

Cutting Eugenics Out of CRISPR-Cas9

Carolyn Brokowskj,^{a,*} Marya Pollack,^b & Robert Pollack^c

^aBioethics (Medical Ethics) Department, Columbia University School of Professional Studies, New York, New York; ^bDepartment of Psychiatry, Columbia University College of Physicians and Surgeons, Inwood Clinic, New York, New York; ^cBiological Sciences Department, Columbia University School of the Arts, New York, New York

*Address all correspondence to: Carolyn Brokowskj, M.S. Candidate; Bioethics (Medical Ethics) Department, Columbia University School of Professional Studies, 203 Lewisohn Hall, 2970 Broadway, MC 4119, New York, NY 10027; E-mail: ceb2185@columbia.edu

ABSTRACT: The use of clustered regularly interspaced short palindromic repeats (CRISPR) and their associated (Cas) proteins (the CRISPR-Cas system) in genomic engineering is among the most promising biomedical innovations to occur in the last few decades. One of this system's most profound features is its ability to edit genomes with impressive specificity, which may cause significant alterations of cellular, tissue, and organismal phenotypes at the near instance of the editing, over the lifespan of the organism and potentially into any number of future generations. We argue that the use of the CRISPR-Cas9 system to edit the human germline should be legally prohibited on account of the system's potential for generating an unjust eugenic future. Its use in nongermline experimentation and applications, however, should not be constrained on eugenic grounds. Such a blanket legal prohibition might limit the progress gleaned from this technology. Allowing experimentation in human subjects more broadly might expose participants to considerable risk and potentially harmful outcomes, and the system might prove unable to realize tangible therapeutic outcomes that seem likely *ex ante*. We conclude that the uncertainty inherent in CRISPR use should not lead to reflexive, preemptive prohibitions, but instead to ethical, fastidious, and controlled experimentation.

KEY WORDS: bioengineering, bioethics, gene editing, genomic engineering, germline editing, medical ethics, research ethics, research involving human subjects

I. INTRODUCTION

Within the infant rind of this weak flower, Poison hath residence, and medicine power; - Friar Laurence, Romeo and Juliet¹

The clustered regularly interspaced short palindromic repeats (CRISPR)-associated (Cas)9 system has expanded the terrain of biomedical innovation.^{2,3} Because of its genome altering capabilities, it has been employed for at least the following uses: constructing novel genomic libraries and genetic screens;^{4–11} creating genetically modified (both knock-out and knock-in) organisms,^{12–16} ranging from viruses to silkworms to primate embryos;^{17–22} analyzing epigenetic modifications and genomic regulation;^{23–25} growing genetically modified plants and foods such as rice and wheat;^{26–28} modulating transcription and metabolism;^{29–31} modifying the mitochondrial genome;³² and analyzing and editing gene function in the genome *in vivo*.^{33,34} In addition, CRISPR systems

currently are being engineered not only to edit the genome permanently, but also to target regulation without permanent genomic sequence alterations through the use of a “dead” version of a Cas9 enzyme that may act as a platform for activator and repressor molecules. In this instance, the guide RNA brings the Cas-9 molecule to a specific gene regulatory site on the DNA, but the modified protein cannot initiate a DNA modification. Instead, it may act as a platform for activator and repressor molecules.³⁵ CRISPR-Cas9 is also thought to hold great promise for studying and potentially offering therapeutic modalities for cancer,^{36–39} muscular dystrophy,^{40,41} parasitic and bacterial infections,^{42–44} neurodegenerative conditions,⁴⁵ human immunodeficiency virus,⁴⁶ and other diseases.

Its promise derives largely from its ability to interact with genomic material with great specificity. Such specificity enables key gene and regulatory regions to be altered, presumably with few, if any, off-target effects and unintended biological consequences. Some off-target effects have been observed, though their frequency and causal weight in determining the phenotypic outcomes of the genetic modifications remain uncertain at this time. Therefore, at the time of this writing it seems reasonable that genetic and genomic modifications of many varieties may produce intended changes in phenotypes in cells, tissues, and whole organisms in a fairly controlled manner. Although it is impossible to determine in advance which modifications will ultimately produce desired, specified phenotypic alterations, most likely there will be at least *some* instances when CRISPR genomic modifications will yield precise, intended phenotypic changes. We argue that while the use of CRISPR-Cas9 in manipulating the human germline should be legally banned because of concerns about rational and irrational eugenics, its nongermline experimentation and applications in humans (i.e., infants, children, adolescents, and adults) may be permissible on account of the system’s promise.

