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Everything in Moderation, Even Hype: Learning from Vaccine Controversies to Strike a Balance with CRISPR

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Abstract

The ease and applicability of CRISPR/Cas9—a new and precise gene-editing and reproductive technology—have garnered hype and heightened concern about its potential "unprecedented and horrific consequences" and have led many scientific leaders to call for a moratorium on its research and use. CRISPR appears distinctly more controversial than previous technological innovations (genetic or otherwise), with a greater reach and speed of human treatment and enhancement; however, we have seen similarly inflated hopes and fears in response to other medical innovations for well over a century. One intervention that has both historically and recently incited alarm—vaccines—serves as a pertinent example of what could go wrong if a technology's reach is shortened due to inflated fears. By comparing the vaccine controversy and the CRISPR debate, we can help separate the hype from the realistic potential of these technologies. How our society grapples with such innovations will determine the extent to which their impact on our individual and collective health will be beneficial. We must recognize the need for a tempered approach to CRISPR conversation leading to regulation and ethical application. Although CRISPR's reach will continue expanding with ongoing research, thus requiring continuous evaluation, the lessons we've learned from the vaccine controversy demonstrate that our approach must not be to shut down regulation and application now, but to thoughtfully conjoin productive debate and action so that therapeutic gene-editing can alleviate suffering as soon as possible without precipitating social outcomes we would belatedly deplore.

1. Introduction

Since the moment of its development in 2012, CRISPR/Cas9 has commanded headlines in scientific, bioethical, and popular-media sources.[1–5] This bold new gene-editing technology (hereafter termed simply "CRISPR"), if applied to somatic cells, would change fundamental traits of a given individual and, if applied to germline cells, would affect the individual's heritable traits.[6] For its ease and vast applicability, and especially for its ability to alter heritable traits, CRISPR has stirred excitement, along with serious concern about its potential "unprecedented and horrific consequences."[7] Many scientific leaders advise caution, recommending an indefinite period of extended education and debate before

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any human applications are attempted;[8] others have called for an actual moratorium on CRISPR research, including its use in any plant or animal species.[8,9]

CRISPR—an acronym for clustered, regularly interspaced, short palindromic repeats—involves a protein, Cas9, attaching to guide RNA to scan, bind to, and cut DNA. This process can be customized to target any site on the strand of DNA by changing the first approximately 20 nucleotides on the guide RNA, while the Cas9 protein remains the same throughout.[10] This means that the Cas9 protein can be mixed with more than one guide RNA at a time to target multiple DNA sequences simultaneously.[11] Thus, CRISPR/Cas9 works very efficiently and easily, and at a lower cost than preexisting genome-editing tools like zinc finger nucleases and transcription activator-like effector nucleases (TALENs).[12] This technology could be used at any point in a human life, from embryo to adult, either for the treatment of genetic diseases or the "enhancement" of an otherwise healthy individual.[13] Currently CRISPR could be used to edit genes underlying monogenic traits,[14–16] while its application to complex traits is limited to genetic diseases, such as inherited metabolic disorders,[17] cancer,[18] and diabetes.[19]

CRISPR's wide-ranging potential applications have fueled both hopes and fears in the scientific and philosophical community, and in trickle-down media versions of them.[20,21] Furthermore, its potential to alter genetic traits and affect individual and public health renders it eugenic, a historically fraught notion that often undergirds societal fear of a new, or even a longstanding, technology that can alter our physical, emotional, intellectual, and social identities. Much of the scientific, scholarly, and popular media debate that has erupted over CRISPR has centered on its potential use to alter heritable traits,[22] a eugenic capability[23] that many fear can precipitate a slippery slope to a genetically engineered society favoring certain traits—intellectual, cognitive, emotional, physical, or racial—above others. The categorization of a technology as "eugenic" can have a profound effect on the technology's sociopolitical success. Therefore, to foster productive conversation that could help establish CRISPR regulations responding ethically to stakeholder groups' opinions, we must grasp this complex concern underlying the already-expressed fear and apprehension.

