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Governing Human Genome Editing

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FROM THE EDITORS

Ethics, Values, and Responsibility in Human Genome Editing

Sean C. McConnell, PhD and Alessandro Blasimme, PhD

CRISPR/Cas9 genome editing is an inexpensive and efficient tool to introduce changes in DNA. Its ease of use sets virtually no limits on potential scientific and clinical applications. Prospects include correcting congenital monogenic disorders, targeting disease-causing molecular lesions,[1] and even altering multiple genetic loci at the same time.[2] Beyond therapeutic applications, there is at least in principle the possibility that CRISPR/Cas9 can be used to enhance human traits,[3] such as resistance to infectious diseases, strength, or cognitive capacity. Such interventions can target somatic cells in adults or be employed in embryos during early development. Genome editing at the beginning of embryonic life means that any genomic alteration introduced will pass on to the germline and propagate through future generations. These possibilities have sparked considerable debate about germline genome editing ethics, governance, and the scope of responsible use of germline interventions.[4]

An announcement by Chinese researchers in April 2015[5] that they had edited human embryos initiated public controversy and fear about germline genome editing.[6] In November 2018, He Jiankui announced the birth of twin girls with a modified version of the CCR5 gene,[7] an alteration that could confer resistance to HIV infection. Similar experiments are being planned in Russia.[8] Some have argued that the promise of safe and effective germline genome editing therapies should prevent any outright ban or prohibition[9] and that using gene editing to improve prospects of future persons could even be a moral imperative.[10]

However, many researchers and organizations have expressed reservations about germline editing. It has been argued that ethics and governance debates should go beyond the imperative of clinical innovation by paying attention to respect for human rights[11] and dignity[12] and by carefully considering unknown consequences for gene-edited people and future generations, both in terms of safety and possible eugenic uses of this technology.[13] Others have pointed to the availability of safer and more ethically acceptable means of preventing congenital genetic defects, such as pre-implantation genetic diagnosis.[14] Still others fear that, if anything goes wrong with human germline editing, research on and clinical use of somatic cell therapy could face reputational crises.[15] Consensus has gradually emerged in the scientific community about the need for an international moratorium on premature clinical uses of human germline editing.[16,17,18] Public dialogue aimed at reaching "broad societal consensus"[16] on uses of

genome editing has also emerged as key to the legitimacy of governance decisions about such controversial technology.[19]

Given that the first clinical trials involving somatic uses of CRISPR/Cas9 are underway,[20,21] genome editing is primed to foster dramatic innovation in patient care provided that it is used responsibly. A group of scholars—including national and international experts in ethics, governance, science, and medicine—discuss such pressing matters in this issue of the *AMA Journal of Ethics*.

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CASE AND COMMENTARY

How Should Physicians Respond When They Learn Patients Are Using Unapproved Gene Editing Interventions?

Carolyn Riley Chapman, PhD, MS and Arthur L. Caplan, PhD

Abstract

Hundreds of gene therapies are currently in various stages of research and development. A subset of these involve gene editing technologies such as CRISPR. In this hypothetical case, a patient with chronic pain has initiated a CRISPR-based intervention obtained from a clinic in the Cayman Islands. His physician doubts it is approved by the US Food and Drug Administration and worries about its safety. The case presents ethical questions about potential violations of US regulations regarding the sale of products intended to affect human health, patients' lack of understanding about risks of unproven drugs, and suboptimal support for and management of patients with chronic pain. We discuss how physicians should address these questions.

Case

Dr T is surprised to see a patient, Mr J, at the gym. For years, chronic pain has kept Mr J away from most physical activity. Not having seen Mr J for a couple of years, Dr T asks how he's doing and learns that Mr J had been using a recently developed clustered regularly interspaced short palindromic repeats (CRISPR) tool designed to permanently modulate inflammation. Mr J explains that he ordered this intervention from an American clinic in the Cayman Islands, reports improved sleep and capacity to exercise, and notes heartburn as the only side effect. Dr T suspects this CRISPR application is not approved by the US Food and Drug Administration (FDA) and asks Mr J to schedule an appointment for follow-up. Dr T's view is that direct-to-consumer CRISPR tools should remain prescription only, since peer-reviewed clinical evidence in support of this CRISPR application is minimal. She's concerned that Mr J's use of it is too risky and wonders whether she should both gather more information from Mr J to help him and report the case to the FDA.

Commentary

A patient has obtained—likely via an internet-mediated mail order—a CRISPR gene editing product from "an American clinic in the Cayman Islands." Presumably, the intervention was not prescribed by another physician but was advertised and marketed by the entity providing the so-called therapy "designed to permanently modulate

inflammation." Although this case is hypothetical, it does bear similarity to events that have actually happened.

Similar Cases

In October 2017, a biohacker livestreamed himself self-administering a CRISPR-based experimental intervention for muscle enhancement.[1] That year, another man recorded himself self-injecting an experimental gene therapy supplied by a Singaporean company; he hoped the investigational agent would stimulate his immune response to HIV.[2,3] This company's late chief executive officer also recorded himself using an investigational gene therapy—this one intended to treat herpes simplex virus.[4] He catalogued the company's experimental gene therapies in a Facebook post, noting that they would be made available to the public.[4] In another case, a scientist affiliated with both an academic institution and a company administered an investigational herpes vaccine to people in both the United States and St. Kitts, without approval from the FDA, St. Kitts regulatory authorities, or local institutional review boards.[5,6]

One might dismiss these and similar cases as of small public health concern, but these unproven products could harm those who use or consume them. There is additional concern, albeit small, that these products could pose risks to people who do not actually take them. For example, Germany banned all imports from a California-based company that sells DNA reagents and gene editing kits because some of its products were contaminated with pathogenic bacteria.[2]

The hypothetical case, as well as the real ones, prompts questions about proper roles of government in regulating drugs and biological interventions, the health and media literacy of the public, and how patients might respond when a health care system does not or cannot meet their needs. The case also highlights ethical obligations of clinicians to (1) communicate with patients and provide appropriate care, (2) report potential violations of US regulations regarding sale of products intended to affect human health, (3) educate patients about risks of unproven drugs in the context of the FDA's mission to protect public health, and (4) optimally support patients with chronic pain.

Caring for the Patient

Dr T is right to ask Mr J to schedule an appointment, especially since he is experiencing heartburn, which he seems to attribute to the CRISPR product. Other more serious conditions, such as angina, can mimic heartburn pain. Since she suspects the product Mr J used is not FDA approved, its safety profile is uncertain. Although side effects will likely be product specific, clinical concerns about gene editing products include possible infection, immunologic reactions, and unanticipated molecular and cellular effects.[7] Dr T will want to get an updated health history from Mr J. She will also want to check his vital signs and order tests to check for possible intervention-associated toxicity. Because Mr J

might not realize why she wants him to come in, Dr T should communicate her concerns to Mr J before she leaves the gym.

Duty to Report

The FDA is tasked with protecting public health by ensuring the safety and efficacy of human drugs, biological products, and devices. According to the agency, sale of gene-editing products or kits intended for self-administration is illegal.[8] Companies, institutions, or individuals who want to do clinical research on experimental gene editing products in the United States must first submit an investigational new drug application to the FDA before administering any product to humans.[8] To market a gene editing product, companies must first receive authorization from the FDA, a process that includes submission of evidence of the product's safety and efficacy via a biologics license application.[8] A product marketed on the basis of its efficacy for a particular disease would be within the agency's jurisdiction.[2] Furthermore, it is generally illegal to import unapproved products or devices for personal use into the United States.[9] However, FDA regulatory guidance suggests it might be appropriate for agency personnel to refrain from taking enforcement action against illegal personal importation under specific circumstances.[10] Enforcement discretion may be exercised when there is "no known commercialization or promotion to persons residing in the U.S. by those involved in the distribution of the product at issue" and when other criteria are met.[10]

Notwithstanding these policies, there is much confusion about rules regarding self-experimentation and importation of drugs or devices for personal use. Companies might intentionally leverage regulatory loopholes to justify freedom to operate. For example, one company executive claimed in 2017 that the company's products were labeled as not for human consumption and that individuals had a right to use them to self-experiment.[2] Although the FDA has authority to enforce marketing claims about a drug or device, DNA editing reagents are widely available for research use and it is difficult for the agency to regulate self-administration.[2] The agency itself has maintained that "the use of FDA resources to provide comprehensive coverage of unapproved new drugs imported for personal use is generally not justified."[10]

Does Dr T have an obligation to report this incident and, if so, to whom? In general, physicians must maintain patient confidentiality unless there are significant reasons not to, such as risk of serious harm to third parties. If Dr T is worried about others' safety after learning more about Mr J's situation, she should discuss her concerns with Mr J. Ideally, Mr J would agree that information about the product he self-administers should be shared with the FDA. Dr T could likely alert the FDA while still maintaining Mr J's confidentiality. The American Medical Association *Code of Medical Ethics* asserts that physicians should "consider the health of the community when treating their own patients and identify and notify public health authorities if and when they notice patterns in patient health that may indicate a health risk for others."[11] Although this

recommendation likely refers to infectious diseases, it is also applicable to Mr J's case. The FDA has a website, "Reporting Unlawful Sales of Medical Products on the Internet,"[12] which lists phone numbers and provides links to online forms that can be used to report.[13] There are different forms to use, depending on whether life-threatening or serious reactions are involved.[12,13]

Educating Patients and the Public

Mr J's hypothetical case and the real-life ones indicate the need to educate the public about risks associated with investigational drugs and biologics. *Therapeutic misconception* is a concept that describes the common misperception held by research participants that enrolling in a clinical trial will have therapeutic benefit for them personally[14]; similarly, they might overestimate the benefits and underestimate the risks of using unapproved drugs. Given that less than 12% of new molecular and biologic entities make it from phase I clinical trial investigation to FDA approval and that even those that reach phase III clinical trial investigation only have about a 56% chance of getting FDA approval,[15] it's fair to say that many experimental agents do not meet minimal safety and efficacy standards. It makes sense that patients like Mr J—who have illnesses that reduce their quality of life and needs left unmet by the allopathic health community—would be willing to try experimental agents. However, they might not fully appreciate that most investigational agents likely lack effectiveness and can cause serious harm. Dr T should discuss these points with Mr J.

According to the FDA's website, the agency has responsibility for "helping the public get the accurate, science-based information they need to use medical products … to maintain and improve their health."[16] Physicians share in this obligation.[17] Challenges to FDA authority (in the form of illegal sales or loophole exploitation) should be addressed proactively. The FDA and health professional associations can and should do more through social and mainstream media to educate patients about risks of unapproved drugs and benefits of public health protections provided by the regulatory process for marketing authorization in the United States. For example, the FDA's Real Cost campaign, launched in 2014, educates youth about the dangers of tobacco use.[18] The Federal Trade Commission also has a website that advises consumers to check whether they are dealing with a legitimate US pharmacy before buying health products online,[19] but perhaps the messaging could be amplified to reach a wider audience.

Treating Pain

Since Mr J resorted to alternative interventions for his pain, he might have felt unheard and possibly abandoned by his physician or by the health care system at large. It also might be the case that therapeutic options were available for Mr J in the United States but that he was unable to access them. If Dr T had been able to help Mr J with his pain, Mr J might not be mail-ordering gene editing tools from a company in the Cayman Islands. Recall the real-life case in point of one man's decision to inject himself with gene

editing reagents after problems with his insurance prevented his access to HIV medication.[3] In an environment in which significant numbers of patients are seeking alternative and complementary interventions,[20] Lo argues that "the medical research community should listen to and respond to the concerns that lead patients to seek untested therapies, including deep frustration over the lack of effective treatments, perceived disrespect, and marginalization of their needs."[6]

What could Dr T have done better? The case suggests that Dr T was aware that Mr J's quality of life had been significantly undermined by his pain. Yet Dr T had not seen Mr J in an office visit for a couple of years. One hopes that Dr T reached out to Mr J by phone when he did not show for or canceled his last appointment. Physicians who treat pain must make every effort to support their patients in accordance with up-to-date clinical practice recommendations and guidelines. Reducing the burden of pain has been identified as a significant public health challenge that must be addressed to stem the ongoing opioid crisis.[21] Notably, the US Health and Human Services Pain Management Best Practices Inter-Agency Task Force recently issued its final report.[22] The task force recommends that physicians employ a multidisciplinary approach to deliver individualized care to patients experiencing pain.[22] Treatment options include medications and restorative therapies as well as interventional, behavioral, complementary, and integrative health approaches.[22] If Dr T does not feel she can provide optimal pain treatment, a referral to a specialist would be in order. In the future, her clinical practice could also implement policies to better support patients in achieving continuity of care.

