soon thereafter, PGD
became associated with a radical expansion of the old eugenics
movement in which parents would be able to select offspring based on
non-pathological characteristics in a free-market form of eugenics.\textsuperscript{483}

These sensational perceptions of technological uses to create
designer babies who are genetically enhanced to be, \textit{inter alia}, “more
intelligent, athletic, musically talented, and the like”\textsuperscript{484} has become an
emblem of misinformation in areas of reproductive technology, and
now genome editing.\textsuperscript{485} Regardless of why some perpetuate the

\textsuperscript{477} Family balancing is a term for the use of PGD in families with one or more children
of one gender seeking to “balance” the offspring gender ratio by ensuring the next child is of the
opposite gender. See Akchurin & Kartzke, supra note 474, at 33.

\textsuperscript{478} See, e.g., Blake Rodgers & Brandon Peterson, \textit{The Ethics of Stem Cell Research and
Prenatal Genetic Alteration, in THE ETHICAL IMPERATIVE IN THE CONTEXT OF EVOLVING
TECHNOLOGIES} 47 (Dan McIntosh et al. eds., 1996), http://www.ethicapublishing.com/3CH3.htm
[https://perma.cc/D5ZU-XBJF]; Akchurin & Kartzke, supra note 474, at 32–33.

\textsuperscript{479} See, e.g., Rodgers & Peterson, supra note 478, at 46–48.

\textsuperscript{480} Id. at 48.

\textsuperscript{481} See, e.g., Akchurin & Kartzke, supra note 474, at 35.

\textsuperscript{482} Rodgers & Peterson, supra note 478, at 47.

\textsuperscript{483} See, e.g., David S. King, \textit{Preimplantation Genetic Diagnosis and the ‘New’ Eugenics,

\textsuperscript{484} Marcy Darnovskyfeb, \textit{Genetically Modified Babies, N.Y. TIMES}, Feb. 25, 2014, at
A25.

\textsuperscript{485} See, e.g., Michael D. Lemonick, \textit{Designer Babies, TIME MAG.}, Jan. 11, 1999, at 64
(arguing—back in 1999—that “[w]ithin a decade or two, it may be possible to screen kids . . . for
an enormous range of attributes, such as‘ height, body type, hair and eye color, intelligence,
personality type, etc.). Accord James Gallagher, \textit{Is It Time to Make Designer Babies?}, BBC NEWS
Antonio Michele Grygotis, \textit{Higher Level of Embryo Testing Raises Questions About Possibility of
Creating “Designer Babies”, TRANSPLANT NEWS, June 30, 2001, at 12; Rubanath Karuthedath,
Biotech Nightmare: Science Fiction Dystopian Visions of Human Genetic Engineering and
Cloning with Special Reference to the Boys from Brazil and Beggars in Spain, 2 RES. J. ENG.
LANGUAGE & LITERATURE} 1 (2014), http://www.rjelal.com/2.4.14/RUBANATH
designer baby canard—whether due to misinformation, intent to deceive, or a desire to sensationalize—the inherent inaccuracies they are promulgating have taken root in the culture and severely interfere with the ability to have a reasoned debate on true issues.

Consider a STAT-Harvard poll on public opinion of genetic editing, testing, and therapy published in early 2016.486 Results revealed that 83% of Americans believe modifying “unborn babies” to improve their “intelligence or physical characteristics” should be illegal.487 Likewise, 65% believe genetic modifications should be illegal even to reduce the risk of developing serious diseases.488

Polling, of course, is not quite a science and certainly is not an exact one. In fact, it is highly vulnerable to the use of specific terminology and ambiguity in framing the questions asked. For instance, there is likelihood of bias in the STAT-Harvard poll’s reference to “changing genes of unborn babies” as opposed to the more technically accurate terms “embryo,” “zygote,” or “germ cells (sperm and eggs),” particularly given the respondents’ probable lack of knowledge that genome editing in a fetus or near full-term baby is not likely to be a viable option. Other polls over the years reflect similar views regarding genetic enhancement to boost intelligence or athletic ability of “designer babies,” but conflict with the STAT-Harvard poll.


487. Id. at 13.

488. Id.

489. Id. (emphasis added).

490. See, e.g., United Kingdom: Reproductive and Research Cloning, Genetic Modification and Selection, Sex Selection, YouGov 6 (Aug. 19, 2005) [hereinafter U.K. Poll], http://iis.yougov.co.uk/extranets ygarchives/content/pdf/TEL050101042_1.pdf (reporting that only 4% of total respondents approve of using genetic modification to improve a child’s academic or sporting abilities); VCU Life Sciences Survey: Public Values Science but Concerned About Biotechnology, VCU CTR. PUB. POL’Y 4, 10 (2003), http://lifesciences.vcu.edu/media/life-sciences/docs/survey2003.pdf (94% of respondents opined that “changing a baby’s characteristics for cosmetic purposes such as eye or hair color . . . is taking medical advances too far”).
in regard to the legality of using genetic modifications to prevent or reduce the risk of serious diseases in offspring or embryos.\footnote{491} Yet, nothing in these observations detracts from the surprising revelation that, according to this poll, a majority of Americans apparently believe that genome modifications can actually be used for altering inherently polygenic—determined by more than one gene—traits such as intelligence, eye color, athletic ability, and beauty—many of which are intrinsically subjective.

Indeed, even discounting the bias in the premise of the poll questions, namely, that the potential for improving intelligence, athletic ability, or appearance is true, the data suggest that the public is largely unaware of what is technologically feasible or not. More importantly, the poll results suggest that the general population cannot recognize, and is highly susceptible to, technological deceptive simplicity.