II. The CRISPR Debate: "Detrimental Eugenics" vs. "Beneficial Eugenics"

Twentieth-century history has imbued the term "eugenics"—literally, "good genes"—with ambiguous connotations. In coining the term, Sir Francis Galton defined it as the science that deals with "all influences that improve the inborn qualities of a race" and "those that develop them to the utmost advantage."[24] More recently, the term "eugenics" has been given various definitions by bioethicists, ranging from the broad, "any policy that alters the composition of the human gene pool,"[25] to the narrow, "coercion of people's reproductive choices, for social ends, which may include improving the quality of the population, preventing suffering of future generations or reducing financial costs to the state."[26] Early twentieth-century eugenic efforts to "improve" humanity through genetic intervention led to the tragedies of the Holocaust, the sterilization efforts in the United States, and other atrocities. In these contexts, "eugenics" connoted the selection for particular traits deemed "desirable" at the expense of any people who had alternative traits. We can designate this representation of "eugenics" as "detrimental."

The consequences of detrimental eugenics obscured the potential for what we might call "beneficial eugenics," namely, the elective elimination of traits that we can universally find harmful to the individual. Erik Parens of the Hastings Center has furthered this latter understanding of eugenics, suggesting how potential applications of CRISPR can fit in to parents' dueling obligations to shape and to accept their children: "[I]s eugenics inherently bad? No, not if by eugenics you refer to parents truly, freely choosing to use knowledge of genetics to promote the chances that their children will have good lives. If those efforts could be done safely and effectively, they would be consistent with parents' ethical obligation to shape their children, and would be good."[27]

In light of discussions like Parens' about the long-term efforts by parents to shape their children—i.e., beneficial eugenics—the explosion of varied reactions to CRISPR might initially seem disproportionate to the technology's potential promises and pitfalls. Furthermore, our survival and success as individuals and as a society have been, to a fair degree, the product of technological and medical intervention. To fear, rather than to research, debate, and refine, an intervention is to stagnate and even threaten the health, longevity, and happiness of our species. Indeed, it is how—not whether—CRISPR will be employed by parents to help shape their offspring, and how regulation can ensure that eugenics measures are beneficial rather than detrimental, that must be considered by scientists, ethicists, and legislators.[28]

The current constraints on CRISPR research, regulation, and application reflect both scientific and societal concern about potential negative effects on our species. Calls for a moratorium on CRISPR research and use,[29,30] U.S. intelligence officials' unnuanced addition of gene-editing to the dangers posed by weapons of mass destruction,[31] and media hype and resultant polarized public opinion have overshadowed the technology's realistic and mostly uncontroversial therapeutic potential uses.[32–34] Alta Charo warns that gene-editing may be at risk of media misrepresentation of its reach and implications. Because "[n]ot everyone reads past the headline,"[35] both hopes and fears surrounding this technology can become overblown. Those eager for CRISPR's availability might fall victim to a "message of hope [that] bolsters the impression that cures are available for other diseases mentioned in media headlines" and perceive "regulatory pathways [as being] too slow."[35] Simultaneously, those dreading the very idea of gene-editing technology are led to anticipate the emergence of "designer babies [that are] available only to the rich."[13]

It is the latter sort of concern—and, more acutely, the fear that CRISPR "raises the specter of Dr. Frankenstein's wild experiments and the eugenic goal of designer babies"[36]—that has particularly influenced government stagnation with respect to gene-editing research, funding, and regulation. The depth of fear even among the scientific community was revealed in the harsh rebuke of David Baltimore's advice to cautiously yet continually revisit the clinical use of CRISPR to conduct germline editing in light of ever-changing science and societal views.[37] But as Baltimore points out, a too-swift ban on research and even use of CRISPR could have unnecessarily deleterious effects rivaling those feared if it is used problematically; he astutely analogizes the potential implications of a CRISPR ban to those of a hypothetical ban on recombinant DNA in the 1970s: "we wouldn't have modern biology —and that means we wouldn't have all of the treatments and drugs that have helped us fight

cancer and heart disease, increase lifespans, and improve the quality of life for so many people."[36] Furthermore, eugenic "enhancement" of complex traits like intelligence remains generally scientifically unfeasible.[36,38] If we allow fear to prevent scientific progress toward the therapeutic application of CRISPR, we will permit otherwise preventable pain and suffering to disrupt and even shorten the lives of those with monogenic disorders.