Firstly, we briefly review the CRISPR-Cas9 system, addressing the specificity and the possible side effects of its ability to alter regulation of sequences and genomes regulation. We then appraise many possible benefits of CRISPR-Cas9 and show why its application may be helpful in advancing our understanding of basic science, biotechnology, and medicine. Secondly, we argue that germline modification by this system facilitates the return of eugenics—the positive selection of the “good” or “desirable” versions of the human genome and a marginalization that becomes a form of negative selection of those that are unmodified and therefore “bad” or “undesirable.”⁴⁷ A brief reflection on both international and national historical events reveals that, however they have been rationalized, legalized eugenics laws and policies have not produced just or even reasonable societal outcomes for many.

Finally, we address three limitations of our argument. First, allowing the CRISPR-Cas9 application for only nongermline editing purposes may limit many of its potential uses in advancing biomedicine. We hold that this restriction is justified, nevertheless, given the risks of improper usage. Second, permitting experimentation, even in nongermline contexts, may pose significant risks to human subjects, due to the possibility of sizeable off-target effects that may broadly and inappropriately alter physiological and developmental trajectories. But we hold that with appropriate ethical and legal oversight as mandated by the Common Rule⁴⁸—the United States federal regulations that apply to 17 federal

agencies overseeing the ethical conduct of human subjects research—such risks may be justified depending on the specifics of the medical research contexts. Third, because of our inability to predict the relative weight of genomic alteration versus individual experience and its epigenetic effects on organisms' phenotypic properties (whether at the level of cells, tissues, or entire organisms) in both the short and long term, there may be a limited probability of actualizing therapeutic outcomes through genomic modulation. Implementing CRISPR genomic modification, when the probability of therapeutic effects is small, indeed opens a possibility that the risks of its use in human subjects might outweigh the benefits of experimentation on them. We maintain, however, that whether such modifications result in positive therapeutic outcomes is an empirical question free from the novel burdens of inadvertent or intentional eugenic consequence.

A. The CRISPR-Cas9 System and Its Prodigious Potential for Advancement

CRISPR-Cas systems are found abundantly in bacteria and archaea,⁴⁹ providing them with acquired immunologic defenses against invading plasmids and viruses.^{50,51} Structural features of CRISPR loci enable these systems to combat a variety of threats (Figure 1).^{52,53} For example, these loci typically contain *cas* genes (CRISPR-associated genes), a leader sequence, and a repeat-spacer array.⁵⁴ The family of *cas* genes encodes proteins such as helicases and nucleases,⁵⁵ which are enzymes that unwind and cut DNA, respectively. The leader sequence, which is directly adjacent to the short repeats (tens of base pairs),⁵⁶ is in a fixed orientation flanking one side of the CRISPR loci. This leader sequence is several hundred base pairs long, and is well conserved.⁵⁷ In bacteria, the repeat-spacer array consists of repeat sequences of bacterial DNA in addition to spacers interspersed between the repeats. It is thought that the spacers are derived from invader (e.g., phage and plasmid) DNA. In the invading DNA, spacers are referred to as proto-spacer adjacent motifs (PAMs).

Although three main CRISPR types have been characterized,⁵⁸ we will focus upon type II in bacteria. In all cases, when invaders attack during the adaptive phase, bacteria respond by integrating the invader's protospacers into the host's CRISPR locus. Next, CRISPR RNAs (crRNAs) are transcribed from this locus and then incorporated into effector complexes, where the crRNA guides the complex to the invading nucleic acid; Cas proteins then degrade it. In the type II system, a transactivating-crRNA (tracrRNA) binds complementarily to the repeat sequences of pre-crRNA resulting in duplex formation. This is cleaved by the RNA ribonuclease (RNase III), forming a crRNA:tracrRNA complex, which then facilitates Cas9 in degrading the invading nucleic acid by creating double-strand breaks in it.