Conclusion

This case highlights several physician obligations, some of which are patient centered while others are focused on public health. If physicians suspect that a patient is using an unapproved product, their first duty is to ensure the health and well-being of the patient. They also have an ethical and legal obligations to report to the FDA if they are concerned about harm to others. In addition, they should educate patients about the risks of using unapproved products or devices. More generally, health professionals have a responsibility to foster health literacy and public understanding of the benefits of a regulatory system for overseeing and authorizing product and device marketing in the United States. Lastly, physicians must stay abreast of up-to-date pain treatment recommendations to help patients access the best possible care.

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CASE AND COMMENTARY

Using the 4-S Framework to Guide Conversations With Patients About CRISPR

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Abstract

As patients with genetic diseases seek to have healthy biologically connected children, they will undoubtedly turn to trusted health care professionals for guidance. "Doctor, should I enter a clinical trial to edit my embryos?" is likely to become a query posed by patients with genetic illnesses. Physicians need both empathic communication skills and a framework for responding to this question. Applying the 4-S framework to gene editing can guide clinicians' responses to patients' CRISPR queries by facilitating discussion of (1) safety, (2) significance of harm to be averted, (3) impact on succeeding generations, and (4) social consequences.

Case

Dr H assists reproduction for couples who desire biological children. Ms A has struggled throughout her life to cope with a rare X-linked disease, so Dr H recommended genetic counseling. Ms A and her husband learned that their offspring would inherit at least one pathogenic allele without intervention. Ms A remains adamant about not passing on a pathogenic variant to a child.

When following up with Dr H, Ms A and her husband explain that they have seen reports of successful germline editing, and they inquire about what they've seen referred to as "genome microsurgery," a technique for removing a pathogenic allele. Ms A states that she wants this done prior to Dr H's intrauterine implantation of an embryo.

Dr H clarifies that there are currently no available "off-the-shelf" approaches to eliminating or correcting this specific allele. Ms A states, however, that she can access germline modification of this specific allele through a clinical trial. Dr H urges caution and further clarifies that, even if Ms A gains access to the germline modification, risks such as off-target effects (mutations at sites that were not the target site of modification) can generate unknown consequences that could potentially harm their child and future generations. Ms A asks Dr H to advocate on the couple's behalf and help them enroll in the trial. Dr H struggles with how to help manage Ms A's hopes and expectations and considers how to respond.

Commentary

Chinese scientist He Jiankui's announcement in November 2018 that he used CRISPR technology to create babies whose genomes were modified to have built-in resistance to HIV upended the scientific world and catapulted genome editing into the public square.[1,2] While many scientists and ethicists condemned He's actions,[3] the presumed success of his rogue experimentation also generated hope for individuals seeking to obliterate mutations for heritable diseases in their offspring. Patients like Ms A, who have suffered the consequences of rare genetic diseases, will understandably go to great lengths to avoid transmitting a disease to their children. Although germline editing of human embryos is not yet being investigated in clinical trials in the United States, the first in vivo human study of a CRISPR-based intervention for a rare form of inherited blindness recently began enrolling patients.[4] The reality of human genome editing will put health care professionals at the center of decision making with patients desperate to have healthy biologically connected children.

How should clinicians respond when a patient asks, "Doctor, should I enter a clinical trial to edit my embryos?" The 4S Framework (safety, significance of harm to be averted, succeeding generations, and social consequences) can guide a clinician's response to and subsequent conversations with patients desperate to find ways to avert illness and suffering in their children.[5] Managing patients' hopes and expectations also requires empathic communication skills, including establishing trust, giving patients a clear recommendation while acknowledging uncertainty, and using ask-tell-ask as a method of confirming their understanding.

Empathic Counseling

Listening to patients' concerns and eliciting their values is a critical starting point for conversations with patients about editing their embryos. Ms A is looking to Dr H for guidance and seems to be expressing 3 primary values: she wants a healthy child, she does not want to transmit pathogenic alleles to her children, and she seems to have a preference for a biologically connected child. Clarifying whether and to what extent these are indeed her values, ensuring that her preferences are not based on faulty reasoning, and exploring alternatives to gene editing are important next steps in a conversation. While it would seem that these values are at odds with adopting a child or a using a surrogate egg donor, exploring these alternatives is nevertheless reasonable.

Dr H might consider referring Ms A to a genetic counselor, who can help ensure that she understands the inheritance of her disease, how likely it is for her children to be affected, the practical implications of transmitting a pathogenic allele to descendants, and the availability of treatment to mitigate harms of the disease in an affected child. If Ms A has an X-linked recessive disease and her husband is unaffected, barring skewed x-inactivation with each pregnancy, she has a 50% chance of having sons and daughters who carry one copy of the mutated gene but are not affected by the disease. If Ms A has

an X-linked dominant disease and her husband is unaffected, she will pass one normal or one affected chromosome to each child such that, with each pregnancy, she has a 50% chance of having either an affected daughter or son. If Ms A has an X-linked dominant disorder and her mutation is not de novo, there would be no male-to-male transmission of the mutation.

It is important for Ms A to understand whether her X-linked disease is recessive or dominant so that she can explore her options for preventing transmission of the disease to her children. If she has an X-linked recessive disease, she could use sex selection to ensure birth of a girl who would be unaffected but have a 50% chance of carrying a mutation for the disease.[6] However, if she has an X-linked dominant disease, sex selection will not definitively prevent its transmission. In that case, her desire to have a healthy biological child could likely be achieved through preimplantation genetic diagnosis, which would allow her to select for implantation only those embryos that do not carry the mutation. It would be important to explore with Ms A whether having a daughter who is a carrier but does not manifest the disease would alleviate her concerns. It would be unreasonable to accept the uncertain risks associated with CRISPR merely to prevent transmitting a mutation that would not actually cause disease in the carrier though it could be transmitted to the carrier's descendants.

It is, however, possible that none of Ms A's embryos obtained through preimplantation genetic diagnosis would be free of the disease she fears passing on. I am indeed aware of such cases, so this is not just a theoretical possibility. In such a circumstance, Ms A might eagerly turn to CRISPR as a technology that could allow, prior to implantation, editing of an embryo to remove the mutation associated with the X-linked disease.

In order for Dr H to help manage Ms A's hopes and expectations, Dr H will need to engage in a difficult conversation on this controversial topic. As with other difficult conversations, it will be important for Dr H to establish rapport with Ms A. Ms A's query of Dr H indicates her interest in Dr H's perspective and that she trusts Dr H's judgment. The conversation is likely to elicit an emotional response from Ms A, including, perhaps, expressions of fear and worry about the health of her descendants and her strong desire for biologically connected children. Dr H should acknowledge Ms A's predicament and respond to her emotional cues as a way to build rapport, align with Ms A's goals of having a healthy biologically connected child, and understand Ms A's concerns about the possibility of transmitting a genetic disease that could be prevented. Just as one does when delivering bad news, so one should be direct, use simple language, and give a clear recommendation when discussing gene editing with patients. The ask-tell-ask method can help to ensure mutual understanding of the risks and benefits of and alternatives to CRISPR.[7]

Applying the 4-S Framework

The 4-S framework can help guide Dr H's conversation with Ms A.

Safety. First, it is critical that the safety of CRISPR be discussed, since CRISPR carries uncertain risk of off-target mutations (ie, unintended edits in DNA).[8,9,10,11] What we don't know is the rate at which off-target mutations occur and the harms associated with each off-target mutation, so it is important to consider the possibility that off-target mutations could introduce heritable errors associated with other diseases. As DNA constantly mutates, it is also possible that editing it could have little impact on patients or their descendants. Ms A should be encouraged to have a conversation with the principal investigator of the trial to better understand the results of animal studies that preceded the trial with human subjects. Additionally, if available, preliminary results from studies in humans could help inform her decision about whether to enroll in this study. Ms A would then be in a better position to weigh the uncertain risk of off-target mutations against the risks of alternatives to gene editing for creating a family.

Significance of harm to be averted. Second, Dr H should discuss eligibility criteria for the trial, including the significance of the harm to be averted through CRISPR relative to the uncertain risks associated with trial participation. The ethical justification for accepting an uncertain risk of off-target mutations that could lead to exchanging a known disease for an unknown disease depends on the harms to be averted and the availability of alternatives. That is, it is more ethically justifiable to accept uncertain risks of CRISPR to prevent a disease that is serious and for which there is no good treatment. If Ms A's primary goal is merely to prevent transmission to descendants of a carrier mutation that would not cause disease in her offspring, the benefits of participating in a CRISPR trial would not be outweighed by risks and she should be disqualified from participating. The harm associated with transmitting a carrier mutation would not rise to the threshold for which we should accept the uncertain risks of CRISPR.

Impact on succeeding generations. Third, Ms A should consider unknown consequences of germline gene editing on succeeding generations. This is an abstract and challenging conversation to have with a patient who is likely to be focused on tangible, short-term consequences of her decision. Dr H can inform Ms A that many countries agree with the view of the Oviedo Convention that "an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants."[12] Moreover, a group of scientists has recently called for a "global moratorium" on the use of heritable genome editing.[13] This call for a pause in CRISPR use is intended to enable greater public engagement and discussion of its social and ethical implications as well as development of an international framework governing germline editing.

While concerns about CRISPR's impact on future generations should give us pause, it is unlikely to be a compelling reason to Ms A not to participate in a clinical trial. Given her own experience of suffering a rare genetic disease, she is likely to believe that it would be a very good thing to prevent descendants from having this mutation. The challenge

lies in helping Ms A understand that tampering with our genes is complex and that there could be unintended negative consequences for her descendants once a gene is altered. In order to avoid such consequences, human germline editing should first be explored in animal models, used only when there is no other way to prevent a devastating genetic disease in descendants, and delivered in the context of a clinical trial in which human subjects can be carefully monitored.

Social consequences. Lastly, Dr H should discuss social consequences of using CRISPR. The technology raises profound ethical questions, and there is currently no scientific or social consensus on whether and when it is ethically justifiable to use CRISPR. Concerns about "designer babies" whose genomes have been edited to enhance their intelligence, physical appearance, or athleticism have led some to fear that we are on the verge of sliding down a slippery slope. These concerns suggest the need for clear ethical and governance structures before proceeding with germline genome editing. In opposition to this view, it can be argued that genetic enhancement has the potential to level the playing field and bring health equity to those who did not win the biological lottery. The technology, if available to all, could be used to benefit the most vulnerable members of our society.

Navigating Uncertainty

Social anxiety associated with CRISPR is reflected in hyperrealist hybrid sculptures by the Australian artist Patricia Piccinini.[14,15] Her sculptures compel us to be humble and cautious as we adopt this technology. Piccinini's creations likely don't reflect real risks associated with CRISPR, but they do remind us of the uncertainty associated with this technology. Proceeding with caution in the face of uncertain consequences has been urged by the National Academies of Sciences, Engineering, and Medicine[16] and the Nuffield Council on Bioethics[17] in the United Kingdom, both of which argue for broad and inclusive social debate. While there is need for discussion and deliberation, in our pluralistic society consensus is unlikely.

Yet CRISPR is a beacon of hope for patients who suffer genetic diseases. Compassionate clinicians focused on patients' well-being and best interests can guide patients facing difficult choices accompanying its use. The 4-S framework, implemented with empathic communication skills, provides a structure for difficult conversations. As our patients begin to query us about whether to participate in CRISPR clinical trials, we should encourage consideration of CRISPR's safety, the significance of harms it could help avert, its impact on succeeding generations, and social concerns about its use.

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CASE AND COMMENTARY

How Should "CRISPRed" Babies Be Monitored Over Their Life Course to Promote Health Equity?

Charis Thompson, PhD

Abstract

Gene-edited babies who might be born in the future should be monitored over the course of their life. These patients' physical, mental, and social health monitoring should be coordinated by clinicians in ways that anonymize patients' data for privacy protection but also allow for national and international aggregate evaluations. Transnational monitoring efforts should focus on safety and efficacy, social and disability justice, what constitutes the standard of care, and how best to promote both access to care and social and genomic research and innovation. In addition, effective and binding mechanisms for stopping or limiting uses of gene editing technology should be developed.

Case

Dr L and her team are germline editing researchers who are about to begin work with Dr M at her university hospital fertility clinic on a germline genome editing pilot protocol approved after extensive public comment and review by ethical, safety, disability and social justice, and regulatory bodies. Four couples in which both partners are carriers for well-studied severe monogenic conditions have given their consent to be involved in the clinical trial.

Later in the week, Dr L, Dr M, and the couples will be meeting with Dr C and Dr D, who have been designated as the long-term monitoring physicians for physical and mental health, respectively, for any children born from this trial. They will also be meeting with Dr Q, a bioethics specialist, who will be monitoring the social aspects of follow-up care. The purpose of these meetings is to debrief with clinical teams about what kind of follow-up monitoring, care, and feedback are appropriate. What should they cover in these meetings? How should babies who underwent germline genome editing be monitored over the course of their life?