Contemplate the claim that genetic modifications can be used to create a superhuman race of geniuses. This claim was precisely the subject matter of an article with a cheeky headline\footnote{492} featured in a popular magazine\footnote{493} pseudo-reporting on BGI,\footnote{494} a Chinese

\footnote{491. Biotechnology Australia, Increasing Public Support for Stem Cell Research 1–2 (July 7, 2003), http://www.geneticsandsociety.org/downloads/20030707_Biotechnology_Australia.pdf [https://perma.cc/HZ65-96UX] (reporting 61% support for genetic testing of unborn children and 79% support for gene therapy to correct any genetic disorders that may be diagnosed); Antonio Regalado, Patients Favor Changing the Genes of the Next Generation with CRISPR, MIT TECH. REV. (Dec. 2, 2015), https://www.technologyreview.com/s/644141/patients-favor-changing-the-genes-of-the-next-generation-with-crispr/ [https://perma.cc/U7LB-FQ3Y]; U.K. Poll, supra note 490, at 6 (noting that 57% and 43% of respondents approve using genetic modifications to “prevent children from suffering serious genetic diseases” or to reduce the risk of developing diseases such as cancer, Alzheimer’s disease, and heart disease, respectively); see also id. (reporting that 51% of respondents believe that it should be legal for parents and doctors to “carry out genetic tests on embryos created during IVF treatment in order to select those with the lowest chances of developing [serious] diseases . . . later in life,” while only 30% believe that such testing should be illegal).

\footnote{492. The article appears in Vice Magazine. It features a picture of school-age Chinese children lined up in a formation that stretches as far as the camera lens can capture and gives the appearance that China is trying to build an army of homogeneous, little human robots. Aleks Eror, China Is Engineering Genius Babies, VICE MAG. (Mar. 15, 2013), http://www.vice.com/read/chinas-taking-over-the-world-with-a-massive-genetic-engineering-program [https://perma.cc/4BSB-5Z7S].

biotechnology firm partly funded by the Chinese government, and its Cognitive Genomics Research (CGR) project. According to BGI, the goal of the CGR branch is to study human cognition and use next-generation DNA sequencing technologies to interrogate the relationships between genes, the environment, and cognitive ability in the human brain.

Although BGI's Gene-Trait Association Study of Intelligence may arguably suffer from cohort methodological flaws related to recruitment of “cognitively gifted” volunteer subjects who meet peculiar—to say the least—qualifying criteria, BGI's approach to human cognition research appears to have nothing in common with the bombastic claims made against it. Furthermore, over the past fifteen years, some BGI-sponsored research has been featured in many of the most prominent scientific journals. There is simply no evidence to suggest that the Chinese government is trying, or even would be able, to create an army of geniuses born out of basic research into human cognition. But that has not prevented the dissemination of misinformation, which is eagerly picked up by diverse media and spreads like wildfire in a dry deciduous forest.
Even more disheartening is the fact that this kind of deceptive simplicity surrounding designer babies has permeated scholarly fields,\textsuperscript{501} including legal scholarship.\textsuperscript{502} Much ink has been spilled entertaining hypotheticals of “made-to-order boutique babies”\textsuperscript{503} to genetically modify traits such as eye, hair, and skin color,\textsuperscript{504} or even more subjective ones like sexual orientation,\textsuperscript{505} beauty, charm, and intelligence.\textsuperscript{506} Such world of “designer genes” would purportedly give parents a menu of choices “from any genes imaginable, human or not.”\textsuperscript{507} It is time to adhere to higher standards in this regard.

\begin{itemize}
  \item \textsuperscript{501} See, e.g., supra notes 479–83 and accompanying text.
  \item \textsuperscript{502} See discussion infra notes 503–07.
  \item \textsuperscript{503} Peter H. Huang, \textit{Herd Behavior in Designer Genes}, 34 WAKE FOREST L. REV. 639, 659 (1999).
  \item \textsuperscript{504} See, e.g., id. at 642 (arguing that in the near future, genetic selection of hair color, skin color, intellectual ability, or behavior pre-dispositions may be feasible); Mahoney, supra note 47, at 313 (proposing that new technology may presumably allow parents to decide eye color and sexual orientation of designed babies).
  \item \textsuperscript{505} Mahoney, supra note 47, at 313.
  \item \textsuperscript{506} See, e.g., Jason T. Corsover, \textit{The Logical Next Step? An International Perspective on the Issues of Human Cloning and Genetic Technology}, 4 ILSA J. INT’L & COMP. L. 697, 744 (1998) (“One can imagine menus offering a price list of particularly desirable traits. . . . For the right price, one may have the option to purchase the DNA of a world class athlete, award winning actor, or a beautiful supermodel.”); Sarah M. Markwood, \textit{Comment, Creating a Perfect Human Is Not So Perfect: The Case for Restricting Genetic Enhancement Research}, 110 PENN. ST. L. REV. 473, 473–74 (2005) (proposing a scenario where genetic enhancement will lead to producing “athletically gifted,” “physically attractive” children, or “a theatrical prodigy, a strong wrestling champion, or a mathematical genius”); Maxwell J. Mehlman, \textit{The Law of Above Averages: Leveling the New Genetic Enhancement Playing Field}, 85 IOWA L. REV. 517, 528–29 (2000) (entertaining the possibility that new technologies may allow genetic manipulation of traits such as beauty, strength, stamina, charm, cheerfulness, confidence, memory, intelligence, and creativity); Daniel L. Tobey, \textit{What’s Really Wrong with Genetic Enhancement: A Second Look at Our Posthuman Future}, 6 YALE J.L. & TECH. 54, 56 n.1 (2003) (asserting that “[g]enetic enhancement will, in the short run, be more concerned with improving present traits such as intelligence, personality, and strength”); Lindsey A. Vaccaro, \textit{Comment, Preimplantation Genetic Diagnosis: From Preventing Genetic Disease to Customizing Children. Can the Technology Be Regulated Based on the Parents’ Intent?}, 49 ST. LOUIS U. L.J. 1181, 1183 (2005) (stating a scenario where PGD will be used “to select for traits such as intelligence, athletic ability, or musical inclination”).
  \item \textsuperscript{507} Huang, supra note 503, at 658 (emphasis added).
\end{itemize}
B. Dispelling the Myth of IQ Heritability—A Case Study

The source of human intelligence and cognition has been the subject of study for well over a century. Francis Galton first proposed in the 1860s that genius and mental ability are as heritable as physical traits. Evidence to support his thesis consisted of "showing how large is the number of instances in which men who are more or less illustrious have eminent kinsfolk." The "laws" of heredity with respect to genius were thus initially laid out by surveying men of high reputation—judges of England, statesmen, literary men, men of science, poets, musicians, etc.—within hierarchies.