The type II CRISPR-Cas9 system may be designed to enable "RNA-programmable" site-specific genomic modifications.⁵⁹ A guide RNA, formed from a hybrid of crRNA:tracrRNAs, recruits Cas9, and then binds to a target DNA sequence through complementary base pairing. Upon the binding of the guide RNA to the double-stranded regions of choice, Cas9 then may create double-strand breaks (Figure 2).^{53,60} Normally, after DNA experiences double-strand

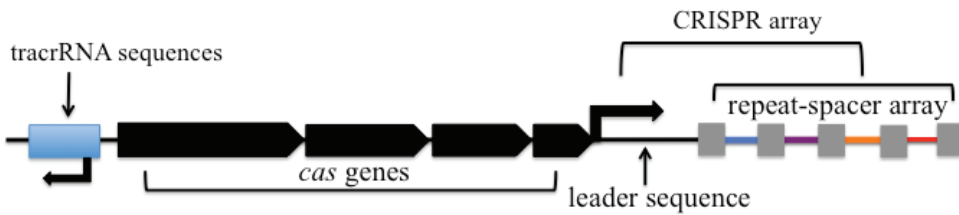


FIG. 1: The type II CRISPR-Cas9 system from *Streptococcus pyogenes* (bacteria) is well characterized. Major defining structural features include the following: *cas* genes encoding the Cas9 endonuclease; a leader sequence; genome-targeting spacers in between the repeats, which may contain palindromic sequences; and DNA coding for transactivating RNA (tracrRNA).

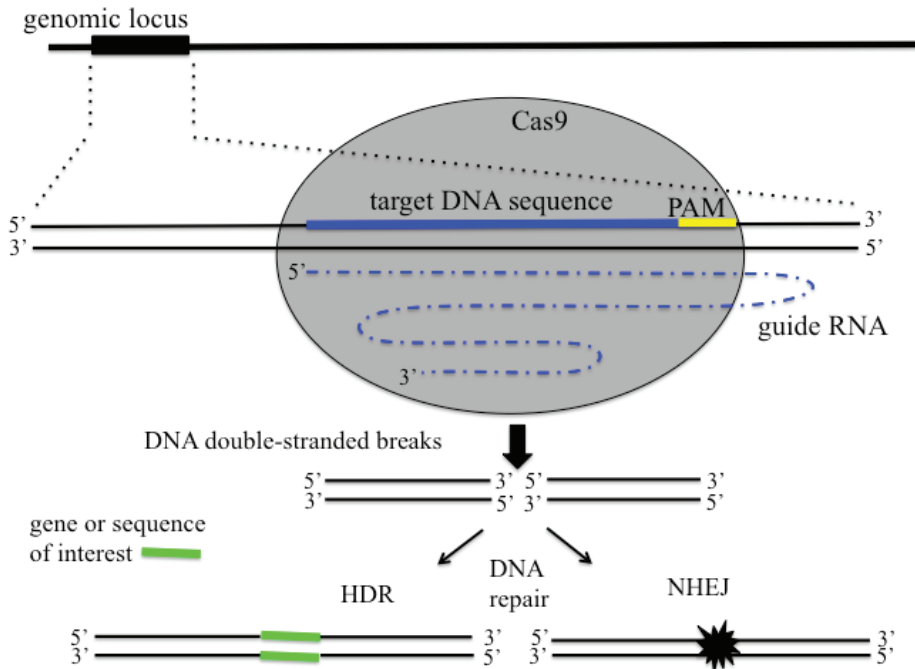


FIG. 2: After several important processing events, transactivating-RNA (tracrRNA) is paired to CRISPR RNA (crRNA) and bound to the Cas9 endonuclease. The tracrRNA:crRNA hybrid acts as a guide RNA, directing Cas9 to the desired cognate target DNA. Once inside the nucleus of a cell, the complex locks onto the protospacer adjacent motif (PAM) sequence (5' NGG 3' for *Streptococcus pyogenes*). Cas9 endonuclease unzips the DNA and matches it to its target RNA. Upon matching, Cas9 cuts the DNA, creating double-strand breaks. To fix the breaks, mammalian cells may employ one of two principal DNA repair mechanisms. Homology-directed repair (HDR) (lower left) can generate precise, defined modifications at target loci by employing an exogenously introduced repair template. Precise genome edits, including the introduction of several or single nucleotide mutations (solid green line), are possible. HDR occurs only in dividing cells, and there is considerable variability in its efficiency. Alternatively, in nonhomologous end joining (NHEJ) (lower right), a repair template is absent; double-strand breaks are simply religated. This process is error prone and can result in insertions and deletions, which might create a premature stop codon terminating translation.

breaks, enzymes detect and repair them, typically by ligating both ends or by homology repair, where donor DNA that has sequences matching the site of the breaks can be integrated into the genome. In the latter way, genetic information may be significantly and precisely altered by addition, deletion, or other sequence modification.