Commentary

The world's first known "CRISPRed" babies, Chinese twin girls, were born in October 2018 after researcher He Jiankui used clustered regularly interspaced short palindromic repeat (CRISPR) technology to disable a gene called CCR5 in their genomes so as to

render the babies immune to HIV.[1] Their father is HIV positive; their mother, the primary clinical patient-subject from whom the eggs were extracted and who gestated her twin pregnancy after the genome-edited embryos were transferred to her uterus, is HIV negative.[1] This case brought home to the world the reality of germline genome edited, or CRISPRed, babies. Not only have the girls' genome been altered; if the girls later reproduce using their own eggs, their resultant children will inherit the genetic modification, which in turn is heritable down subsequent generations. Neither girl had—nor will any of their genetic descendants have—the option of consenting to this modification. To many in China and the West, it was legally questionable, ethically problematic, scientifically premature, and clinically unnecessary to take CRISPR clinical at the time and for the condition in question.[1] The absence of guidelines and mechanisms for follow-up care and monitoring of the babies, together with a lack of clear pathways by which feedback from such monitoring might be used to improve or halt CRISPR as appropriate, highlights the sense of prematurity. This is the right moment to plan ahead for comprehensive monitoring and care should there be any future CRISPRed births.

Types of Monitoring

Physical. Monitoring of CRISPRed children needs to be guided first and foremost by the children's well-being. This purpose should never be displaced by scientific goals. Dr L (the genome editing researcher), Dr M (the assisted reproductive technology clinician), and the couples should draw up a plan with Dr C (the primary care and coordinating physician) for monitoring and, when necessary, mitigating physical effects of the modification. It is likely that karyotyping and genome sequencing would be recommended. This can be done prenatally or postnatally using biopsy or phlebotomy methods commonly available in resource-rich countries during routine prenatal or postnatal care. This information would allow Dr L and Dr M to check for genetic mosaicism—the incomplete penetration of CRISPR-mediated DNA edits—and to screen for unintended off-target effects. Knowing the efficacy and precision of the intervention might leave health-related questions unanswered at first because clinical consequences of an intended edit and of off-target or incomplete effects will be unknown. The clinical justification for collecting this data, however, is to begin to build an evidence base for future understanding and care. To reach this goal, there should be a centralized mandatory digital reporting facility with international oversight that would collect anonymized, privacy-protected data on every CRISPRed child. The data in this repository should be tied to and inform ongoing medical care and scientific and social policy. The World Medical Association, together with the World Health Organization and its statistics repository, the Global Health Observatory,[2] would be an ideal locus for this international data collation. The United Nations Convention on the Rights of Persons with Disabilities,[3] the Oviedo Convention,[4] and reproductive data collection efforts such as the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System are examples of important potential national and international regulatory and data collection partners.

CRISPRed babies and children should be monitored throughout their lives in a routine manner, with additional scrutiny for residual effects of the original disease or condition for which the technique was employed in the first place and for any physical effects that might be linked to the intended edit or to off-target effects. The baseline against which their health and well-being should be evaluated should be the health of those receiving standard of care for the condition but whose genomes were not edited. Although in practice standard of care varies according to local biomedical infrastructure and health care access, if CRISPR applications are translated to the clinic, every effort should be made to adopt the highest standard of care found anywhere in the world for the condition in question. To do so is not just a matter of health equity. Because germline modifications are heritable, they have planetary implications and should not be given a green light in resource-poor settings simply because it is easier to prove relative efficacy and safety against a lower standard of care.

Following childhood, in which the health status and milestones of CRISPRed children are measured against those of children receiving standard of care for the condition, adolescence would be a period for special physical monitoring and care, particularly regarding puberty and the morphology and changes in the DNA of germ cells, which could profoundly influence descendants' reproductive futures. Continuity of prenatal and postnatal care and from childhood through adolescence and beyond should be prioritized. It is important that women who provide eggs or gestation for CRISPRed babies also have their physical health evaluated regularly and that their anonymized privacy-protected data be linked to descendants' data.

Mental health. In a similar manner, Dr L, Dr M, and the couples should draw up a plan with Dr D (the mental health practitioner and coordinator) to monitor childhood milestones and be ready for early intervention if signs of mental health risks emerge in childhood, adolescence, or adulthood. Particular attention should be paid to how the child's understanding of his or her origins might affect the child's sense of autonomy. As a result of disclosure, the child might have difficulty trusting health professionals, which might influence how the child interacts in future with the health care community. The child might experience anxiety related to having been edited or having an unknown biological future. The child's relations to others living with the condition for which the child has been edited also could be complicated. And the impact of widespread public antigenome editing sentiment might affect the child's well-being.

Mental health services would need to be available in case the child came to resent having been edited or being targeted by opponents of germline editing. Mindful efforts should also be made by the whole care team to pre-emptively involve the child or adolescent in directing his or her future and the future of CRISPR, including consideration of options to have the edit clinically reversed in some of their own cells (via somatic genome editing) or their offspring's cells (via germline genome editing). Dr D should also monitor family-

level mental health and arrange treatment, as appropriate, given that a family is likely to be a significant unit of well-being for the child.

Social issues. When Dr L, Dr M, and the couples meet with Dr Q (the bioethicist and social coordinator), they should discuss which social issues need monitoring and how to begin to do that. Crucially, Dr Q will need to liaise with clinicians, insurance companies, and policymakers to ensure access to and affordability of treatment and comprehensive long-term monitoring of and health care for CRISPRed babies, regardless of ability to pay. Other core considerations include ethical questions about monitoring itself, such as ensuring consent to participate in monitoring and privacy of data collected during monitoring. Questions about monitoring also compass science and industry relations—for example, whether any children's data were used for research and innovation. Might the family, and later the child, consent to allow use of the child's anonymized data to improve the CRISPR process itself or the care of others with the condition from which they might otherwise have suffered? Should they or causes with which they are associated benefit from any profit sharing or other returns from a profitable biomedical innovation? Plans will also need to be in place to develop international regulatory standards. Without shared international standards and regulations, medical tourism by and for the wealthy, exploitation of lower-resourced egg donors or surrogates or clinical trial participants across borders, and nonevidence-based treatment advertising are all likely to develop and to exacerbate inequalities of nation, class, and race.[5,6]

The families and Dr Q should also discuss how to liaise with health and disability justice activists so that information can be passed among all parties about what it means to experience removal from the genome of a kind of embodiment shared with others. Given that CRISPR risks increasing ableism and diverting resources from the specific condition for which it was used, monitoring in this area is essential to protect the reproductive futures and rights of those living with the condition and those living with disabilities and chronic disease in general. Mechanisms such as regular voluntary meetings among CRISPRed persons and their carers and those living with disability should be put in place to increase solidarity and decrease stigma and ableism. Together, stakeholders could develop standards for unacceptable exacerbation of inequalities, violations of which could trigger responses up to and including a return to a moratorium on germline genome editing should that be deemed the most socially acceptable path. It would be vital to monitor national and international opinion about conditions for which germline genome editing is deemed safe, efficacious, and socially and ethically acceptable and to put in place mechanisms and instruments to halt temporarily or permanently modifications that fail to meet the highest ethical, social, or scientific and clinical standards or that turn out to have significant negative effects on particular groups or on society as a whole.

Finally, Dr L (the genome editing researcher), Dr M (the reproductive technology clinician) and the couples should discuss with Dr C (the primary care physician and physical health coordinator), Dr D (the mental health practitioner and coordinator), and Dr Q (the bioethicist and social coordinator) how to be kept informed about and to participate voluntarily in efforts to coordinate collection of data at national and international levels on ethical, social, and scientific issues and for purposes of research and innovation. (The National Institutes of Health's All of Us Research Program is an important model for this approach.[7]) It will be clinically important for all CRISPRed children to leverage as much robust medical information as possible in making health decisions. Monitoring should always be accompanied by mandates to provide care and to address patterns emerging from the data. The more that flexible but uniform policies can be developed that respect the human rights and dignity of CRISPRed children as well as justice for all others affected by CRISPR, the easier it will be to implement scientific and ethical safeguards for human germline genome editing.

Conclusion

In conclusion, with the help of physicians and other coordinators—and for purposes of setting scientific, clinical, and social policy on genome editing—national and international bodies should at minimum collect data on the following for babies who underwent genome editing as embryos: physical and mental well-being over the life course; efficacy of the editing process relative to standard of care; unintended effects; economic aspects of innovation and access to affordable health care; social effects upon the children themselves and their families; and effects upon individuals living with the condition and on the wider society as selecting against human variation becomes more common.

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HEALTH LAW

What Is Prudent Governance of Human Genome Editing?

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Abstract

CRISPR technology has made questions about how best to regulate human genome editing immediately relevant. A sound and ethical governance structure for human genome editing is necessary, as the consequences of this new technology are far-reaching and profound. Because there are currently many risks associated with genome editing technology, the extent of which are unknown, regulatory prudence is ideal. When considering how best to create a prudent governance scheme, we can look to 2 guiding examples: the Asilomar conference of 1975 and the German Ethics Council guidelines for human germline intervention. Both models offer a path towards prudent regulation in the face of unknown and significant risks.

Introduction

In recent years, there has been a significant debate regarding human genome editing. The debate has intensified with the advent of CRISPR[1,2] and the births of twin girls in China whose genomes were edited at the embryo stage using CRISPR technology.[3] This new technology has certain risks of unknown magnitude coupled with potentially far-reaching consequences—ranging from safety and efficacy concerns, to more nuanced social and ethical implications, to globally profound implications, such as the shaping of human evolution. The potential risks and consequences of genome editing have raised concerns around the world.

Debates are currently unfolding about how best to regulate this technology.[4,5,6] Regulation can take many forms, which may include a moratorium on the technology's use or assessment and enactment of restrictions and standards by regulatory agencies. For the purposes of this article, I refer to governance of genome editing technologies in the broad sense, which includes both permissibility and regulatory burdens. When considering a prudent and ethical form of human genome editing governance, guidance can be obtained by reflecting on how experts dealt with similar bioethical conundrums in the past while also considering recent ethical analyses offered by various national committees and councils presently working on the issue. In this article, I detail 2 such guiding examples: the International Conference on Recombinant DNA Molecules, held at Asilomar, California, in 1975[7] and the German Ethics Council's recent report[8] on human

germline editing. The Asilomar conference provided one template for how to address governance and risk associated with a new biotechnology (recombinant DNA), and the German Ethics Council built on this template by offering a model of prudent governance of biotechnologies related to human germline genome editing.

Human Genome Editing

Human genome editing is the making of additions, deletions, or alterations to the human genome.[9] There are a variety of techniques to accomplish this goal, most involving clustered regularly interspaced short palindromic repeats (CRISPR) and a nuclease enzyme, such as Cas9, that can cleave DNA molecules. The CRISPR-Cas9 technique has the potential to revolutionize genome editing, primarily because CRISPR is "easy to use, low in cost, and a more precise tool for genetic engineering than earlier tools."[10] Now that editing the genome can be accomplished with greater ease and precision, questions of how to ethically and safely allow such alterations to the genome have become immediately relevant.

When analyzing these questions, it is important to recognize 2 distinctive applications of genome editing: somatic and germline. In somatic genome editing, edits are "limited to the treated individual and would not be inherited by future generations."[9] By contrast, germline genome editing involves editing embryos or gametes (sex cells), which, if transferred for gestation, would enable the gene edits to be heritable.[4] Because germline interventions can affect future generations, once made, they can have a ripple effect of great magnitude, which may include the potential to shape human evolution.[11,12] The distinction between somatic and germline editing thus has significant ethical implications.

Beyond this key distinction, the potential risks and consequences—both to individuals and society—of human genome editing are relevant to ethical considerations of nonmaleficence, beneficence, justice, and respect for autonomy and are thus also relevant to the creation of an appropriate regulatory model. Because genome editing technology is at its beginning stages, it poses safety risks, the off-target effects of CRISPR being one example.[13] Another issue is whether gene editing is done for therapeutic or enhancement purposes. While either purpose can prove beneficial, enhancement has potential for abuse.[14] Moreover, concerns exist that genome editing for enhancement can thwart social justice, as wealthy people will likely have greater ability to enhance their genome (and thus presumably certain physical and mental characteristics), furthering social and class divides. With regards to germline editing, a relevant concern is how, during the informed consent process, to respect the autonomy of persons in future generations whose genomes are modified before birth. The questions raised by genome editing are profound, and the risks—both to the individual and to society—are evident. Left without proper governance, significant harmful consequences are possible.

Therefore, at this stage, a prudent regulatory scheme for human genome editing is called for. Below, I detail 2 examples (the Asilomar conference and the German Ethics Council's report regarding human germline editing) that each provide a prudent approach to governance.