From the start, this field was destined for controversy and prone to racial animus masquerading as science. The founding father of the field sponsored racial hierarchies, affirmed the superiority of the ancient Greek race, and professed "the average intellectual standard of the negro race is some two grades below [his] own." Galton's vitriol had few limits. He even expressed that he often felt ashamed of being human when flagrantly pondering about the "idiocy among the negroes." Galton's ideology cemented racial contempt into the foundation of the pseudoscience surrounding hereditable human intelligence and mental cognitive ability.

General cognitive ability (GCA), also known as general intelligence, or g, was first formally introduced in 1904. Research on familial and twin studies in the early twentieth century


510. Id. at 6.
511. See id. at 2.
512. Id. at 338, 340.
513. Id. at 339.
515. See, e.g., HENRY HERBERT GODDARD, FEEBLE-MINDEDNESS: ITS CAUSES AND CONSEQUENCES vii (1914); HENRY HERBERT GODDARD, THE KALLIKAK FAMILY: A STUDY IN THE
cemented the notion of the heritability of intelligence. Adoption studies contributed a layer of complexity by concluding that the environment has some considerable effect on a child’s intelligence quotient (IQ). Current estimates of g heritability attributed to genetic factors ranges from 0.5 to 0.7 and to as high as 0.8. Studies over decades have consistently shown that g is a highly heritable trait. Although the extent of the range of g heritability estimates has been contested, the bulk of literature demonstrates that g is at least reasonably heritable.

Empirical evidence for g heritability provided by quantitative genetics highlights the issue of whether there are specific genes and Single Nucleotide Polymorphisms (SNPs)—variations in single nucleotides at specific positions in the genome—responsible for intelligence and GCA. Thanks to the advent of DNA sequencing technology in the twenty-first century, attempts to identify the “intelligence” gene(s) at the molecular level are underway. The search, however, has proved the gene(s) to be incredibly elusive.

To date, several Genome-Wide Association Studies (GWAS) have interrogated potential connections between various SNPs and g. For instance, a GWAS of intelligence in middle to older adulthood probing nearly 600,000 SNPs in approximately 3,500 individuals found no specific genetic variants robustly associated with human intelligence.
intelligence. Although a prior published gene-based test for association had found one genome-wide significant association with the gene FNBP1L, which is highly expressed in neurons in developing brains, the GWAS failed to replicate that result using an independent sample.

Members of the same team followed up with another GWAS, this time focusing on childhood intelligence from nearly 18,000 individuals (ages six to eighteen) in six discovery and three replication samples. Again, the study failed to identify individual SNPs associated with childhood intelligence. Gene-based analysis revealed that SNP rs236330, located in FNBP1L, was strongly associated with childhood intelligence. Yet, not even this SNP could explain more than 0.24% of the total phenotypic variation, suggesting that the largest effects of such SNPs are so minuscule that other smaller-effect SNPs are virtually undetectable. Both studies concluded that intelligence is highly heritable and polygenic, yet GWAS results are consistent with a model of intelligence under which many genetic variants have very small additive effects.

A little over one year ago, an independent group attempted to replicate the findings related to general cognitive ability and FNBP1L via a more robust method (GWAS Plus) using nearly 2.6 million SNPs. Results could not corroborate the aforementioned findings and no gene reached statistical genome-wide significance using the same methodology of the prior report. Polygenic scores from all SNPs considered could not even account for 1% of the total variance (0.7%).

524. G. Davies et al., Genome-Wide Association Studies Establish That Human Intelligence Is Highly Heritable and Polygenic, 16 MOLECULAR PSYCHIATRY 996, 1001 (2011).
525. Id. at 999 (citing Jimmy Z. Liu et al., A Versatile Gene-Based Test for Genome-Wide Association Studies, 87 AM. J. HUM. GENETICS 139 (2010)).
526. Id.
527. B. Benyamin et al., Childhood Intelligence Is Heritable, Highly Polygenic and Associated with FNBP1L, 19 MOLECULAR PSYCHIATRY 253 (2014).
528. Id. at 257.
529. See id. at supp. fig. 6, https://genepi.qimr.edu.au/contents/p/staff/BENYAMIN_FNPB1L_MOLPSYCH_OSI.pdf [https://perma.cc/QF6H-DYPZ].
530. Id. at 255.
531. Id.
533. Id. at 10.
534. Id.
A recent GWAS meta-analysis of more than 125,000 individuals identified ten SNPs associated with increased educational attainment, three of which had genome-wide significant associations. However, the contribution of each genetic locus was incredibly small and the largest estimated effect was 0.02% of the variance. The findings hint that the genetic basis of complex behavioral phenotypes—e.g., intelligence—is far more diffuse than that of complex physical traits. Three additional SNPs spanning genomic regions across the KNCMA1, NRXN1, POU2F3, and SCRT genes—all predicted to be involved in the glutamate neurotransmission pathway and synaptic plasticity—were identified in a subsequent publication using an alternate method. These SNPs were statistically associated with cognitive performance in the cohort, but like other preceding reports, the estimated effect for each SNP was negligible (0.02%).

The heritability of fluid general cognitive function in middle and older age was studied in a large meta-analysis GWAS of nearly 2.5 million SNPs in approximately 54,000 individuals. Genomewide significant SNP associations were identified in three genomic regions comprising thirteen SNP variants, associated with, inter alia, MIR2113, AKAP6, NPAS3, TOMM40, and APOE. Gene-based tests of association yielded one genome-wide significant result for HMGN1, a gene that has been linked to some neurodevelopmental disorders. Together, all SNPs identified barely accounted for 1% of the total variance, corroborating the conclusion that general cognitive function is heritable and highly polygenic as others have shown before.