Theoretically, CRISPR-Cas9 should permit reversing the modifications. However, whether it is possible under any conditions for a given phenotype to revert to its premodification state remains to be determined. In addition, the system may be used to edit the genome epigenomically, by chemically modifying, but not altering, its base pair sequences themselves. One approach involves inactivating the Cas9 enzyme such that, instead of cutting DNA, it is used only for regulating gene expression. Nevertheless, both nucleic acid sequence modifications and directed epigenetic changes in regulatory control brought on by the use of “dead” versions of Cas-9 affect gene expression in critical ways: both affect the phenotypic outcome to which they are causally tied, albeit perhaps to different extents. As such, it seems that there is no material basis for the claim that either approach would entirely avert ethical concerns about the use of the CRISPR-Cas9 system in humans.

Completely banning the use of CRISPR-Cas systems would be to deprive the world of considerably promising innovation that may have far-reaching beneficial effects for humanity (Table 1).^{5,7,9,10,15,23,28,32,33,39,42,43,61–84} Yet great power should command great responsibility. Accordingly, it is critical to manage risk.

B. A Legal Prohibition Against Germline Experimentation is Warranted to Avert Eugenics

CRISPR system use in nongermline experimentation and applications in nongermline tissues of embryos, infants, children, adolescents, and adults should be legally permissible because of the system’s probable ubiquitous capacity for biomedical advancement (Table 1). Because of the important relationship of genomic modification at critical growth and developmental periods, it is essential to allow for interventions across an organism’s lifespan. For example, during the third week of human gestation, neural tube closure commences in the developing embryo, and the success of this process requires many timed signaling genetic events to be executed properly.⁸⁵ Contributions from WNT, SHH, retinoic acid, and genes affecting the cell cycle; apoptosis; the integrity of the extracellular matrix and cell surface; and regulatory machinery controlling these events all play critical roles in determining neural tube closure.^{86,87} Altering abnormal gene sequences themselves, or their expression levels (or both), may result in beneficial short- and long-term effects and help to prevent and ameliorate conditions such as anencephaly, iniencephaly, encephalocele, and spinal bifida.⁸⁸

But, if creating gene modifications should be legal and encouraged at the aforementioned stages, why impose a ban at the germline level? One plausible reason is that germline modification has a direct connection with eugenics. History reveals that societies where it has been legalized often have had great difficulty managing it without severe human rights concerns and violations.

TABLE 1: CRISPR-Cas9 Innovations

Discipline	Author(s)	Contribution
Basic science	Basset et al. (2013)	Highly efficient mutagenesis in <i>Drosophila</i>
	Basset et al. (2015)	Genome-wide CRISPR library for high-throughput screening
	Bhattacharya et al. (2015)	Loss of function tool to screen human disease genes in <i>Xenopus</i>
	Carroll et al. (2015)	Mouse model for cardiac-specific gene deletion
	Flowers et al. (2014)	Highly efficient mutagenesis screen in axolotl
	Hilton et al. (2015)	Epigenome editing
	Hodgkins et al. (2015)	Database for genome engineering
	Li et al. (2015)	Metabolic engineering of <i>Escherichia coli</i>
	Nihongaki et al. (2015)	Optogenetic genome editing
	Ran et al. (2015)	<i>In vivo</i> genome editing
	Wang et al. (2014)	Genetic screens in human cells
	Yang et al. (2014)	Generation of genetically modified mice
	Biomedicine	Bellec et al. (2015)
Bogerd et al. (2015)		Transcription activators may be used in screening for endogenous genes that affect virus replication
Chen et al. (2015)		Engineering human stem cell lines with inducible knock out
Fujii et al. (2015)		Genetic engineering of human intestinal organoids
Hammond et al. (2015)		Gene drive system in malaria
Hart et al. (2015)		Cancer genetics
Jing et al. (2015)		RNA (miR-155) genome knockout in human macrophage cell lines
Jo et al. (2015)		Mitochondrial genome editing

TABLE 1: (continued)