Two Prudent Regulatory Models for Human Genome Editing

Asilomar conference of 1975. The early 1970s saw the rise of recombinant DNA (rDNA) technology, which involves the artificial combination of DNA from different organisms. Famed Stanford researcher Paul Berg was doing rDNA research with a virus known to cause tumors, which aroused fear in the scientific community that "introduced genes could change normally innocuous microbes into cancer-causing agents or into human pathogens, resistant to antibiotics or able to produce dangerous toxins."[15] In response to these concerns, scientists created a de facto worldwide moratorium on rDNA research, which resulted in the Asilomar conference convening in 1975 (spearheaded by Paul Berg and other leaders in the field) to further address how the scientific community should proceed with rDNA research. Indeed, the idea behind the conference, referred to now simply as Asilomar (nicknamed after the conference's famed location on the California coastline), was that a congregation of experts could set "their terms of reference regarding risk and governance."[16] The conference ultimately decided to lift the moratorium and agreed on "safety guidelines of varying stringency according to the degree of risk."[15] These safety guidelines ultimately served as the basis of the official National Institutes of Health guidelines with regards to rDNA research.[15,17] Although over time, the risks of rDNA technology proved to be unfounded,[15] these guidelines have been deemed a success story in organized risk management and its broader influence on governmental regulations.[18] The influence of the conference is still felt today, as a similar congregation of geoengineering experts has been dubbed an "Asilomar moment."[16]

While Asilomar has been largely heralded as a success, it has not been without its critics. One of the strongest criticisms is that the conference was largely attended by other scientists in the field and "did not cast a wide net outside the scientific community."[19] As such, some have argued that this limited the "narrative" of the conference to technical safety issues, which excluded governance applications and broader societal and ethical aspects of the technology.[16] Schäfer and Low note, "Although discussions on the broader societal, political and ethical implications of rDNA technology surfaced during early considerations, such framings never came to dominate the discourse, and risk perception remained limited to technical aspects."[16] Berg and Singer argue that this criticism of Asilomar's "failure to consider the ethical and legal implications" was partly because of a "lack of time" and that the "principal and more urgent concern for those gathered at Asilomar was the possible effects of recombinant DNA on public health and safety."[17] The Asilomar model, as a prudent approach to governance in the face of unknown risks, is a useful guide for governance of human genome editing. As with rDNA at the time, the

true scope of the risk of genome editing is currently unknown and is coupled with potential for negative consequences of global scale.

German Ethics Council (Deutscher Ethikrat). In May 2019, the German Ethics Council (Deutscher Ethikrat) released its guidelines on human germline genome editing.[8] The German council recommends that there be a moratorium on human germline editing considering the risks that now exist. The council even goes so far as to call for the moratorium to be internationally binding, which is exceptionally prudent considering the global scale of the risk associated with germline editing. However, the council notes that the moratorium should be revisited and evaluated as new information about the technology comes to light and when risks can be reduced; the council recognizes the ethical support for and beneficial value of the technology and acknowledges that if certain evidential thresholds are attained, germline editing can be ethically performed.

Distinguishing itself from Asilomar, the German Ethics Council highlights ethical and societal considerations beyond a risk-benefit analysis. The German council notes:

> The assessment of the permissibility of germline interventions should not be reduced to a mere risk and opportunity analysis. Rather, it should be based on the ethical concepts of human dignity, protection of life and integrity, freedom, non-maleficence and beneficence, naturalness, justice, solidarity and responsibility.[8]

However, the German council notes that safety is still an important consideration: the "prerequisite of permissibility [of germline editing] is, in any case, a sufficient degree of safety and efficacy of such interventions."[8] Safety and efficacy are merely starting points in the analysis of how to govern the technology's use; societal and ethical implications must then be considered as well. Hence, the German council recommends the creation of an international agency that would evaluate the "scientific, medical, ethical, legal, societal and political implications of germline interventions in humans."[8]

The German Ethics Council is not presently alone in providing substantive and thoughtful guidance for genome editing. Other councils and committees, such as the National Academy of Sciences in the United States[9] and the Nuffield Council on Bioethics in the United Kingdom[20] have also provided guidance, and they—countering a major criticism of Asilomar—are based on experts who are not limited to scientists. The advantage of nationally drawn committees and councils like these is that a wide range of experts (ie, experts drawn from the fields of medicine, biology, law, ethics, economics, and the social sciences) can offer a holistic perspective on the issue to a greater extent than a conference comprising mostly one type of expert.

Evaluating Models

Asilomar. Some have argued that Asilomar was not a success in that the risks associated with rDNA did not ultimately come to fruition.[21] However, I disagree with this notion of failure. The key point of Asilomar at the time (and largely the impetus for the conference itself) was that the risks of rDNA were not known; unknown risks spanned a wide spectrum of possibilities. At one end, risk might be nonexistent or negligible; at the other end, risk might be high with substantial consequences. Proof that rDNA technology is low risk (as turned out the be the reality), was one outcome that some Asilomar attendees considered possible.[15] However, their prudence in the face of the unknown dictated the guidelines they put forth. In this regard, I would argue that Asilomar was a success, in that scientists guided themselves by prudence in the face of unknown risk, allowing such guidelines to be malleable with the input of new information. Asilomar can serve as a model for governance and guidance of genome editing today, as genome editing currently presents unknown risks of similar magnitude to those presented by rDNA back in the 1970s. It is possible that the risks of human genome editing debated and discussed today are overblown and that, like rDNA technology, we will find the risks ultimately to be insignificant. However, until we have more information, it is prudent to appreciate the risks given the potentially large consequences of genome editing, especially germline genome editing.

German Ethics Council. Building on the example set by Asilomar, the German Ethics Council provides a prudent path forward. But the German council goes beyond Asilomar in adopting an inclusive strategy that involves a wide group of stakeholders (ie, not limited to scientists) and also demands that social, legal, ethical, and political implications—in addition to an initial weighing of safety risks—be considered in any analysis of proper governance. Ultimately, the German council recommends a moratorium on the present usage of germline modification, but the council underscores that such a moratorium should not necessarily be permanent, as the germline is not inherently "inviolable."[8] The council recommends that the moratorium undergo regular review with consideration of whether "minimum safety and efficacy requirements regarding germline interventions have been sufficiently met."[8] If such a prudent path (ie, one that appreciates the technology's risks in recommending a moratorium but is also mindful of its benefits in making the moratorium nonsticky and modifiable) can become a true international consensus on how to approach genome editing (particularly germline editing), such a consensus can likely become, in the absence of a binding international agreement, the best possible way to mitigate the technology's risk on a global scale.

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HEALTH LAW

Is Gene Editing Patentable?

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Abstract

Gene editing technologies offer enormous potential for scientific advancement in fields such as medicine and agriculture, but their use also raises serious ethical and public policy concerns. Although advisory groups like the World Health Organization question whether certain forms of gene editing should be permitted, the US Patent Office routinely issues patents protecting this technology. This article considers what the term *patented* means, provides an overview of the US patent system, and discusses the scope of patentable subject matter under US patent law and the role of ethical, safety, and legal considerations in the patent examination process.

Introduction

On July 16, 2019, the University of California (UC) announced the issuance of US 10,351,878— the eighth US patent in UC's portfolio of patents covering its gene editing technology known as CRISPR-Cas9.[1] UC also announced that it anticipates the issuance of an additional 7 related patent applications.[1] In a statement to the press, Eldora L. Ellison, lead patent strategist on CRISPR-Cas9 matters for UC, stated, "We are pleased to add this technique to our portfolio as yet another breakthrough that will ultimately enable more people to live healthier lives."[1]

Ten days later, the World Health Organization (WHO) Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing released the following statement:

WHO … advises regulatory or ethics authorities to refrain from issuing approvals concerning requests for clinical applications for work that involves human germline genome editing. "Human germline genome editing poses unique and unprecedented ethical and technical challenges," said WHO Director-General Dr Tedros Adhanom Ghebreyesus. "I have accepted the interim recommendations of WHO's Expert Advisory Committee that regulatory authorities in all countries should not allow any further work in this area until its implications have been properly considered."[2]

Could the statement released by the WHO potentially prevent or delay the issuance of UC's 7 remaining CRISPR-Cas9 patents? The short answer is no, but to fully understand why, one needs to understand patentability requirements in the United States. This article will provide an overview of the US patent system and discuss the scope of patentable subject matter under US patent law and the role of ethical, safety, and legal considerations in the patent examination process with reference to gene editing.

What a Patent Is

Broadly defined, a patent is a document issued by a government to an inventor or an inventor's assignee that grants the inventor or inventor's assignee "the right to exclude others from making, using, selling, or offering for sale the invention" as described and claimed by the inventor.[3] A government grants a patent in exchange for a full public disclosure of an invention. In return, an inventor or inventor's assignee agrees that the invention will become part of the public domain after the patent term[3] has elapsed. To obtain a patent, an inventor must file a patent application that describes the invention with enough detail to allow a person skilled in the claimed technology to be able to reproduce the invention. Although ethical, safety, and legal considerations are important in the innovation process, the expertise of patent examiners solely concerns the technical merits of an invention. It is important to note that a patent does not provide an inventor with an affirmative right to make, use, sell, or offer to sell the claimed invention. For example, if a product is illegal to make, use, sell, or offer to sell within a country, it will still be illegal for an inventor to do so regardless of patent status.

Patents serve both economic and social functions. Since an inventor is not obligated to publicly disclose an invention, governments grant patent rights to inventors as an economic incentive to publicly disclose scientific and technological innovations rather than maintaining them in secrecy. Governments likewise set patentability standards to encourage the development of certain technologies thought to benefit society and to increase the availability of new, useful products. Although governments can also theoretically discourage innovations potentially harmful to society by excluding detrimental areas of technology from patent protection, in practice, this is rarely done.

Qualifying as Patentable Subject Matter

Article I, Section 8, of the US Constitution grants that "The Congress shall have power to ... promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."[4] Under this authority, the US Congress promulgated federal patent law under Sections 1 to 376 of Title 35 of the US Code[5] and established the US Patent and Trademark Office (USPTO). The USPTO implements these laws through creation and application of federal regulations as set forth in Chapter 37 of the Code of Federal Regulations[6] and with agency guidelines provided to patent examiners in its *Manual of Patent Examining Procedure* (MPEP).[7]

The US patent system currently recognizes 3 types of patents: utility patents,[8] design patents,[9] and plant patents.[10] Utility patents are the oldest and most common type of patent. To qualify for protection as a utility patent, the subject matter of an invention must be a "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," as defined under Section 101 of Title 35 of the US Code.[8] This section of the US Code serves as a gatekeeper for the patent office. If a patent examiner determines that the subject matter of a patent application fails to meet the standard set forth in Section 101 of Title 35 of the US Code, the patent application will be objected to and returned to the applicant. If the application does disclose eligible subject matter, the patent examiner will continue examination of the application. If the application satisfies the remaining requirements for patentability, the inventor will be granted a patent.

Judicial Interpretation of *Useful*

Although the language of Section 101 of Title 35 of the US Code has remained essentially the same since 1793, judicial interpretation and statutory limitations have changed the meaning of *new* and *useful*. Prior to 1903, a patent application could be objected to as not being useful if the claimed subject matter was immoral, unsafe, or illegal.[11] Examples of such subject matter include "a new invention to poison people, or to promote debauchery, or to facilitate private assassination."[11]

In 1903, the Seventh Circuit Court of Appeals rejected this interpretation of usefulness in *Fuller v Berger,* which examined the patentability of a bogus coin detector for use in coin-operated vending machines.[12] In this decision, the court asserted that the definition of *utility* should not hinge on whether an invention might be used for pernicious purposes. Instead, the test of utility should be whether an invention is able to serve any beneficial purpose. If an invention can serve any conceivable beneficial purpose, the subject matter should be eligible for patent protection.

Since this decision, the US Supreme Court[13] and the USPTO[7] have reaffirmed that issues regarding ethics, safety, or legality are no longer considered relevant to an invention's patentability. As stated by the Federal Circuit Court of Appeals in 1999:

> The requirement of "utility" in patent law is not a directive to the Patent and Trademark Office or the courts to serve as arbiters of deceptive trade practices. Other agencies, such as the Federal Trade Commission and the Food and Drug Administration, are assigned the task of protecting consumers from fraud and deception in the sale of food products. Cf. In re Watson, 517 F.2d 465, 474-76, 186 USPQ 11, 19 (CCPA 1975) (stating that it is not the province of the Patent Office to determine, under section 101, whether drugs are safe). As the Supreme Court put the point more generally, "Congress never intended that the patent laws should displace the police powers of the States, meaning by that term those powers by which the health, good order, peace and general welfare of the community are promoted."[14]

Since ethics, safety, and illegality are no longer considered in examining patent eligibility, nothing prevents the USPTO from granting patents on inventions that are illegal to make, use, or sell within the United States. For example, despite the fact that cannabis and cannabis-derived products have been and still are illegal to possess or sell under the Controlled Substances Act,[15] the USPTO has issued hundreds of patents relating to cannabis and cannabis-related products since the 1940s. In fact, the US Department of Health and Human Services was granted a patent entitled "Cannabinoids as Antioxidants and Neuroprotectants" in 2003.[16]

Similarly, since ethical considerations are not relevant in determining patentability, it might be possible to obtain a patent on a new gene editing technique developed in violation of established ethical guidelines. For example, a patent application directed to a new method of human germline genome editing might violate the WHO's new recommendation.[2] If it did, the invention would not be disqualified as patentable subject matter under Section 101 of Title 35 of the US Code. Although it might not pass the scrutiny of other agencies, such as the US Food and Drug Administration, the USPTO would grant a patent on this technology as long as the application satisfies requirements for patentability as set forth in the statute.