III. Learning from Vaccine Controversies

CRISPR appears distinctly more controversial than previous technological innovations (genetic or otherwise), with a greater reach and speed of human treatment and enhancement; however, we have seen similarly inflated hopes and fears in response to other medical innovations for well over a century. One intervention in particular—vaccines—offers a pertinent example of what can go wrong if a technology's reach is shortened due to inflated fears. Like gene-editing technologies, vaccines occupy a liminal position between pure treatment and straightforward enhancement, appearing at first to serve as preventative treatment, but then forcing us to grapple with the question of where treatment ends and enhancement begins. We must remember that vaccines' aim is to provide a protection that we lack originally; they essentially make up for a somatic deficit. So, even though they do not manipulate preexisting traits, they induce cellular changes that allow individuals to avoid devastating, and even life-threatening, illnesses. By allowing people to avoid (by means of vaccines) or reverse (by means of CRISPR) debilitating or even life-shortening disorders, both technologies harbor the innate power to alter—to improve—individual and societal medical narratives. However, without a legal mandate, these technologies force us to confront the question: would it be ethical for the scientific community or consumers to refuse the use of these technologies?

By comparing the controversies surrounding vaccines and those surrounding CRISPR, we can discern what detriments to individual and public health can arise when we are overly suspicious.

A. A Brief History of Vaccine Controversy

Like reproductive genetic technologies, vaccines have transformed human health and longevity, eradicating smallpox and rinderpest and bringing many other major diseases—such as measles, mumps, rubella, and polio—under control.[39] For a vaccine to result in control and even eradication of a disease, consistency is key: everyone must get vaccines for vaccine-preventable disease. However, as the prevalence of a disease diminishes,[39] people's reluctance to be vaccinated increases, most likely because vaccines "involve doing something, most often by injection, to healthy people"[40] and because as herd immunity is achieved, individuals have less to gain from their own vaccination.[41]

Well before our current vaccine controversies, America saw vaccines being condemned for risks associated with their administration. For example, when progressives in the late 19th century sought to eradicate smallpox by means of compulsory vaccination, they encountered resistance because the initial method was arm-to-arm, which involved the risk of transmission of syphilis.[42] The founder of the Anti-Vaccination League, Charles Higgins,

asserted in 1907, “We must see that our children’s education is not predicated on the point of the poisoned quill. We must see to it that the subcutaneous injection of an absolute poison does not take the place of sanitation and hygiene.”[43] Another anti-vaccinationist, James Loyster, whose own son had died as a result of vaccination complications, managed to have New York’s compulsory vaccination law repealed.[44] Anti-vaccinationists in the 19th and 20th centuries fought against such laws in fear of vaccines’ potential or partial dangers, in protest of these laws’ adverse effect on individual autonomy, and in objection to what they believed to be physicians’ desire to profit from compulsory vaccinations.[45]

In recent decades, we’ve witnessed renewed controversy over childhood vaccinations, specifically the contention that they cause autism. The correlation between the age at which autistic signs typically surface and the age at which many vaccines are administered has led anti-vaccinationists to presume iatrogenic autism. Andrew Wakefield’s 1998 study apparently showing such causation of autism by the measles-mumps-rubella vaccine served as a perfect buttress for anti-vaccinationists’ protests. Of course, it is now common knowledge that the original publisher of Wakefield’s work, *the Lancet*, both questioned and retracted the article and that Wakefield was stripped of his medical license.[46,47]

B. The Intransigence of Fear

Although Wakefield’s twelve-child study has since been debunked by dozens of studies, each with thousands of subjects,[48] enough fear has persisted to precipitate a return of previously well-controlled diseases like measles.[40] Why is this?