Discipline	Author(s)	Contribution
Biomedicine (Continued)	Hou et al. (2015)	Human CXCR4 gene is efficiently disrupted by genome editing, leading to HIV-1 resistance of human primary CD4+ T cells
	Long et al. (2014)	Prevention of muscular dystrophy in mice
	Shi et al. (2015)	Identification of potential cancer drug targets
	Sollelis et al. (2015)	Genome editing in parasites
	Vinayak et al. (2015)	Genetic modification of diarrheal pathogen
	Yang et al. (2015)	Inactivation of endogenous porcine retroviruses
Biotechnology	Čermák et al. (2015)	Modification of the tomato
	Du et al. (2016)	Mutagenesis in soybeans
	Jiang et al. (2014)	Evidence that the system is applicable in algae
	Ito et al. (2015)	Possible application to tomato fruit ripening
	Li et al. (2014)	Describing methods for genome editing in Arabidopsis and tobacco
	Li et al. (2015)	Soy bean genome editing
	Mikami et al. (2015)	Optimized mutagenesis in rice
	Shan et al. (2014)	Protocol for genome editing in rice and wheat
	Svitashev et al. (2015)	Targeted editing in maize
	Woo et al. (2015)	DNA-free genome editing in plants

An obvious example of such misuse occurred in Nazi Germany. German social Darwinists, many of whom were well-respected physicians and scientists, feared the overall degeneration of the human race and therefore promoted racial hygiene policies (*Rassenhygiene*), whose goal was to provide preventive medicine for the “German germ plasm” by legally blocking the “breeding of inferiors,” by mocking the choices of celibacy and birth control, and by marginalizing feminists who threatened the reproductive performance of the family unit.^{89,90} Social Darwinism, with its rhetorical misuse of natural selection to order diverse social phenomena in terms of survival of a “race” within the human species, and eugenics-promoting policies with the support of state authority,

triggered massive widespread abominations. These included the sterilization of hundreds of thousands of individuals and the deliberate, selective ethnic cleansing of millions via euthanasia programs, death camps, and other egregious crimes against humanity.⁹¹

France, Brazil, Denmark, Britain, Russia, and the United States also enacted eugenic laws.^{92–94} Even though the legalization of eugenics did not result in equivalent atrocities on the same scale, severe legal injustices pervaded in many cases. In the early twentieth century in the United States, for example, eugenicists were greatly concerned with the sexual behavior of the “feebleminded”—persons who may or may not have had psychiatric illnesses or neurological limitations of some variety. To prevent these individuals from reproducing successfully, Indiana in 1907 was the first state to pass mandatory sterilization laws; over time, more than 30 additional states followed suit.^{95,96} Involuntary sterilization policies created great marginalization and injustices for anyone perceived as mentally inferior, regardless of the truth of the diagnosis. Consider, for instance, the 1927 Supreme Court case *Buck v. Bell*.⁹⁷ Carrie Buck was considered a feebleminded woman and as a result was institutionalized in a state psychiatric facility. Her condition purportedly had been in her family for three generations, and she was to be the first person subjected to mandatory sterilization under Virginia law. Hence, the validity of the Virginia statute permitting sterilization of the mentally ill for eugenic purposes was in question before the Court.⁹⁸ More specifically, the question at hand was whether the law denied Bell the right to substantive due process and equal protections under the 14th Amendment. Associate Justice Oliver Wendell Holmes famously upheld the law, infamously arguing, “The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes. Three generations of imbeciles are enough.”⁹⁸ Ironically, the evidence of the case strongly suggests that there were no imbeciles in any of the generations involved.⁹⁹ But in any case it is not obvious today why state interest should have led to sterilization, except for the presence of a eugenic component to United States law at that time emerging from the eugenic notion of serving public health through the selective weeding and breeding of people.

But how, if at all, might eugenics via the use of the CRISPR-Cas9 system for germline modifications result in oppressive, harmful future outcomes? It might not. This bioengineering technology might be the biomedical invention par excellence. However, if possible, and for the right price, some will seek to employ the system for nonmedical purposes, such as eye and skin color modifications, boosting intelligence and height, and altering other traits. Although this is an empirical matter, with growing economic disparities on the rise in America,¹⁰⁰ it is plausible that this technology will only exacerbate our unfortunate situation. Those in higher income brackets will have access to methods of creating “designer” children, leaving to the fates the genetics of those with more modest means.¹⁰¹ This risks the creation of a de facto tiered biological class system, perhaps resulting in even greater inequalities than those existing based on race.