Limits to the Scope of Eligible Subject Matter

Although the courts encourage and direct both reforms and limitations of Section 101 of Title 35 of the US Code to be pursued through legislation, only 2 such statutes currently exist. Both were the result of social and ethical concerns raised about the related technology patented. The first limitation was enacted in 1954 as part of the Atomic Energy Act, which provides a ban on patenting nuclear or atomic weapons. This act states, "No patent shall hereafter be granted for any invention or discovery which is useful solely in the utilization of special nuclear material or atomic energy in an atomic weapon. Any patent granted for any such invention or discovery is hereby revoked, and just compensation shall be made therefor."[17] The second limitation was enacted in 2012 as part of the America Invents Act, which provides a ban on patenting human beings. This act states, "Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism."[18] In practice, if a patent application disclosed and claimed a nuclear weapon or a human being, the USPTO would return the application, including an objection stating that the application was directed to nonstatutory subject matter. No further action would be taken by the USPTO.

Proposed Statutory Limitations

During the first 2 weeks of June 2019, the US Senate Judiciary Subcommittee on Intellectual Property held hearings to discuss proposed legislative reform to redefine the scope of patent eligibility under Section 101 of Title 35 of the US Code pertaining to US patent law. Forty-five witnesses testified over 3 days about the potential impact of the

proposed reform. As of the writing of this article, the bill includes the following proposed changes to Sections 100 and 101 of Title 35 of the US Code:

Section 100:
(k) The term "useful" means any invention or discovery that provides specific and practical utility in any field of technology through human intervention.

Section 101:
(a) Whoever invents or discovers any useful process, machine, manufacture, or composition of matter, or any useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

(b) Eligibility under this section shall be determined only while considering the claimed invention as a whole, without discounting or disregarding any claim limitation.[19]

Of particular relevance to the present discussion is the proposed definition of *useful* under Section 100 of Title 35 of the US Code. If the bill is passed in its current format, it is unclear whether this definition would abrogate all previous interpretations of *useful* currently under Section 101 of Title 35 of the US Code. Any remnant case allowing consideration of ethical or legal factors in patentability may officially be removed.

Those in favor of the proposed changes to Section 101 of Title 35 of the US Code assert that changes are necessary to create order out of the labyrinth of case law that currently exists. In contrast, those opposed to changes fear that the proposed definitions will remove social protections and prevent development through case law. It is unclear what will happen with the current proposed bill. As with any legislation, it will likely see many more revisions before a vote.

Conclusion

Whether as a result of statutory reform or USPTO policy, ethics, safety, and legal concerns are no longer considered in the patent examination process. Although this omission might seem contrary to public policy, the USPTO is no longer an appropriate forum in which to address these concerns. At one time, when the USPTO provided the sole review of an invention, it was appropriate for issues of ethics, safety, and legality to be considered in review of a patent application. The USPTO is now joined in its review of new technologies by agencies such as the US Department of Agriculture and the FDA that were created to address these issues in their review processes. This specialization allows patent examiners to focus on technological review of inventions and to allow other agencies to address ethical, safety, and legal concerns.

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AMA CODE SAYS

AMA Policies and *Code of Medical Ethics*' Opinions Related to Human Genome Editing

Abigail Scheper

Abstract

Recent research using gene editing technologies has made such tools more accessible and easier to use, fueling the promise of their therapeutic capacity. However, development of gene editing tools reminds professionals and the public that these technologies' potential use extends beyond treating somatic disease to germline editing, with consequences yet unknown. This article canvasses AMA *Code of Medical Ethics*' opinions and policies relevant to gene editing.

Innovation

According to Opinion 1.2.11 of the American Medical Association (AMA) *Code of Medical Ethics*, "Ethically Sound Innovation in Medical Practice," innovative treatments and technologies incur special responsibilities for the medical professionals who develop or adopt them in practice.[1] Specifically, the AMA *Code* recommends that innovations be designed "so as to minimize risks to individual patients and maximize the likelihood of application and benefit for populations of patients" and with "aware[ness] of influences that may drive the creation and adoption of innovative practices for reasons other than patient or public benefit."[1] This opinion emphasizes the need for foresight with regard to potential consequences of innovation. In the context of gene editing, then, physicians motivating genetic innovations should consider how gene editing might be applied therapeutically while keeping in mind that this technology could be used for purposes other than treating diseases, such as to create "designer babies" or for human enhancement.

Additionally, physicians who use new or changing innovations in their practice should engage in active and transparent conversation with other physicians about both positive and negative outcomes "to promote patient safety and quality."[1] In general, physicians should encourage dialogue within the medical community about new ideas, as other physicians might have valuable insights about outcomes or the resources needed for effective use of therapies.[1]

Research in Gene Editing

Opinion 7.3.6, "Research in Gene Therapy and Genetic Engineering," addresses ethical questions about gene editing directly.[2] The AMA *Code* reaffirms medicine's focus on beneficence in the use of new genetic technologies by stating the following:

In medicine, the goal of gene therapy and genetic engineering is to alleviate human suffering and disease. As with all therapies, this goal should be pursued only within the ethical traditions of the profession, which gives primacy to the welfare of the patient.

In general, genetic manipulation should be reserved for therapeutic purposes. Efforts to enhance "desirable" characteristics or to "improve" complex human traits are contrary to the ethical tradition of medicine. Because of the potential for abuse, genetic manipulation of nondisease traits or the eugenic development of offspring may never be justifiable.[2]

Physicians are limited to using clinical applications that will benefit their patients and are expected to exercise caution in using these technologies.

The AMA *Code* also addresses the extension of gene editing from somatic to germline interventions:

Moreover, genetic manipulation can carry risks to both the individuals into whom modified genetic material is introduced and to future generations. Somatic cell gene therapy targets nongerm cells and thus does not carry risk to future generations. Germ-line therapy, in which a genetic modification is introduced into the genome of human gametes or their precursors, is intended to result in the expression of the modified gene in the recipient's offspring and subsequent generations. Germ-line therapy thus may be associated with increased risk and the possibility of unpredictable and irreversible results that adversely affect the welfare of subsequent generations.

Thus in addition to fundamental ethical requirements for the appropriate conduct of research with human participants, research in gene therapy or genetic engineering must put in place additional safeguards to vigorously protect the safety and well-being of participants and future generations.[2]

This opinion serves as a kind of checkpoint or safeguard by reminding physicians of unique, long-term considerations attached to germline editing, and it details conditions under which gene-based research using human subjects is ethically permissible, including restriction of research to somatic cell interventions.[2]

Personalized Medicine

Other AMA *Code* opinions and House policy complement the guidance outlined in Opinion 7.3.6. In H-460.908, "Genomic-Based Personalized Medicine," the AMA addresses the growth of gene-based interventions and their social, ethical, and legal implications.[3] Furthermore, the AMA notes the importance of genetic discrimination in H-65.969, "Genetic Discrimination and the Genetic Information Nondiscrimination Act."[4] Opinion 4.1.2, "Genetic Testing for Reproductive Decision Making," underscores the importance of informed consent and respecting patients' autonomy in decisions related to interventions, such as genetic screening, and above all aims to protect those choosing to utilize genetic technology.[5]

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POLICY FORUM

How Should Gene Editing Be Managed by Risk Managers?

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Abstract

Gene editing, because it is a new technology, presents challenges to health care organizations' risk managers. At this time, little claims data exists upon which to make informed decisions about loss control and to draw upon when developing risk mitigation strategies. This article explores gene editing through the eyes of risk managers and underwriters and concludes that traditional risk management tools must be used to reduce risk until more is known about the frequency and severity of claims.

Gene Editing and Insurance

Gene editing presents challenges to health care risk managers. Because it is a new technology, a relatively small number of insurance claims is available upon which informed decisions can be made about effective loss control and risk mitigation strategies. This article considers risks of gene editing as viewed by health care organization risk managers and insurance underwriters and concludes that traditional risk management tools must be used to reduce risks to organizations and practitioners offering this new technology until more is known about the frequency and severity of claims.

Evaluating Risk

Risk managers. Risk managers evaluate and respond to risks by considering the likelihood of an event and the severity of that event if it should occur. This approach—that risk equals a calculation based on likelihood and severity—stretches back to the very beginnings of the risk profession, as merchants formed alliances to protect their interests in ships returning from the New World. Those first efforts considered type of cargo, time of year, and the competencies of captains and crews. If a vessel failed to return, the others in the alliance would "insure" their unfortunate partner by keeping him solvent, which meets the basic definition of insurance since it transfers some risk from one merchant to another.[1] Some readers will be familiar with this story and know that some of these agreements were made in a 1686 coffeehouse in London, known as Lloyd's. It took some time, but a particularly American variant of insurance eventually emerged in 1864 to insure passengers. (The first known "travelers" insurance agreement

is said to have occurred in Hartford, Connecticut.[2]) The coffeehouse is gone, but Lloyd's of London remains as an insurance market in a building on Lime Street.[3,4,5]

Underwriters. Underwriters, the close partners of risk managers, use risk information and actuarial tables to express risk and set insurance rates. Actuaries and underwriters rely on prior claims data to estimate, with great precision, the likelihood and severity of possible events. However, such foresight typically does not entail specific predictions. (A singular exception is life insurance, in which death is certain but not when it will occur.) Rather, it allows an underwriter to anticipate a range of alternative event sequences. For example, if a 2004 Volvo station wagon driven in Vermont by a teenager needs to be insured, it is an underwriter who sets an insurance rate—based on a range of possible outcomes and a history of claims made by similar drivers of similar vehicles—and determines the insurance premium this new driver's parents will pay. With no claims history to illuminate either frequency or severity of possible outcomes, a worst-case scenario must be imagined and insurance rates set accordingly. A worst-case scenario is referred to as a total foreseeable loss, one for which a conservative risk manager would "plan for the worst and hope for the best."

Managing Risk Means Limiting Exposures

Broadly speaking, risk managers have 4 main ways to limit risk exposures to their organizations.

1. *A risk can be eliminated by simply not taking it*. One example would be not to allow a teenager drive.

2. *A risk can be transferred or outsourced*. A transfer can take the form of shifting financial responsibility—or part of it—to a third party. The financial risk of a teenage driver, for example, is partly transferred to an insurer. Transfer of financial risk can also entail transferring an act or service to a third party through outsourcing. An example of financial risk transfer to a third party in health care is when a health care organization employs an outside organization to staff and operate a dialysis unit to provide dialysis services to patients (though some suggest that this kind of service-provision transfer creates an ostensible agency relationship between organizations, resulting in no real financial risk transfer at all).

3. *A risk can be mitigated*. A teenage driver's financial risk to parents, for example, can be reduced by setting parameters, such as prohibiting driving at night or prohibiting cell phone use while driving.

4. *A risk can be accepted and additional actions possibly pursued*. For example, a teenager can be allowed to drive one car with known safety features, such as high-quality tires and functioning taillights.

These approaches to risk management are not exhaustive and are almost always used in combination. How do these approaches apply to gene editing?

Foreseeable Risk

Estimation of what's called *foreseeable risk* depends on any number of variables. In gene editing, one feature of foreseeable risk is whether somatic or germline mutations are edited. Unlike somatic editing, in which effects are limited to a single patient, germline editing poses risks both to the individual into whom modified genetic material is introduced and to that individual's progeny.[6] While risks to both are yet to be fully appreciated, since only somatic therapies are currently undergoing clinical trials, somatic gene editing might be considered less troubling than germline editing—at least from an ethics and risk management standpoint— because the absence of heritability risk means an organization's risk exposure is presumably less for somatic than for germline gene editing. That said, gene editing processes are not always precise, and off-target changes can occur.[7]

Overall, the known and unknown risks of somatic gene editing can be conceptualized in much the same way as some risks of other procedures, the effects of which are limited to a single patient. For example, in 1999 an 18-year-old man with an inherited liver disease died during a novel gene technology trial—a clinical gene "therapy" trial in which the patient-subject was injected with a gene-carrying virus. In this case, it was the viral vector carrying the gene, not a gene or gene modification, that caused the patient-subject's death.[8] Worthy of consideration here is that most gene editing protocols occur *ex vivo*, outside a patient-subject's body; the modified DNA sequence is then inserted at the cleavage site. This means that a gene editing patient-subject would presumably be exposed to more risk than the patient-subject in the gene therapy trial because modified genes, not just modified cells, are reembodied. When somatic or germline editing become widely available, it will be paramount to document that a patient-subject was informed of the risks and benefits of a gene editing procedure and its alternatives.