Conflicting research and the manifest failure to reproduce GWAS results connecting specific genes with human cognition have prompted some scientists to call into question the validity of nearly a decade’s worth of research. For instance, a study published in 2012...
sought to replicate findings related to a dozen other genes reported to be associated with $g$.\footnote{Christopher F. Chabris et al., \textit{Most Reported Genetic Associations with General Intelligence Are Probably False Positives}, 23 PSYCHOL. SCI. 1314 (2012).} Using data sets from three large, independent, and well-characterized longitudinal studies, the group found only one SNP associated with $g$ that was nominally significant, despite expectations of finding ten to fifteen significant associations.\footnote{Id. at 1319.}

The failure to identify unequivocal correlations prompted the group to conclude that most reported genetic associations with GCA are likely false positives.\footnote{Id. at 1314.}

Given the existing body of literature in quantitative and molecular genetics concerning $g$, it is not surprising that, to date, "[n]o single SNP has yet been replicably associated with human intelligence at genome-wide significance levels."\footnote{Kirkpatrick et al., \textit{supra} note 532, at 10.} Although there is consensus regarding the heritability of $g$, the hunt for the "intelligence gene(s)" has largely proved to be an exercise in futility.

The molecular underpinnings of intelligence may ultimately be a question that science will wrestle with for some time. The genetics-based view that mere SNPs account for highly complex and polygenic traits such as intelligence may very well be a gross underestimation of the unknown truth. The missing heritability of intelligence may be due to uncommon polymorphisms our current technologies cannot detect or Copy Number Variations (CNVs)—deletions or duplications of large sections of DNA.\footnote{Id. at 11.} In other words, entire sections of DNA, as opposed to SNPs, could be responsible for a large proportion of human genetic variation.\footnote{See Andrew T.M. Bagshaw et al., \textit{No Effect of Genome-Wide Copy Number Variation on Measures of Intelligence in a New Zealand Birth Cohort}, 8 PLOS ONE e55208 (2013).}

On this point, several CNV regions have been shown to carry genes related to development and cognitive ability.\footnote{Id. (citations omitted).}

Alternatively, the basis for intelligence may rest in epigenetic mechanisms. In contrast to genetics, which focus on the four nucleotides (A, C, G, T) of the DNA alphabet, epigenetics is far more complex in nature.\footnote{See Enriquez, \textit{supra} note 465, at 471, 483.} Epigenetic mechanisms are capable of altering gene expression without ever changing DNA sequences and comprise post-translational modifications of histones and other proteins.\footnote{See, e.g., Andre Fischer et al., \textit{Recovery of Learning and Memory Is Associated with Chromatin Remodelling}, 447 NATURE 178 (2007) (studying the role of histone acetylation and chromatin remodeling on learning and memory access).}

\footnote{544. Christopher F. Chabris et al., \textit{Most Reported Genetic Associations with General Intelligence Are Probably False Positives}, 23 PSYCHOL. SCI. 1314 (2012).} \footnote{545. \textit{Id.} at 1319.} \footnote{546. \textit{Id.} at 1314.} \footnote{547. Kirkpatrick et al., \textit{supra} note 532, at 10.} \footnote{548. \textit{Id.} at 11.} \footnote{549. See Andrew T.M. Bagshaw et al., \textit{No Effect of Genome-Wide Copy Number Variation on Measures of Intelligence in a New Zealand Birth Cohort}, 8 PLOS ONE e55208 (2013).} \footnote{550. \textit{Id.} (citations omitted).} \footnote{551. See Enriquez, \textit{supra} note 465, at 471, 483.} \footnote{552. See, e.g., Andre Fischer et al., \textit{Recovery of Learning and Memory Is Associated with Chromatin Remodelling}, 447 NATURE 178 (2007) (studying the role of histone acetylation and chromatin remodeling on learning and memory access).}
DNA modifications—e.g., methylation—and regulatory RNA molecules. Collectively, these epigenetic processes add an incredible degree of complexity to gene regulation that takes into consideration dietary, nutritional, social, cultural, pharmacological, and environmental exposures.

Yet another basis for heritability could rest on principles of pleiotropy—one gene affects many traits—and epistasis—one gene affects expression of one or more genes. An article published recently performed a systems-level analysis of genome-wide expression data to reveal the existence of conserved gene-regulatory networks enriched with genetic variants linked to human cognitive abilities. One such network comprises up to 150 genes with tight coexpression relationships. It may be the case that hundreds or thousands of genes clustered into networks contribute to genetic associations and heritability of $g$. It has been proposed that human intelligence is not unitary, but rather rises from multiple cognitive components organized into functionally specialized brain networks.

As detailed in this Section, the potential complexity for highly polygenic traits such as intelligence is remarkable. The take-home message is that deceptively simplistic notions of "gene X is responsible for trait Y" breed mass misperceptions about the role genetic associations play in trait formation and development. In the case of genome editing, one common "concern" advanced by some is that genome editing technologies are inherently insidious because they will eventually lead to creation of "designer babies" with a panoply of artificial traits; high intelligence is purportedly one of them. However, as documented in this Section, anyone who claims that technology is at the verge of enabling the creation of genius designer babies has simply fallen prey to, or wishes to distract others with, deceptive simplicity.