What if the use of the CRISPR-Cas system in germline modifications were only legalized for strictly therapeutic purposes? At the time of this writing, whether CRISPR can be employed successfully for *any* therapeutic purposes is undetermined and in need

of rigorous experimentation through carefully controlled clinical trials involving human subjects. Admittedly, we cannot advance to this testing stage with a legal prohibition in place.

Why, then, is the germline ban necessary? A practical reason in favor of the ban is that the probability of off-target genotypic, and therefore phenotypic, effects remains uncertain; reports about CRISPR-Cas9 efficiency are conflicting.^{102–111} Before the introduction of drugs and other pharmaceutical products into humans, United States federal law requires that significant data about the toxicity and physiological effects of the agents must be obtained first by testing in animals.¹¹² Because of the uncertainty associated with off-target effects, a similar protocol for CRISPR-Cas9 should be followed in humans. Until the technology of targeting with absolute specificity is developed, and until the consequences of off-target DNA modification are better understood, the risk to human subjects exposed to germline modification would be too great to justify potential benefits. Moreover, when more reliable animal data arise, to better understand efficiency limitations of the system, it will be optimal to begin testing with nongermline modification and then possibly reevaluating whether germline modification for therapeutic purposes seems like a reasonable experimental or therapeutic option.

CRISPR-Cas9 genomic engineering does not exist in a vacuum. Clearly, the ways in which it influences societal outcomes are an empirical matter, and even the best intentions about how it *should* be used are insufficient to determine how it *will* be used. Other factors, such as economic conditions and the medico-legal structures and norms of the society, contribute just as much if not more in shaping such outcomes. Moreover, to avert potentially grave harms to human subjects, it is optimal to determine the system's efficiency in nongermline contexts before considering experimentation with the germline, even for therapeutic purposes; such data will contribute to informed decision making, instead of merely firing shots in the dark. Finally, under the best of possible outcomes with respect to safety, efficacy, and specificity, a person born of one or two gametes with modified germlines will be inherently different, from infancy on. The risk is that such a person will be, in social and political terms, also inherently better. Completely successful, completely benign germline modification through CRISPR would in this way lead to a social upheaval that would end the possibility of equal justice and equal citizenship.

C. Limitations on Innovative Potential, Safety, and the Ability to Actualize Therapeutic Outcomes

At least three potential objections to our position may arise. One is that the legal prohibition on CRISPR-Cas9 germline editing may limit the knowledge, experimentation, and overall progress gleaned from this technology. For instance, though it affects the pancreas, intestines, kidneys, and liver, cystic fibrosis (CF) primarily is a lung disorder characterized by the accumulation of unusually thick, sticky mucus that is the site of frequent infections. Most cases of CF are caused by an autosomal recessive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, resulting in a misfolded CFTR protein channel.¹¹³ The CFTR channel regulates the flow of water and

chloride ions through cells. CFTR mutations lead to blockage of the channel and consequently, to the development and buildup of abnormal mucus and to chronic infections. If CRISPR-Cas9 editing was approved for germline modification, CF carriers could have their genomes edited to restore the mutated *CFTR* gene to a fully functional, unaffected copy. In this way, these individuals would be able to avoid passing on a mutated copy to their immediate offspring and to subsequent generations.

Although this seems like a promising idea, even if CRISPR-Cas genome editing was guaranteed to produce a wildtype *CFTR* gene—through substitution, sequence modification, or regulatory alterations—concerns about off-target effects remain. For the reasons discussed in the previous section, it seems optimal to first experiment in nongermline contexts. Such experimentation could take place, for instance, *in vivo* during lung development. However, the details about the risk involved would depend upon the specifics of the proposed research.

A second potential problem with our argument is that even nongermline experimentation may expose human subjects to considerable risk and potentially devastating biological outcomes, such as severe injury, disability, or death. And with genomic engineering, there is the risk that modifications may be imprinted permanently. If a gene were modified using the CRISPR-Cas system, then the same system should in principle be available to reverse the modification at a later time. But with the passage of time, it would not be possible to be certain that a sequence reversal would generate a complete phenotypic reversal in cells and tissues descended from the originally modified cells or gametes. If a gene was modified using the CRISPR-Cas system, then it is likely that there would be a mechanism to reverse the modification. But as mentioned earlier, it is difficult to know whether phenotypic effects of the alteration can be reversed to their premodification state. It likely would depend on the phenotypes (proteins, cells, tissues, organisms) in question and the extent to which they had been shaped by environmental interactions over time. However, it is possible that unintended and unknown off-target effects might arise on account of the CRISPR-Cas system. Such effects could be passed down in ignorance and eventually harm the carrier.