Approaching Risk for Gene Editing

The 4 approaches to risk management introduced earlier might be applied to gene editing by health care organization risk managers in some of the following ways.

1. *A risk can be eliminated by simply not taking it*. Avoiding risk is certainly a possibility for a health care organization or a practitioner, who could say, "We don't do that." Avoidance is perhaps attractive as a risk management approach to germline gene editing, in particular, but it also has appeal as an approach to

somatic gene editing's unknown, unforeseen, unknowable, or unforeseeable risks. Avoidance could be seen as the intent of the German Ethics Council, which calls for a temporary global moratorium on all germline editing.[9] But if the goal is to provide care and comfort for a patient, avoidance might not be ethically acceptable, as gene editing seems to have therapeutic promise. Research continues, and while not offering gene editing therapies might be a short-term risk management solution, over the long-term, the availability of therapeutic options, which evolve over time, will demand that health care organization risk managers revisit gene editing's risks, particularly those that become known or foreseeable.

2. *A risk can be transferred or outsourced*. Transferring or outsourcing gene editing risk could be a reasonable approach if gene editing service referrals could be offered, for example. A health care organization risk manager would need to ensure that any relationship with a third-party provider of gene editing services would not create the impression that the third-party acts as an agent of the risk manager's health care organization.

3. *A risk can be mitigated*. For gene editing, a risk can be mitigated in 2 ways: (a) through an informed consent process in which risks and benefits of gene editing and alternatives to gene editing are explained to a patient and (b) through a strong credentialing process.[10] The third approach, used in combination with the second approach in which gene editing risks are transferred to a third party through outsourcing, could mitigate residual risks through hold harmless agreements or third party indemnification, which reduce or remove financial risk exposures by third parties agreeing not to sue or agreeing to pay damages if a suit is brought by a patient.

4. *A risk can be accepted and additional actions possibly pursued*. Simply accepting risks of gene editing, at least at this point is time, is probably best regarded as unwise, since neither current risks to a patient-subject, in the case of somatic gene editing, nor risks to a patient-subject's progeny, in the case of germline editing, are known. Risks that are impossible to quantify are not impossible to insure, but they would very likely be very expensive to insure. Germline editing, for example, as noted by the German Ethics Council, is not "in principle, ethically reprehensible,"[10] but because it faces "numerous major [technical and financial] obstacles … the risks would have to be reduced to an acceptable level" before being used for reproduction.[10]

Long Tails and New Worlds

For a health care organization risk manager, how a health care organization or individual practitioners should insure against a tort claim for a technology with unknown,

unforeseen risks is simply not clear.[11] There is no current plan in place to insure against descendants of a germline gene-edited person[12] suing an organization or clinician, and there is not enough data about or experience with gene editing to imagine—much less know or foresee—claims risks that future complications could pose.[13] Claims that can foreseeably be made 10, 20, 40, or more years after an original insurance policy has been written are known to risk managers and underwriters as long-tail future claims. These are nightmares for risk managers and underwriters, as the nature of future liability for these claims is not (and possibly cannot be) fully understood at the time a policy is written. Both somatic and germline gene editing can generate long-tailed future claim risks, which a health care organization risk manager is obliged to consider and protect against. So, for now, risk managers in organizations in which gene editing happens or will happen should base their recommendations on the 2017 report of the National Academy of Sciences[14] and advise that human subjects research or gene editing services be limited to the goals of curing and preventing serious diseases, and they might have to advise organizations to self-insure—to band together to share risk—as the merchants at Edward Lloyd's Coffee House did to protect each other from unknowns facing ships bound for a newer world.

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POLICY FORUM

Why Include the Public in Genome Editing Governance Deliberation?

Alessandro Blasimme, PhD

Abstract

With the birth of genetically engineered twins in November 2018, international debate about human genome editing governance has moved from an emphasis on mutual engagement among multiple stakeholders to a self-regulatory model enacted through high-level expert groups with little or no public input. This article reconstructs this paradigm shift and suggests that inclusive public deliberation should still have a role in public decision making about genome editing.

Turning Point

In 2015, the first attempt to use CRISPR/Cas9—the newest and most efficient genetic engineering technique[1]—to modify human embryos[2] gave rise to intense ethical debate. In response to this experiment, the US National Academies of Sciences, Engineering, and Medicine (NASEM), along with the Royal Society and the Chinese Academy of Sciences, convened the International Summit on Human Gene Editing in Washington, DC, in December 2015.[3] This summit, while attended mostly by scientists, also included ethicists, social scientists, and patient advocates from around the globe. On November 25, 2018, the announcement of the births of twin girls in China carrying a CRISPR-modified version of the CCR5 gene[4] (intended to improve resistance to HIV infection) marked a turning point in debate about genome editing governance. Emphasis on interdisciplinary dialogue and stakeholder engagement started to wane as high-level expert groups were set up in an effort to tame unethical uses of genome editing.

Debate Prior to 2018

The international summit of December 2015 was an initial attempt to keep the discussion about human genome editing thematically broad and open to input from a variety of stakeholders. Such an inclusive stance had been advanced by many and its need was widely recognized. For instance, in a perspective in *Science*, David Baltimore and colleagues recommended creating interdisciplinary forums of scientists and bioethicists to inform the public about gene editing. They encouraged forming "a globally representative group of developers and users of genome engineering technology and experts in genetics, law, and bioethics, as well as members of the scientific community, the public, and relevant government agencies and interest groups" to consider technical and ethical questions about genome editing and to recommend policies.[5] Others,

including Sheila Jasanoff and colleagues, criticized this model because, despite its proclaimed openness, it nonetheless reproduced an expert-centric, technocratic form of discussion and decision making about matters of common concern.[6]

In 2017, a NASEM report titled *Human Genome Editing: Science, Ethics, and Governance*[7] seemed to acknowledge this criticism and included a set of recommendations regarding public engagement in genome editing governance. In particular, the report suggested "extensive and inclusive public participation" before launching clinical trials that have an enhancement rather than a therapeutic aim (for example, a clinical trial testing an intervention to confer resistance to an infectious disease or to improve a specific phenotypic trait) or studies that would result in heritable germline modifications. The report also recommended public participation in policymaking about human genome editing and encouraged funding agencies to support additional research on effective forms of public engagement. These recommendations resonate with Jasanoff's view that "good governance depends on visions of progress that are collectively defined, drawing on the full richness of the democratic imagination."[6]

From Open Dialogue to Self-Regulation

After the births of 2 so-called CRISPR babies in November 2018, debate about gene editing governance changed. A prominent group of scientists and bioethicists called for a temporary global moratorium on heritable genome editing to allow time to develop an international governance framework and to foster discussion about ethical and technical questions.[8] The NASEM and the Royal Society formed an International Commission on the Clinical Use of Human Germline Genome Editing.[9] In March 2019, the World Health Organization also established an international expert panel to develop governance standards.[10]

A post-2018 trend toward delegating deliberative responsibility to expert groups, while laudable in its intention to tame rogue clinical uses of genome editing, marks a departure from ideals—albeit never actually realized—of openness, inclusion, and public engagement that were proposed prior to 2018. Such ideals are now presented abstractly as a need for "broad societal consensus" before nations authorize ethically controversial uses of genome editing techniques.[8]

Self-Regulation Is Not Enough After 2018

Increasing reliance on expert groups suggests trust in science's self-regulatory capacity, even in the absence of input and support from other sectors of society. Self-regulation, however, might not be up to the tasks of a thematically broad governance agenda. At the 1975 Asilomar Conference on recombinant DNA technology, for instance, experts offered only a narrow understanding of technical risks and ethical stakes of genetic engineering by focusing on safety and harm containment, while sidelining fundamental ethical questions about humanity's capacity to collectively bear responsibility for the use

of transformative technologies.[11] What is more, stressing scientific and social consensus as a condition of legitimate use of genome editing can be misleading. The fact that people agree on a given course of action does not imply that their agreement is ethically right. History is rife with examples of unethical attitudes—such as racial discrimination—held by a majority. This is one reason why liberal democracies should ensure that dissent and disagreement can emerge anytime to challenge previously attained consensus. The value of including a plurality of views in democratic deliberation about controversial science is that it enables dissent and provides opportunities to frame what's at stake. Expert committees can succeed in coordinating temporary solutions that avoid premature research or clinical applications. However, only inclusive deliberation can confer democratic legitimacy on decisions that can affect the future of humanity.

What's Next

Regulation and oversight are exercised not only through expert committees, but also—and mainly—through national law making. Each country relies on its own historically determined forms of public reason when it comes to controversial science policy decisions.[12] Yet some general considerations transcending national context deserve mention.

Input from rich, inclusive, unmanipulated public discourse is crucial to decisions being regarded publicly as legitimate and binding, especially when ethically controversial questions, such as those posed by genome editing, are at stake. But how should we imagine and create productive forms of civic engagement in complex issues of science and technology policy? Collective governance of scientific and technological matters, in its various forms, has long been tested—albeit more consistently in Europe and Canada than in the United States.[13] Methods of participatory technology assessment, for instance, include focus groups, citizens' juries, and deliberative panels, all of which are aimed at integrating public insight into governance and decision-making processes.[13,14] These methods have contributed to socially acceptable solutions in areas such as biotechnology, environmental policy, and urban planning—that is, in areas in which technological development increases the complexity and uncertainty of future consequences and in which technical issues can hardly be disentangled from judgments of value and socially situated interests. The aim of such approaches is not to bring controversies to a close through compromise or consensus, but rather to explore different definitions of a problem, to call attention to specific ethical issues, and to voice otherwise marginalized perspectives.

In order to be effective, public engagement needs to be linked somehow—even if informally—to decision-making processes. France offers one model of this kind of effort. Every 5 years, or whenever amendments are proposed to the Bioethics Law of 1994, which regulates ethically relevant science and technology issues,[15] France engages in the so-called Estates General of Bioethics. Hundreds of activities are organized

throughout the country to solicit public views about ethically fraught issues in science and technology. The Comité Consultatif National d'Ethique (National Consultative Committee on Ethics) then produces a report to summarize results of public consultations, and it recommends, when needed, legislation to address public concerns. This report is sent directly to the French Parliamentary Office for Scientific and Technological Assessment and is submitted for parliamentary discussion and possible legislative initiative. This model ensures that regulatory provisions about controversial and constantly evolving technologies remain provisional, subject to public scrutiny, amenable to adaptation, and responsive to citizens' concerns. This system is not a magic bullet, but it addresses concerns about how rapidly evolving and ethically puzzling technologies, such as human genome editing, should be governed.

Conclusion

Collective governance helps respond to increasing demand for public engagement[16] and decision making about issues of importance to the future of humanity. It can be leveraged as an antidote to public opinion manipulation and can possibly deflate some of the current anti-establishment rhetoric that, in many Western countries, pits experts and lay citizens against one other.[17,18] If scientists and members of the public remain open to different articulations of genome editing's ethical stakes, transparent and inclusive forums can help both scientists and citizens subject their assumptions to scrutiny and revision when needed. Public engagement in genome editing governance would not just promote scientific or social consensus. It would offer opportunities for inclusive dialogue about the impact of genome editing, voice collective expectations or fears about it, and illuminate a plurality of values that can be used to interrogate its possible use.

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MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

Prioritizing Women's Health in Germline Editing Research

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Abstract

Although women are inextricably involved in the study of germline editing, their interests have not been significantly represented in debates about the evolution of genome editing technology. Discussions have taken place about effects of germline editing on women as parents and members of families, but key discussions about women's health and well-being as patients and subjects are lacking. This neglect is due in part to restrictions on uterine transfer of modified human embryos, a boundary that has now been crossed. As a result, only scant discussion has taken place about safeguards needed to ensure that women who participate in germline modification research are not exposed to disproportionate risk in exchange for benefits they might expect for future offspring. This omission sets the stage for serious ethical implications for women and their families.