This Section used intelligence as a model for confronting deceptive simplicity. However, the same principles apply to other

553. See, e.g., Swati Gupta et al., Histone Methylation Regulates Memory Formation, 30 J. NEUROSCIENCE 3589 (2010) (investigating the role of the H3K4me3 epigenetic mark in memory formation).
554. See Enriquez, supra note 465, at 471.
555. See id.
557. Id.
558. Adam Hampshire et al., Fractionating Human Intelligence, 76 NEURON 1225, 1233 (2012).
559. See, e.g., discussion supra note 506 and accompanying text.
designer baby polygenic traits, such as height. Simply put, human knowledge is vastly incomplete concerning the genetics of these complex polygenic traits. And the lack of knowledge does not justify entertaining far-fetched hypotheticals in legal scholarship. It is imperative that future scholars inform themselves about the scientific matters on which they choose to comment. Scholarly standards ought to be higher. Deceptive simplicity may appear benign at first glance, but, as the next Section demonstrates, misinterpreting science and spreading misinformation can lead to catastrophic societal consequences.

C. Buck v. Bell—The Prototypical Fruit of Deceptive Simplicity

Buck v. Bell is among the most horrid illustrations of deceptive simplicity in the exercise of American jurisprudence. In a surreal series of events, government-sanctioned sterilization arrived at the most powerful court in the world: the US Supreme Court. It made its case before learned judges and came out victorious without a single word in opposition. A near unanimous Court upheld—eight to one—the constitutionality of a Virginia statute that legalized the involuntary sterilization of individuals deemed “mental defectives” in state institutions, provided it was in “the best interest of the patients and of society.”

Writing for the Court, Oliver Wendell Holmes, Jr. infamously memorialized what is arguably among the most incendiary and ignorant language ever published in the United States Reports. “It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind . . . Three generations of imbeciles are enough.”

The question presented in Buck was whether a statute authorizing compulsory sterilization of the “feeble-minded” violated the Due Process and Equal Protection clauses of the Fourteenth

560. At least 180 genetic variants have been reported to influence height in humans. Hana Lango Allen et al., Hundreds of Variants Clustered in Genomic Loci and Biological Pathways Affect Human Height, 467 NATURE 832 (2010). Thus, it is preposterous to claim that, at this time or any time in the near future, genome editing technologies will allow humans to engineer a world-class basketball player in a petri dish. See, e.g., Corsover, supra note 506, at 744.


562. Justice Pierce Butler dissented from the Court’s decision, but filed no opinion of his own. Id. at 200, 208.

563. Id. at 205–06.

564. Id. at 207 (emphasis added) (internal citation omitted).
Amendment. The Court belabored—in one-third of its nearly three-page decision—the argument that Carrie Buck had sufficient procedural Due Process at law. Yet, the Court virtually ignored the Equal Protection challenge, ridiculing it as a desperate “last resort” argument for defending individual rights.

The entirety of the opinion cited no constitutional authorities, save for Jacobson v. Massachusetts, an inapposite case that sanctioned the exercise of State police powers to authorize compulsory vaccination statutes. At the same time, the Court ignored a series of State cases dealing squarely with the Equal Protection question. Applying a primitive form of modern rational basis review, the Court determined the State had a legitimate legal and policy justification to sterilize Buck and promote the welfare of society by severing her fallopian tubes. Notably, the decision did not examine any scientific evidence to support its assertion that mental deficiencies are congenital.

Appellant Carrie Elizabeth Buck, a teenager who had been raped and institutionalized was characterized by the Court as “a feeble-minded white woman . . . daughter of a feeble-minded mother . . . , and the mother of an illegitimate feeble-minded child.” Reporters and scholars who met Buck before her death in 1983 all agreed that she was not “feeble-minded” as the Court had stated, but appeared to be a woman of normal intelligence. Furthermore, research revealed that Vivian, Buck’s daughter who lived until the age of eight, had been an average student in school and was not mentally disabled. Some have argued that the case itself was fraudulently pursued. In any event, one can hardly disagree with the view that what was done to Carrie Buck was gravely unjust and remains a stark blemish on American law.

565. Id. at 205.
566. Id. at 206–07.
567. Id. at 208.
568. Id. at 207 (citing Jacobson v. Massachusetts, 197 U.S. 11 (1905)).
569. See id. at 200; see also Haynes v. Lapeer, 166 N.W. 938, 939, 941 (Mich. 1918) (declaring Michigan’s sterilization law unconstitutional); Smith v. Bd. of Exam’rs of Feeble-Minded, 88 A. 963, 964, 967 (N.J. 1913) (striking, on Equal Protection grounds, New Jersey’s sterilization law); Davis v. Berry, 216 F. 414, 418 (S.D. Ia. 1914) (prohibiting the enforcement of vasectomies for criminals twice convicted of a felony in Iowa).
570. Buck, 274 U.S. at 205.
572. Buck, 274 U.S. at 207.
573. See Gould, supra note 50, at 331, 336.
574. Id. at 337–38.
575. LOMBARDO, supra note 571, at 154–55.
Many have chronicled the history and legal implications of *Buck* in books and legal scholarship. Consequently, this Article will not belabor and rehash what has already been said about the case. The conventional view is that *Buck*’s holding is illegitimate because it rests on false science and incorrect moral and ethical principles. This Article rejects that conventional view and instead contends that *Buck* is not the result of false science, but instead of deceptive simplicity. In fact, as this Article argues below, *Buck*’s ruling is grounded more on deceptive simplicity than on the “science” of the time, which was greatly void of empiricism, reproducibility, adequate statistical methodology, and did not even come close to establishing the heredity and genetic contributions of intelligence.

To support this proposition, consider first and foremost the substantively porous decision published by the Court. Holmes cited not a single scientific source for the Court’s lending of credence to the precarious notion that “heredity plays an important part in the transmission of insanity, imbecility, etc.” In fact, the Court was blatantly clear that its decision relied on “general declarations of the Legislature” and “experience” showing the heritability of traits related to cognitive deficiencies. The “experience” Holmes referred to was quite probably the direct derivation of Galton’s showing numerous instances in which illustrious men engender illustrious kindred.

576. For a good, detailed historical account of the events leading up to the Supreme Court litigation and the decision’s aftermath, see *id.* at 149–55.