Parents’ dueling obligations to accept and shape their children are laced with fear: fear of not doing enough to ensure their children’s health, and fear of doing too much and risking dangerous side effects of medical and beneficial-eugenic interventions. The latter concern can be heightened by influential organizations’ promotion of risk aversion—for example, in the vaccine-autism context. One such organization, the National Autism Association (NAA), whose self-proclaimed mission is to “respond to the most urgent needs of the autism community [and] provid[e] real help and hope,”[49] includes a blog post on its website by its co-founder and Executive Director Lori McIlwain stating that at the time of her son’s vaccination, she “blamed the needle prick itself for traumatizing him to the point of withdrawal.”[50] Mainstream hype has been cultivated by celebrities like Jenny McCarthy, Rob Schneider, and Charlie Sheen.[51] These ostensibly trustworthy sources present a powerful combination of regret about prior vaccine use and an urgency in their mission to educate a misled public about vaccines’ continuing dangers.

The result has been a threat to herd effects—or, infection control[41]—for certain vaccine-susceptible diseases, like measles, as noted above. While a population can maintain herd effects even while accommodating a small percentage of so-called “free riders”—individuals who opt not to receive vaccines for themselves or their children[41]—too many free riders will tip the balance and result in a population-wide exposure to disease. Herd effects for certain diseases have been achieved by compulsory vaccination programs; however, whenever “expected risks of vaccine injury outweigh those of illness,”[41] sufficient numbers of people will choose not to vaccinate their children and spark a “tragedy of the commons, in which society loses an important benefit because of competing individual

interests."[41] The result of a tragedy of the commons is both an individual and societal harm: the increased risk of falling prey to dire diseases otherwise avoidable via vaccines. When the "expected risks" tipping the balance out of favor with herd effects spring from fear-mongering or bad science, this *tragedy* of the commons is particularly salient.

IV. Applying the Lesson of the Vaccine Controversies to CRISPR

With CRISPR emerging as a new and wide-ranging technology with possible human application in the near future, we can anticipate protests and legal cases analogous to those in the vaccine context. Claims in the vaccine context include allegations both of scientifically disproven causal harm of autism and of scientifically feasible causal injuries included in the Vaccine Injury Table,[52] as well as emotional distress and other tort claims not covered by the National Childhood Vaccine Injury Act.[53,54] Just as "a small minority will suffer adverse reactions" from otherwise beneficial vaccines,[54] some recipients of CRISPR gene-editing can be expected to experience detrimental results, including those related to off-target effects. Claims centering on CRISPR might similarly include causal harm of unforeseen or unintended injuries by either somatic or germline gene-editing, as well as wrongful life caused by germline gene-editing, which might be understood to engender entire physical and even emotional and intellectual identity changes sufficient to support a claim that a different identity—a different person—was made to come into existence when it otherwise would (or should) not have.

The vaccine controversies can serve as a harbinger of challenges to come if we cling to fear, but also of potential benefits if we cautiously embrace scientific advancements. Will there be a tragedy of the commons, as with vaccines, when herd effects are threatened or thrown out of balance? What will be the implications for decision-making autonomy when choosing—or choosing not—to utilize a technology? With these concerns in mind, we can briefly revisit Erik Parens' question, "Is eugenics inherently bad?" Can excessive concern regarding CRISPR endanger its ethical regulation and eventual therapeutic application?

At the heart of these questions is the distinction—if we perceive one—between vaccines and gene-editing technology. We must determine what a "tragedy of the commons" in the CRISPR context would imply, and whether we can expect our society to find CRISPR less acceptable than it does vaccines. Just as vaccines aim to provide protection we lack genetically, so, too, would CRISPR in its therapeutic application to preexisting genes containing painful and even life-threatening disorders. With copious evidence of their profound health benefits,[55–57] vaccines serve as a seasoned correlate to CRISPR, which has already been proven to provide cures for cancer and eye diseases.[18,58–60] (Furthermore, the benefits achievable via CRISPR gene-editing applied to the germline could be rendered closer to permanent within a familial line or even society at large: if monogenic diseases are edited out on the germline, gene therapy would be needed for those genetic glitches only if they reemerge as spontaneous mutations.) Thus, we can reason that to protest the therapeutic application of CRISPR without firm scientific support for doing so is equivalent to—or perhaps even worse than—opposing vaccine administration.