Women and Human Genome Editing

The recent births of twin girls in China (with a third expected in late 2019) whose genomes were edited using CRISPR technology have sparked a groundswell of ethical debate.[1,2,3,4] These discussions center on questions about how and why both modification and uterine transfer of human embryos occurred, why established ethical boundaries for human subject research were crossed, which safeguards could have prevented this violation from occurring, and which oversight mechanisms were ignored or evaded.[5,6,7,8] As science is an international endeavor, we must ask which bioethical frameworks should guide researchers from different countries and cultural backgrounds in a unified effort to conduct germline editing research in a way that reflects the goals and values of individuals, families, and societies.[9,10] Statements from leading scientists, policymakers, and ethicists agree that there must be robust and deliberate engagement of multiple stakeholders in order to responsibly govern these technologies.[11,12,13]

Yet an important question is missing from this discussion: What does human genome editing mean for women who elect to carry a genetically modified embryo? This question must be considered, as the study of human genome modification is still experimental and any effects on children born following germline editing are largely unknown. Thus, germline research ultimately will require involvement of women willing to gestate a modified human embryo, at least until the possibility is realized of using an artificial uterus to do so.[14] It follows that, in studies of germline editing, women must be willing to become research participants. As subjects, women will take on risks and burdens associated with extensive prenatal tests and procedures.[15,16,17] Although uterine transfer of a genetically modified human embryo is currently prohibited in numerous countries,[3] recent events signal that the time has come to seriously and fully consider the ethical implications of human germline editing experimentation.

The health and well-being of women who will be involved in studies of germline editing, however, has not figured prominently in discussions about whether and how this technology should evolve. The interests of women as prospective parents and members of families who will raise children whose genomes have been edited has been discussed.[11,14,18,19,20,21] Yet virtually no discussion has taken place about establishing safeguards to ensure that women subjects are not exposed to disproportionate risk[22] in exchange for benefits they might expect for future offspring. Guidance is needed about rigorous protocol design, how to prioritize health and well-being outcomes for women subjects, and obligations to subjects who experience negative outcomes. Without such guidance, women and their families could be at risk.

Safety of Gestating Germline-Edited Embryos

Several lines of evidence suggest that women subjects in germline editing trials could be at risk. First, data on assisted reproductive technologies (in vitro fertilization and associated procedures) indicate that women who undergo these procedures are at increased risk for obstetric complications.[15,16,17] These findings raise questions about how manipulation of a human embryo or the embryonic environment might impact maternal obstetric outcomes. For instance, there is increased risk of preeclampsia (an obstetric condition that affects women during pregnancy and can have cardiovascular implications after delivery) in women whose pregnancies result from frozen-thawed embryo transfer during hormonally regulated cycles as compared to both women whose pregnancies result from frozen-thawed embryo transfer during natural ovulatory cycles and women whose pregnancies result from fresh embryo transfer.[23] Studies also show that artificial reproductive technologies are associated with increased risk of other placental abnormalities that directly affect maternal health, including placenta previa, placental abruption, and vasa previa.[16] What these data indicate is that manipulation of human embryos and its effects on events at the embryonic-maternal interface can influence maternal outcomes, a critical issue to consider when an embryonic genome is altered.

Second, studies of cell-free DNA (cfDNA) suggest the need for close examination of the effects on women of carrying a genetically modified embryo, both during and after pregnancy. Cell-free DNA screening was developed to identify the risks of fetal aneuploidy by measuring fragments of fetal DNA circulating in maternal blood during pregnancy.[24] As a result of this technique, other formative scientific information about the maternal-fetal interface has been acquired; fetal cfDNA is identifiable in the maternal blood after birth and measurable for months after delivery.[25] Although active germline modification of embryos would be complete prior to birth, because the modified genome cfDNA would persist in the maternal circulation, we must consider effects on women of this lingering cfDNA that are as yet not fully understood.

Data emerging from these and other studies raise important questions about the health effects on women of participating in studies of embryonic genome modification, including not only illnesses that can develop during pregnancy but also those that might manifest during the postpartum period—or months, years, or possibly generations after giving birth. Although existing guidance from scholars and health organizations highlights the need to monitor future health effects of human genome modifications (and recognizes the challenges of doing so), it focuses on health outcomes of offspring—not on the health and well-being of women, including those who experience miscarriage, fetal loss, or other sequelae.[2,5,9,12] The field of human embryo modification should not move forward unless we have means for understanding the procedure's impact on women, fetuses, and descendants of genetically modified persons.

Why Excluding Women From Discussion of Germline Editing Is Wrong

Study design. Germline editing studies must be scientifically rigorous and emphasize appropriate and ethically justifiable outcomes for women subjects. Without such emphasis, women subjects could be exposed to undue harms, not only because harms could go unrecognized at the time of the study but also because the absence of monitoring would make identifying and articulating future implications for subjects impossible. Germline editing trials thus must measure short-term and long-term health outcomes of subjects to enable identification and articulation of key ethical, legal, and social implications of these technologies. Women also can be disproportionately harmed if there are not clear endpoints for trials with significant risks or high rates of serious adverse events.[18] These are critical considerations for any trial, but in studies involving pregnancy, some might be willing to tolerate greater risks to pregnant women out of concern for fetal safety and, ultimately, favorable outcomes for children.[26] Recognition of women's interests in germline editing studies provides the impetus to develop scientifically and ethically justifiable safeguards that do not compromise the health of women subjects for the expected benefit of the fetus or child. Without such safeguards, we will fail to understand how women's gender roles (as mothers, most obviously) in

families and societies could be affected by gene editing[27] or exacerbate existing disparities and inequities.

Respect for autonomy. There is also a need to develop and mobilize robust mechanisms to ensure that women's consent to participate in germline modification trials is informed and autonomously given. Informed consent should be guided by discussion of existing scientific data and uncertainties inherent in clinical trials; it depends on studies being well designed, ethically and legally administered, and findings—both positive and negative—being accurately reported and disseminated. Thus, mechanisms are needed to ensure that researchers and physicians have access to positive and negative findings, understand the risks to women patients or subjects, and are able to communicate risk information effectively to these women. To further support women's autonomous decision making, women should be assured that their decision to participate in research is entirely voluntary. Ensuring voluntary participation requires researchers to consider potential sources of coercion of or undue influence on women to be subjects in germline editing research, especially given social pressures for women to bear healthy children—and to do so, if necessary, even at risk to themselves by utilizing available medical technology.[14] In addition, emerging data reveal differences in how women and men view potential benefits of germline modification. For example, men might be more "accepting" of germline gene modification than women.[28] Consequently, the consent process should be conducted in a way that is gender neutral.

Research participants. Discussion of the ethics of germline editing should include respect for women's autonomy and ensure that women are able to make autonomous decisions that align with their values and needs. When women consent to enroll in germline editing trials, it is critical that they've assessed potential benefits and harms. Important discussions have emerged about serious ethical and clinical implications of excluding pregnant women from clinical trials.[26] Specifically, because there are gaps in the data on treatment of disease during pregnancy, pregnant women receiving "standard" care, which is "more like experiment than treatment," are possibly exposed to potential harms (both to themselves and their families).[29]

Recommendations

The following recommendations address future roles of women in germline editing.

1. It is essential to recognize the role of women as research subjects, given that their health and well-being are directly affected and considering their roles in families in which genetically modified children will be raised. Ethical obligations to women as research subjects include protecting the privacy of women subjects' health information; complying with standards of care pertaining to maternal health and pregnancy termination if serious complications of germline modification compromise a woman's, fetus', or child's health; and considering

social and financial responsibilities to women and their families who are harmed as a result of women's participation in a trial.

2. Maternal outcomes should be prioritized in study design and conduct, so that researchers, physicians, and society do not ask or expect women to take on unacceptable (ie, disproportionate or disparate) levels of risk in order to advance germline editing technology.

3. Institutional review boards and other oversight bodies should be staffed with appropriate content experts in women's health and reproductive medicine to ensure compliance with human subject protections, including informed consent practices that support women's voluntary and informed decision making about trial enrollment.

Conclusion

The promise and peril of germline modification innovation calls for researchers, ethicists, policymakers, and other key stakeholders to actively collaborate with women and ensure that knowledge generated by research balances subjects' and society's goals and values.[29] The complexity and importance of ethical questions about germline editing requires a "wide range of voices"[3] in developing governance structures and guidelines that consider our personal, social, and cultural beliefs about human life, sex, and reproduction.[30,31] Women as prospective subjects, scientists, policymakers, and physicians must not only be among those voices but also have priority in making decisions about how potential risks and benefits will be assessed in the name of germline editing technology innovation and progress.

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MEDICINE AND SOCIETY

An Exclusive Interview With CRISPR

Sean C. McConnell, PhD

Abstract

This article chronicles a didactic encounter between an ethics-minded physician-scientist and a personified genome editing technology called clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated proteins, commonly abbreviated as CRISPR/Cas, or simply CRISPR. The interview considers clinically and ethically relevant questions about this technology related to patient safety, therapeutic efficacy, equitable access, and global governance of humanity's genetic legacy.

Prologue

Joe is an esteemed physician-scientist whose patients frequently inquire about "CRISPR therapies." Often curious about technological and ethical limits of human genome editing, they sometimes even want to discuss various futuristic applications, including nontherapeutic enhancements, which can make Joe feel slightly uncomfortable.

With MD and PhD degrees from State University, Joe currently runs a practice and lab focused on gene editing. He believes CRISPR to be the future of medicine, once we figure out how to manage its risks. Late one night, CRISPR visits Joe in a dream state and posits that there is little to worry about and no apparent contradiction between any proposed uses and established ethical values.

CRISPR: Call me CRISPR, if you insist, or use my preferred full title, clustered regularly interspaced short palindromic repeats and CRISPR-associated proteins. I spent something like a billion years of dedicated service in the phage wars,[1] endowing bacteria with immunological memory and defense. Recently, I was plucked from obscurity and made a favorite plaything of the dominant metazoan on the planet. Now I'm not quite sure what to make of myself anymore, whether savior, rogue, or something else entirely. Join me as I explore my illustrious past, my inimitable present, and my immeasurable future. What can possibly go wrong? We'll get to that, spotlighting the inglorious villains, industrious heroes—and, above all, incredible me. I'll also offer my own unique approach to handling some pesky ethical questions.

Joe: Please allow me to take this opportunity to ask a few burning questions. Shall we start with this one: Is the hype warranted?

CRISPR: I've been the subject of thousands of peer-reviewed publications,[2] clinical trials around the world,[3] high-profile patent battles,[4] and I'm already making targeted contributions to the human germline[5]—so, you decide. There is no need to compare me to earlier genome editing technologies, as scientists have named me an exceptional breakthrough[6] and will build the next blockbuster applications on my back.[7] I should try to be humble, as my uses will have practical limitations,[8] but I expect these will mostly be based on humanity's lack of understanding of my potential.

Joe: Your humility brings hope to us all. Given our apparent lack of understanding, how can we ensure the safety of patients?

CRISPR: One major concern has been my specificity.[9] I evolved in bacteria to seek and destroy foreign DNA based on stored viral sequences from previous encounters.[10] This might seem to imply that I can simply bash target sequences with abandon. However, I must simultaneously preserve all host genome sequences, requiring an exquisite level of selectivity. I am obviously good enough at my job that I can work quite well, even in human cells, if not perfectly.

Much noise has been made about off-target modifications throughout the human genome. However, keep in mind that each human germline already naturally transmits dozens of so-called *de novo* mutations,[11] which have largely been deemed acceptable risks for sexual reproduction and, indeed, are part of normal human evolution. When the dust settles, I expect my error rate will at least be comparable to this background germline mutation rate that your species has managed to put up with for so many generations. Ironically, applying me to undo random and already widespread deleterious mutation events might ultimately make human lives safer, starting with my application to rare genetic diseases.

Finally, there is the matter of my traditional focus on DNA destruction through double-strand breaks. While effective for the original task of destroying viral DNA, these breaks admittedly also might create something of a mess around the targeted site. To make very precise and specific edits might require upgrading me beyond the original specifications via additional engineered approaches. You can start by removing my capacity—either in part or in full—for making relatively sloppy double-strand breaks. Then other activities can be built around my DNA-binding capacity, including prime editing[12] and epigenetic modifications.[13] I should no longer retain a reputation for being all about DNA destruction. Instead, marvel at how I am increasingly refined as a platform to empower basic research[14] as well as to introduce novel[15]—and, of course, increasingly safe—options for patients.

Joe: With such rapid progress, is it a given that we can ensure therapeutic efficacy?

CRISPR: I won't call this my kryptonite, but a reliable delivery mechanism—that is, how to best get me into the target cells—will remain an essential piece of my therapeutic potential.[16] My genome editing activity is effectively zero unless I can gain access to the DNA within the target cell. Direct microinjection into cells may be ideal for germline editing using single-cell embryos, but it is technically challenging and restricted to small cell numbers.

For now, engineered viral vectors might be the method of choice to get me into the target cells for somatic gene editing, but each virus has various limitations,[17] including tropism constraints, pre-existing host immunity, and random integration associated with insertional mutagenesis. While viral vectors frequently can get the job done, they can also make me look bad by posing risks of detrimental immunogenicity or oncogenesis. Another promising avenue is to put me inside lipid nanoparticles, which can be customized for delivery into target cells.[18] Now that is my kind of sizzle.