579. See, e.g., Lombardo, *supra* note 577, at 69 n.84, 69 n.85, 70–71 n.90 (citing Res. 247, 149th Gen. Assem., Reg. Sess. (Ga. 2007), which referred to the “so-called science of eugenics” as a “pseudo-scientific movement”); Nourse, *supra* note 50, at 107 (arguing *Buck* is not part of constitutional law curricula partly because it “is seen as a case about a false science”).


582. *Id.* at 207.

583. *Id.* at 206.

science. Instead, it wholly deferred to the Legislature and treated the heredity of insanity and imbecility as a foregone conclusion.

Consequently, the notion that Buck’s holding was based on false science rests on an analytically precarious foundation. Simply put, Buck relied on no science at all.

The case epitomizes an instance where the Supreme Court allowed a State’s erroneous scientific assertions to go unchallenged and ruled on the basis of those faulty assertions. Although the Court is not required to cross-examine every statement made by a legislative branch before properly ruling on a given issue, it ought to consider, at the very least, whether “general declarations” and “anecdotal experience” constitute unequivocal evidence that withstands constitutional scrutiny. Such analysis is imperative, more so in cases where fundamental rights may be curtailed. In light of its blank endorsement of compulsory sexual sterilization for mentally defective and undesirable individuals—all justified by public welfare pretenses—the Buck Court might as well have been acting as a lifeless extension of a State’s legislative branch.

Had the Court bothered to critically examine and analyze the state of the science, it would have discovered that, contrary to popular belief at the time, heredity’s role in cognition and other traits was highly inconclusive, contentious, and likely supported by flawed methods. On this point, perhaps one of the most prominent examples was the discovery of inheritance-independent genetic mutations by Thomas H. Morgan, the late Nobel Laureate, in 1910. Morgan observed that one white-eyed fruit fly had inexplicably appeared from a contained stock of wildtype red-eyed flies in his laboratory. The implications of this realization were that certain traits are not merely inherited, but rather appear spontaneously as a result of mechanisms—e.g., mutations—other than Mendelian genetics.

Morgan’s observation and subsequent experiments using the white-eyed mutant fly provided the foundations for the establishment of the modern theory of the gene, which expanded and challenged the simple model of Mendelian inheritance established at the turn of the twentieth century.

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587. Morgan, supra note 585, at 120.
588. Mendel’s theory of inheritance was derived from his experiments of pea plants that displayed only one physical trait—e.g., seed color (green or yellow), plant height (tall or short), etc. Mendel challenged the existing view that all offspring were a combination of parental traits
Morgan, who initially supported but later renounced the eugenics movement after uncovering empirical scientific truth through his research, eloquently presented the problem of the modern interpretation of Mendelian inheritance when he stated:

[F]acts are being transformed into factors at a rapid rate.... The superior jugglery sometimes necessary to account for the result, may blind us, if taken too naively, to the common-place that the results are often so excellently "explained" because the explanation was invented to explain them. We work backwards from the facts to the factors, and then, presto! explain the facts by the very factors that we invented to account for them ... yet I cannot but fear that we are rapidly developing a sort of Mendelian ritual by which to explain the extraordinary facts of alternative inheritance.... [I]t is only fair to state that those who are doing the actual work of progress along Mendelian lines are aware of the hypothetical nature of the factor-assumption. But those who know the results at second hand and hear the explanations given, almost invariably in terms of factors, are likely to exaggerate the importance of the interpretations and to minimize the importance of the facts.

In time, others too began to publicly oppose eugenics along with its racist and classist undertones as a pseudoscience. However, despite the shouts of a few dissenting voices, eugenics became deeply rooted in American culture, garnering support from elites, scholars, and several institutions, including the Supreme Court. Between 1907, when the first sterilization statute passed in Indiana, and 1930, a total of twenty-three states had enacted

blended together. Among his scientific contributions are the laws of allele segregation and independent assortment. See generally Mendel, supra note 58, at 1–2, 4.


592. Francis Galton was Charles Darwin's half-cousin and is considered to be the father of eugenics. See LOMBARDO, supra note 571, at 7. He defined eugenics as "the science of improving stock ... which, especially in the case of man, takes cognisance of all influences that tend ... to give to the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable." FRANCIS GALTON, INQUIRY INTO HUMAN FACULTY AND ITS DEVELOPMENT 17 n.1 (1883) (internal citation omitted).

593. See PAUL POPENOE, APPLIED EUGENICS 15–16 (1918) ("The distinguished father is likely to have a distinguished son, while the son of two 'nobodies' has a very small chance of becoming distinguished. ... [T]he son of a distinguished judge has about one chance in four of becoming himself distinguished, while the son of a man picked out at random from the population has about one chance in 4,000.").

594. See, e.g., LOMBARDO, supra note 571, at 155–56 (describing views from a Harvey Wickham book, critical of outdated Mendelian inheritance, that was published just before the announcement of the Buck decision).

eugenical sterilization laws.\footnote{596} By 1933, four years after \textit{Buck}, twenty-two states introduced new sterilization laws.\footnote{597} During the span of seven decades (1907–1979), a total of more than 65,000 sterilizations in thirty-two states took place in the United States.\footnote{598}

Morgan’s conceptualization of second-hand explanations that lead to exaggeration, oversimplification, and a poor understanding of scientific progress is precisely the deleterious essence of deceptive simplicity, which is broader and more damaging than mere pseudoscience.

The distinction is crucial. Whereas false, or pseudo, science refers to a system of theories and rules configured to give the appearance of being grounded in scientific methodology,\footnote{599} deceptive simplicity dangles from vague intuition derived from reductive explanations that strip logic beyond a bare minimum.