Because the CRISPR-Cas9 system is fairly new, and because much remains uncertain, the aforementioned examples of unintended harm are very real possibilities. However, these risks are present across many types of human subject research. Positive and negative pharmacologic pleiotropic effects have been identified in a wide variety of pharmaceuticals. Moreover, at certain dosages many mutagenic anticancer modalities, such as bleomycin, cyclophosphamide, mitomycin C, procarbazine, and radiation, have been found to induce germline mutations in animals and humans.^{114–117} Yet without these drugs to combat the progression of the malignancy, many patients would die much more quickly, without any chance of achieving remission even for a period of time. Sometimes, risks involved may be worth the benefit. Fortunately, US federal regulations established for handling the permissibility of such research enable each prospective research proposal to be scrutinized by a given institution's institutional review board (IRB).^{118–120} As more animal data are available, and as research proposals seek to engage in non-germline

experimentation, institutional IRBs will already have a constantly changing framework for deciding about whether the research CRISPR-Cas9 proposals are ethical. Even with the possibility of altering the germline unknowingly and indefinitely, the manner of weighing the possible risks and benefits of each study remains largely unchanged. In short, the uncertainty and risks presented by CRISPR-Cas9 are not wholly unlike those presented by other types of studies that include human subjects. It is an emphatically empirical question by how much, if at all, the risks presented by mutagenic agents differ from those presented by possible off-target effects of genomic engineering technology. This answer may be determined only by reliable data generated by rigorous, controlled experimentation. Thus, depending on the specifics of each research protocol, as determined by an IRB, nongermline experimentation in human subjects should be permitted.

A third concern is that, even if the CRISPR-Cas9 system works in humans as many hope—with great precision and with minimal off-target effects, there is increasing evidence that the causal weight of gene expression on certain phenotypic outcomes is questionable. Instead, in at least some diseases, environmental exposures and lifestyle play considerable roles. For example, Wu et al.¹²¹ provided compelling evidence that intrinsic factors contribute 10% to 30% to the lifetime risk of developing cancer and that the rates of endogenous mutation accumulation by intrinsic processes do not adequately account for the observed cancer risks. As such, they maintain that cancer risk is significantly influenced by extrinsic factors. Additionally, many diseases, especially psychiatric diseases such as schizophrenia, bipolar disorder, autism spectrum disorder, and Alzheimer's disease, are largely thought to be of multigenic etiology.^{118,119} It is unclear how genomic engineering might be effectively employed to coordinate genomic expression from multiple genes, even if it were determined for certain that some disease phenotypes result largely from inappropriate gene expression. Finally, genetic pleiotropic effects are an important source of phenotypic variability in humans. Even if it were determined that genes play *the most* important causal role in disease development, it is unclear how CRISPR-Cas systems might be able to account for pleiotropic effects, which may modify or obliterate some disease phenotypes entirely.

Although these concerns about limited therapeutic efficacy are warranted, they are insufficient to bar experimentation with CRISPR-Cas9. After all, if we were certain that this system would not yield any therapeutic potential, it would be unethical to use it for experiments with human subjects. But since we remain uncertain about the system's effects in humans, and since there is a theoretical possibility of significant benefit that is increasingly supported by recent scientific findings, experimentation on humans is ethically supported. Only with cautious, controlled experimentation can we learn whether using the CRISPR-Cas system is a reasonable approach to therapeutic development.

II. CONCLUSION

Undoubtedly, CRISPR-Cas9 has great potential to revolutionize biological and biomedical innovation in ways not yet fully conceived. Nevertheless, eugenics lurks in the shadow of CRISPR. Any opening to germline, sperm, and egg modification is, simply

put, the opening of a return to the agenda of eugenics: the positive selection of “good” versions of the human genome and the weeding out of “bad” versions, not just for the health of an individual, but for the future of the species. To learn from errors of the past, to avert potentially lethal disasters, and to provide positive outcomes, it will be critical to know when to accelerate and when to apply the brakes, especially as this technology already comes equipped with such a prodigious accelerator.

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