We have already heard some commentators shun CRISPR by insisting on the overarching need to maintain genetic diversity, even if it means that the few—i.e., those with severe impairments—suffer physically and emotionally in order to bring that genetic diversity to the species. This speculative argument has been seen before, in the context of preimplantation genetic diagnosis. Others make the more compelling and nuanced argument that if we were to eradicate a gene responsible for an impairment, we would relieve the suffering associated with that impairment but might inadvertently eliminate a beneficial trait located on, or interacting with, the same gene. A clear example of this phenomenon would be the eradication of sickle cell anemia at the expense of a reduction of protection against malaria.[61] Such careful interrogation of the implications of gene-editing will only strengthen further research and help refine its eventual application so that the benefits can more heavily outweigh the risks. To deny CRISPR's already-known benefits because of its already-known risks would be to truncate scientific progress that could result in both an individual and utilitarian good.

V. Conclusion

Controversy ensues whenever a new technology—especially one predominantly affecting human identity, reproduction, and/or children—presents a novel way of performing and thinking about medical intervention. But for better or worse, CRISPR has already begun to lag behind the hype, even while continuing to speed ahead of legislation. Fears of CRISPR's being used to engineer so-called "designer babies" are as yet unfounded: although CRISPR is being used to fight polygenic diseases like cancer and diabetes, many traits—physical, emotional, cognitive—could not be edited to create a designer baby.

The potential route to safe, effective, and ethical gene-editing is the subject of an ongoing discussion internationally by leading scientists and ethicists. The debate seeks to reconcile scientifically and ethically justified concern about certain potential dangers of germline gene-editing—such as unforeseen side effects,[20,62] lack of future children's informed consent,[20,62] and, of course, detrimental eugenics[23]—with the need to foster rigorous research and eventual application of CRISPR to somatic cells in order to eradicate individuals' genetic diseases. With respect to germline gene-editing, several countries, including Canada and Mexico, already have a legislative ban, while others, including China and India, have instituted bans within guidelines, which carry less force than legislation.[63] These bans, fueled by "an exaggerated but potentially pervasive view that gene-editing technologies will lead to science-fiction scenarios in which humans are bred upon design leading to a whole array of unanticipated effects,"[64] threaten scientific progress, both with respect to gene-editing (germline and somatic) and generally: the inflated nature of such fear could precipitate increased "distrust [of] scientists and overcaution on the use of the current technologies, which may inhibit their full exploitation for less problematic and more fruitful applications in somatic gene therapy, biotech and biomedical research."[64] The intense focus on the germline is delaying—potentially indefinitely—life-improving and -saving research on the eradication of painful genetic disorders.

It is critical for not only scientists, ethicists, and lawyers working on possible vaccine and gene-editing regulations, but also for the public as potential consumers, to ascertain the

character and likelihood of these technologies' potential dangers. Physicians and patients alike are certainly right to seek to the medical risks of vaccines, such as allergies to certain ingredients like eggs or latex,[65] and the rarer risks of anaphylaxis and encephalopathy[52]; likewise, they must consider the predominant medical risk of CRISPR—off-target effects[66,67]—which scientists are working to diminish.[68] However, to allow fear of these risks to obfuscate these innovations' very tangible benefits would be an irresponsible and potentially more dangerous option. Scientists, lawyers, ethicists, and the public must engage in thorough, thoughtful debate and research into how—not whether—to best use these technologies in service to our individual and collective health. By examining the individual and public-health dangers associated with vaccine abstention, we can discern the need for a tempered approach to CRISPR conversation that might lead to regulation and ethical application. Although CRISPR's reach will continue expanding as research continues, therefore requiring continuous evaluation, the answer is not to shut down regulation and application now, but to thoughtfully conjoin productive debate and action so that therapeutic gene-editing can begin to alleviate suffering as soon as possible without precipitating social outcomes we would belatedly deplore.

So before we leap to protest CRISPR, let's collect scientific, ethical, and legal knowledge; engage in hearty and productive debate; and be sure not to throw out the proverbial—and literal—baby with the bathwater.

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