Accordingly, Galton’s elaborate, hyperbolic, cognitive hereditability theses and explanations, which worked backwards “from the facts to the factors,” were so “excellently explained”\footnote{600} because he created a counterfeit theoretical basis to support his unscrupulous racist ideology. It was false science. In contrast, Holmes’ opinion in \textit{Buck} did not even attempt to embellish its reasoning with false science. \textit{Buck} institutionalized compulsory sterilization using vague intuition born out of second-, third-, and fourth-hand reductive explanations that diminished heredity to a deceptively simple catchphrase \textit{popularized by} false science: imbecility is a heritable disease. Consequently, \textit{Buck} embodies a conclusory ruling bereft of legal or scientific reasoning. It was deceptive simplicity, bred to be more dangerous than false science. Indeed, the Nazi party relied on \textit{Buck} and its deceptive simplicity to legitimize its eugenic agenda.\footnote{601}

Pseudo-intellectual hogwash became the deceptive simplicity that propelled, maintained, and expanded the eugenics agenda. The

\begin{footnotes}
\footnotetext[596]{HARRY H. LAUGHLIN, THE LEGAL STATUS OF EUGENICAL STERILIZATION 7, 57 (1930).}
\footnotetext[597]{Nourse, supra note 50, at 103 n.18 (quoting VICTORIA F. NOURSE, IN RECKLESS HANDS: SKINNER V. OKLAHOMA AND THE NEAR TRIUMPH OF AMERICAN EUGENICS 24 (2008)).}
\footnotetext[598]{LOMBARDO, supra note 571, at xiii, 294 app. C.}
\footnotetext[600]{Morgan, supra note 591, at 365.}
\footnotetext[601]{See, e.g., TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS VOL. IV 1158–59 (1950) (publishing an extract from a document entered on behalf of Otto Hofmann, a high ranking SS officer and key contributor to Nazi Germany’s eugenics laws, citing \textit{Buck} v. \textit{Bell}, 274 U.S. 200 (1927) to establish that Nazi eugenic practices during World War II were derived from race protection laws in other European countries and the United States).}
\end{footnotes}
historical account is crystal clear: *Buck* did not rely on false science; it was the product of pervasive deceptive simplicity concerning a rationale for the heritability of human cognitive abilities and mental deficiencies. No legitimate scientific debate existed regarding the simplistic pre-twentieth century view of Mendelian inheritance adopted by the Court in 1927.

At the time *Buck* made its way into the Supreme Court, eugenics was not a real scientific movement but rather a reductive political and social fad that fed off of outdated scientific theories, misinformation, and gossip. The propaganda had been de facto codified into popular culture by deceptive merchants with ulterior motives and dangerous agendas. And Justices of the US Supreme Court, despite all their education and intellect, proved to be highly susceptible to it.

Given the fact that *Buck* lacked any constitutional or scientific support for its holding and came thickly veiled with deceptive simplicity, the decision amounts to no more than institutionalized legal quackery built upon social and scientific quackery.

**D. Forging a Path Forward**

This Article's genome editing primer coupled with the proposed normative legal framework makes the case that a jurisprudence of scientific empiricism is the best available weapon against the deleterious harms of deceptive simplicity. Judicial review is in dire need of structure when addressing questions of science in law.

One promising sign that the Supreme Court is open to adopting a jurisprudence of scientific empiricism is the 2013 decision in *Myriad*. The case contemplated whether isolated DNA segments

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602. For instance, during the 1920s, only approximately 10 percent of members of the Advisory Council of the American Eugenics Society were trained geneticists. Cynkar, *supra* note 577, at 1426.

603. *See discussion supra* notes 565–70 and accompanying text.


605. In *Myriad*, the Supreme Court considered the patentability of two types of DNA molecules: DNA fragments isolated from naturally occurring genomic DNA and complementary DNA (cDNA). The Court held that genic sequences isolated from genomic DNA were not patent eligible under section 101 because they are products of nature. *Id.* at 2120. In contrast, the Court held that cDNA was patent eligible under section 101 because it is "not naturally occurring." *Id.* at 2119. The decision to distinguish between these types of DNA molecules raises some uncertainty about the patent eligibility of other types of DNA molecules under section 101, many of which are used in biotechnological research. See *id.* at 2120 (withholding judgment on the applicability of section 101 to DNA in which the order of the naturally occurring nucleotides has been altered because it "presents a different inquiry").
from naturally occurring genes are patent eligible under 35 U.S.C. § 101.\footnote{Id. at 2111.} Justice Thomas prefaced the Court’s unanimous opinion with a foundation of genetic concepts relevant to the question presented.\footnote{Id. at 2111–12.} Despite some inaccuracies related to protein synthesis,\footnote{“Sequences of DNA nucleotides contain the information necessary to create strings of amino acids, which in turn are used in the body to build proteins.” Id. at 2111. This statement is incorrect because amino acid “strings” are not used in the body to build proteins. Amino acid “strings” are the proteins themselves in an unfolded state. As ribosomes synthesize polypeptide chains (“strings”), a series of intermolecular forces—ionic interactions, hydrophobic effect, hydrogen bonding, and others—begin the process of protein folding. Thus, the strings of amino acids fold into proteins. Proteins can come together to form (“build”) complexes. Protein Structure Jmol: Primary Structure, CTR. BIOMOLECULAR MODELING, http://cbm.msoe.edu/includes/modules/jmolProteinStructure/primarystructure.html [https://perma.cc/6U5-K62V] (last visited Feb. 15, 2017). Alternatively, the Court could have been referring to messenger RNA (mRNA) molecules, which are used by the ribosomes as templates to create (“build”) the strings of amino acids. CHRIS R. CALLADINE ET AL., UNDERSTANDING DNA: THE MOLECULE AND HOW IT WORKS 14 (3rd ed. 2004).} RNA processing,\footnote{“Transcription results in a single strand RNA molecule, known as pre-RNA.” Myriad, 133 S. Ct. at 2111. This statement refers to the transcription of DNA into primary transcripts—a single stranded RNA molecule that has not been processed. Suzanne Clancy, DNA Transcription, 1 NATURE EDUC. 41 (2008). A primary transcript is later processed to yield various forms of RNA molecules—e.g., mRNAs, piRNAs, miRNAs, tRNAs, IncRNAs, rRNAs, etc. Anita Quintal Gomes et al., Non-Coding RNAs: Multi-Tasking Molecules in the Cell, 14 INT’L J. MOLECULAR SCI. 16010 (2013). The Court may have been referring to mRNA processing, in which a pre-mRNA (not pre-RNA) molecule undergoes processing to become a mature mRNA. Introducing mRNA Processing, VIRTUAL CELL ANIMATION COLLECTION, http://vcell.ndsu.edu/animations/mrnaprocessing/index.htm [https://perma.cc/7FGX-T9GW] (last visited Feb. 15, 2017).} and DNA non-coding regions,\footnote{“Nucleotides that do not code for amino acids ... are known as ‘introns.” Myriad, 133 S. Ct. at 2111. This statement is factually inaccurate because many non-coding nucleotides exist in promoter, enhancer, silencer, and other regulatory regions of the genome that are not introns. The Court may have been referring to non-coding nucleotides within a gene’s open reading frame (ORF) that are spliced out during processing. Lucy W. Barrett et al., Regulation of Eukaryotic Gene Expression by the Untranslated Gene Regions and Other Non-Coding Elements, 69 CELLULAR & MOLECULAR LIFE SCI. 3613 (2012).} the Court more or less accurately described the science—certainly enough to competently rule on the merits. The Court’s efforts to ground its decision in scientific facts should be commended.\footnote{So should US District Judge Sweet, who published a substantive section in his lower court ruling. See Ass’n for Molecular Pathology v.} However, other recent
decisions\textsuperscript{612} suggest that \textit{Myriad} may have been an outlier case as it dealt with patent law, which is fundamentally scientific and highly technical.

Both the legal and scientific communities should strive to eradicate the influence of deceptive simplicity. Such a task is not monistic and will require interdisciplinary cooperation. For example, the Buck-era eugenics movement was successful partly because scientists with the most relevant knowledge were largely confined to a life of research and failed to effectively communicate with the public to correct scientific misperceptions. At the same time, the legal community’s disengagement from science was partly responsible for the failure to overcome scientific deceptive simplicity in the judiciary. Building a system structured in a manner that encourages lawyers to weld scientific empiricism and jurisprudence would greatly benefit society.

Many questions will be raised and answered regarding numerous aspects of genome editing biotechnologies in the near future. Lawyers and scientists must be careful to properly frame those questions rationally and fairly. An example of a legitimate issue regarding genome editing is whether the technology will be safe for clinical use in the near future.\textsuperscript{613} However, constructing arguments based on impracticalities when supporting or opposing technological advances should have no place in jurisprudential calculus. Seeking to ban a genome editing technology because of a perceived threat of the possibility of introducing designer babies, when no evidence exists to suggest that the technology is capable of delivering such outcomes, makes as much sense as seeking to ban space travel because we might encounter an extraterrestrial race that will want to annihilate...
humankind. At this moment in time, designer babies are as hypothetical as extraterrestrial monsters.

Rather than advocating haphazard bans on genome editing technologies as some have proposed, this Article advocates for a system that lays a doctrinal foundation to proliferate rejection of deceptive simplicity. This concept is more sensible because, unlike outright banning technologies that the public is unfamiliar with, it promotes broad debate of the issues and does not dictate unilaterally what should or should not be permissible in society.

In sum, the normative framework advocated here seeks to cultivate and expand Myriad's roots of scientific empiricism. This approach is broadly applicable to other fields of law in which scientific inquiry may play important or dispositive roles.

VI. CONCLUSION

CRISPR systems and their future progeny hold the power to change the world. This nascent biotechnology has incredible potential, but its future is filled with uncertainty regarding how the law will treat it going forward. The scientific community has made efforts to begin a dialogue about genome editing technologies and their implications for the future of humankind. However, the legal community has yet to fully address the significant challenges that genome editing will pose for law and policy making. The void in legal scholarship is quickly growing to the detriment of society. This Article marks a first step toward closing the gap between science and law regarding this momentous scientific breakthrough.

Cooperation between lawyers and scientists will be pivotal as genome editing technologies continue to develop and mature in an increasingly globalized and interconnected world. Thus, a uniform doctrinal structure is sorely needed to address future questions that will be raised by the ensuing applications of CRISPR-based technologies. To that end, this Article presents a robust and comprehensive primer on genome editing as a resource and proposes a jurisprudence of scientific empiricism as a normative legal framework to broadly address questions of science in law. This paradigm seeks to promote a system in which lawyers are able to fuse scientific

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614. See Lanphier et al., supra note 28 and accompanying text.

615. If there is anything this Article would support banning, it would be the use of the term "designer babies"—alongside its derivations—in future discussions concerning genome editing technologies. See discussion supra Part V.A. This Article's position is that it makes no sense to pollute debate of scientific advances with the use of such misleading terminology.

616. See Enriquez, supra note 24, at 1289–91, 1336.
empiricism and jurisprudence to combat scientific illiteracy, as well as the oversimplification and misinterpretation of scientific advances, which are all common substantive impediments to constructive debate. It is time to adhere to higher standards in this regard.

Taken together, a compilation of the genome editing research performed globally over the last three years begins to paint a very specific portrait: genome editing biotechnologies, and CRISPR systems in particular, represent not only tools for basic research, but gateways to significant medical and scientific breakthroughs to come. This Article provides a foundation for a series of forthcoming articles that will analyze many of the prospective benefits and risks associated with the use of genome editing biotechnologies from statutory, constitutional, international, ethical, regulatory, egalitarian, and policy standpoints. The goal is to jumpstart a scholarly dialogue, highlight the crucial roles that law, science, and public policy will play in the development of this emerging technology, and encourage debate grounded in reason rather than baseless conjecture.

We owe it to ourselves and future generations to treat this remarkable new technology with the gravitas it deserves.

617. See, e.g., Enríquez, supra note 31. Collectively, these works seek to build a foundation for what may be considered "genome editing law" in general, and "CRISPR law" in particular.