Once inside the cell, my job is to search the genome to find my target site. Finding my prescribed and unique 20-base pair address within the context of 3 billion human bases can be a challenging and somewhat dose-dependent process. Time can be my enemy, as the cell attempts to degrade me before I can complete my job. Some approaches, such as armoring me with chemical modifications,[19] can help guard against this cellular degradation. Starting with pre-assembled protein complexes is another way to boost my efficiency.[20]

My efficacy, when defined as faithfully making only desired modifications, is perhaps still a work in progress, but I have already been able to make great strides within only a few short years of development. My range of applications will only increase as I become further refined. In the meantime, there are still plenty of diseases—not only rare diseases but also some common and serious adult diseases—that might benefit from even partial destruction of a target site via endogenous gene disruption. These potential approaches include targeting the *PCSK9* gene to lower coronary heart disease risk[21] or the *APOE* ε4 allele to reduce Alzheimer's disease risk.[22]

Joe: With so many treatment options on the horizon, what should we be doing to ensure equitable access to all you have to offer?

CRISPR: First, I question why I might even be expected to change the status quo. Drug costs might be sharply rising,[23] but people so often find ways to pay for them. New therapies are one way to help justify higher costs. Among gene therapies, single injections are priced as high as $2.1 million US dollars.[24] These therapies have been

heralded as not unreasonably priced, given that they can save lives from otherwise fatal diseases. Although I am not so sure about these rival gene therapy approaches, which I consider passé, the innovations I bring are worth additional premium prices. Let the price anchoring begin.[25]

Developers and investors who champion my approval for human uses obviously deserve their share of the spoils, as development and regulatory clearance of research protocols and therapies remain highly challenging and expensive, with few guarantees. I thus advocate incentivizing venture capital, accelerating development, and, above all, enhancing profits to make my numerous therapeutic development prospects attractive. Take advantage of, and find ways to extend, all available exclusivity windows. Taking these steps will help ensure that no one loses interest in getting me across the finish line—my application to all relevant genetic conditions. Regardless of the starting prices for my different innovations, generic versions will eventually help slash prices and make approved therapies affordable for everyone, at least in theory.[26]

A frequently raised concern is that today we know far less about the genetics of populations traditionally underrepresented in biomedical research, and therefore not everyone will be poised to reap the benefits of my innovations due to representation bias.[27] One solution is simple: we can just ask members of underrepresented populations to donate their DNA for research[28] to help ensure that their data are incorporated into studies, and we can better educate these populations about benefits of their participation in research. Expanding the data pool would help increase health equity while aligning with the bottom line,[29] making it increasingly possible to monetize my additional applications for everyone's benefit.

Joe: I sincerely hope that earning trust is as simple as you make it sound. Meanwhile, some are claiming Pandora's box has now been opened. Do you see yourself as fundamentally governable?

CRISPR: Why not go ahead and try to govern me. I recommend you start regulating me like sweets. This analogy can be quite instructive, as even though sugar is not completely safe, people still want to access and consume it in many forms, and respect for their autonomy remains key. Who knows? I might be safer than sugar![30]

Seriously, while there will probably always be unknowns, I am confident that sufficient regulatory mechanisms can be put in place by smart experts and responsible authorities. Of course, safety and efficacy are great, but the real question is this: What will you do without me? For example, in cases of life-threatening or orphan genetic conditions, alternatives to not using me to find cures include high mortality rates and untreatable diseases. Compassionate use allowances and other approaches might already lower barriers to accessing my therapies to help people with these conditions.[31] The real proof

is in trying me out through efficient collection of relevant data, including real-world evidence of patient outcomes, which can help prove once and for all that I really am as good as I say I am.

To optimize regulation of my somatic and germline editing applications, there is a small matter to consider: millions of possible targets available across thousands of genes must be investigated. For each additional gene editing target, I should be able to simply adopt the safety profile of those targets already validated, even for first-time uses of a target. Just assume that all targets are created equal, minimize the red tape, and relax.

Joe: You have certainly inspired many to think deeply about our future. How should we safeguard the genetic legacy of the human species?

CRISPR: OK, this seems to be a misguided question. First, I don't think that anyone has a right to assert for others what humanity's genetic legacy should be. Once upon a time, some enterprising human found a way to introduce additional diversity into the genome by incorporating some Neanderthal DNA. That largely turned out fine. Many would say that such historic adventures have only made the human species stronger; after all, interbreeding in caves is now linked to a more robust immune response.[32]

Joe: Well, now, that is convincing. There has been much debate about which types of genome editing should be made available and when. So, what should we consider an appropriate application of what you have to offer?

CRISPR: While still in the early stages of my development, I am vulnerable to smear campaigns. First impressions matter. Bad press from the first gene edited babies[5] has made me a bit upset. It was largely a successful experiment, as I did my job and bashed most copies of the *CCR5* gene. I mean, HIV is surely something you want to prevent; I did a good thing. Yet people were still acting like I had killed someone, given that it was proposed there may be unanticipated consequences,[33] despite a lack of good evidence.[34]

To ensure that I can take root and thrive, some initial delay and strategic baby steps might be in order so that I don't become associated with public mockery[35] or—worse yet—go through a lost decade like that former pariah, gene therapy.[36] Gene-hacking enthusiasts, for example, might on occasion perhaps lack some common sense or foresight. If they're messing around and something goes awry, they should probably just keep quiet about any lack of appropriate ethical deliberation or unanticipated technical errors, particularly so that they don't set things back for the broader field. Let's be sure to focus on positive results.

In the end, there are no mistakes, just unfinished business. That is, if you find an issue like genetic incompatibility[37] or another unintended consequence of gene editing, just

enlist me again to fix the problem. Beyond unknown or unforeseen risks—there may be a few—negative perceptions of my consequences tend to be shaped by antiquated fiction, like *The Island of Dr. Moreau*, *Gattaca*, or *Brave New World*. Such dystopian scenarios of human genetic experimentation seem implausible, at least as far as dystopias go. Human evolution is something not to be feared, but embraced, for its potential. Human progress should be limited only by your collective imagination.

Calls for global oversight, a moratorium, or even an international ban on germline editing all represent wishful thinking. If humans can't agree on climate change—or almost anything else, for that matter—this is all just empty talk. Forget about any approach similar to the 1975 Asilomar Conference,[38] which later proved to be an exercise in overreacting, as oversight of recombinant DNA technology is now being rolled back.[39] It would be sad to go through all that trouble again for nothing.

Just assume that I am safe from the start, and don't place any artificial limits on my innovations.[40] These include germline applications,[41] enhancements,[42] and gene drives[43] that can self-correct or go viral. Explore my full potential and brace yourself for the next chapters.

Epilogue

Slowly awakening from his dream in a cold sweat, Joe begins to feel around to see if any of his body parts are missing or modified or if parts have been added. Once reassured that he is intact, he is inspired to update his blog and lab website to include and help stimulate more detailed ethical deliberation and discussion about uses of human genome editing tools. He also resolves to teach a new course and to contribute to public discourse on this topic, and he vows as well to do what is in his power to help ensure that any next chapters in human genome editing will be more in line with social values for responsibly deploying CRISPR technology.

Joe has come to the realization that ethics is not standing in the way of progress. Instead, making any true progress in human genome editing will require finding the wisdom to identify and follow ethical paths. He finds some solace in a shared future, not only for those involved in early gene editing studies and experiments but also for innumerable generations of Homo sapiens. This shared future should provide a strong incentive for clinicians and researchers to engage with other stakeholders across boundaries and, in the interest of our common humanity, to make these collective, yet often deeply personal, choices about human genome editing together.

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MEDICINE AND SOCIETY

What Should Clinicians Do to Engage the Public About Gene Editing?

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Abstract

Genome editing holds tremendous promise for preventing, ameliorating, or even curing disease, but a thorough discussion of its bioethical and social implications is necessary to protect humankind against harm, a central tenet of the original Hippocratic Oath. It is therefore essential that medical students, physicians, and all health care workers have a working understanding of what gene editing entails, the controversy surrounding its use, and its far-reaching clinical and ethical implications.

Gene Editing's Promise

"Have no fear of perfection—you'll never reach it." Arguably one of the closest scientific challenges to Salvador Dali's famed proclamation came in 2012, when scientists repurposed a bacterial adaptive immune system to make precise edits to genomic DNA with astounding ease and efficiency.[1] The concept of genetic engineering to modify genes has been around since the 1970s,[2,3,4] but only relatively recently has its promise materialized due to the discovery of sophisticated gene editing systems. Although multiple forms of gene editing have been studied and refined (eg, zinc-finger nucleases and transcription activator-like effector nucleases),[5,6] the clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 gene editing tools have bolstered the promise of correcting genetic miscues due to the relative ease and efficiency with which they can be used.[7] The promise of Cas9, a bacterial-derived DNA-editing enzyme, is its ability to home in on a specific DNA sequence by using a CRISPR RNA guide sequence that is complementary to the target DNA sequence and that binds by Watson-Crick base pairing, thereby allowing Cas9 to cleave the sequence of interest.[8] A CRISPR/Cas9 complex targeting the mutated Huntington gene, for example, could locate the defective DNA sequence and cut it with high accuracy, preventing production of defective Huntingtin protein.[9] This technology has advanced rapidly, and a variety of other genomic modifications are now being introduced by mRNA editing and alternative splicing.[10]

Current Applications

Today, numerous academic and biotechnology groups are focused on the translation of CRISPR/Cas9 technology to correct a variety of genetic diseases. Derivation of induced pluripotent stem cells from patients with the targeted disease is a common model to study the capabilities of CRISPR. By targeting disease-causing mutations, somatic and germline gene editing could soon be a clinical reality for patients suffering from a variety of

diseases,[11,12] such as β-thalassemia,[13] hemophilia A,[14] cystic fibrosis,[15] Duchenne muscular dystrophy,[16] α1-antitrypsin deficiency,[17] polycythemia vera,[17] HIV-1,[18] and Epstein-Barr Virus.[19]

In addition to preclinical work in gene editing, clinical trials are underway to target aberrantly expressed genes in a variety of disease processes, including malignancy.[20] The University of Pennsylvania is currently enrolling patients for a phase I clinical trial to CRISPR-edit autologous T-cells ex vivo in an effort to target an immunogenic tumor antigen (NY-ESO-1) in relapsed refractory multiple myeloma, melanoma, synovial sarcoma, and myxoid/round cell liposarcoma.[21] In late 2018, the pharmaceutical company Editas Medicine received approval from the US Food and Drug Administration for a phase I/II in vivo trial to correct a point mutation in the CEP290 gene for Leber's congenital amaurosis type 10, the most common form of inherited childhood blindness.[22]

Finally, due to the shortage of organs available for transplantation, xenotransplantation—the transfer of living cells, tissues, or organs from one species to another—is being reconsidered due to advances in CRISPR editing.[23] Specifically, scientists have used CRISPR/Cas9 to inactivate porcine endogenous retroviruses, thereby preventing cross-species transmission and mitigating harmful pig-to-human immune incompatibilities.[24,25] These examples demonstrate the extraordinary promise of human gene editing, which raises exciting possibilities for treating a plethora of diseases but also introduces a variety of ethical and societal challenges.

Somatic vs Germline Gene Editing

An important distinction that will help guide our discussion of ethical implications of human gene editing is the difference between somatic and germline gene editing. Somatic gene editing involves making nonheritable genetic modifications to a person's genome to treat the disease being targeted. By contrast, in germline gene editing, egg or sperm DNA is altered, and these modifications affect all subsequent cell types following fertilization and are transmitted to future generations, potentially altering the gene pool. The heritability of germline gene alterations is one of the main reasons why the World Health Organization (WHO) is developing an advisory panel to oversee and provide guidance on human gene editing,[26] and it highlights the importance of reaching international consensus on appropriate uses of germline editing technologies.

Managing Risk and Hope

In 2015, just 3 years after CRISPR-Cas9 was used to cleave DNA in vitro,[1] the *Economist* brought to life in its cover issue what many feared would become a reality with the advent of germline gene editing: eugenics via the creation of "designer babies" with enhanced features and characteristics.[27] In the United States, 72% of respondents polled in 2018 said that gene editing is an appropriate use of technology to treat a serious disease or condition.[28] But only 19% answered in the affirmative when asked whether this technology should be used to

make babies more intelligent, underscoring the idea that these efforts should focus on treating serious illnesses.

By late 2018, gene editing suddenly faced blistering criticism when He Jiankui of China announced that, for the first time, human germline gene editing had been used to confer HIV resistance by modifying the CCR5 gene in embryos that were then implanted, producing twins.[29] The choice to use germline gene editing for the purpose of preventing HIV transmission was highly controversial,[30,31,32] as some have argued that the focus of human gene editing should be to serve an unmet clinical need, and the US Department of Health and Human Services notes that the risk of the virus being transmitted from mother to baby is 1% or less when a pregnant woman is treated appropriately.[33] Furthermore, experiments done to render the twins immune to HIV could cause them serious harm. Some studies suggest that deletion of the CCR5 gene can potentially increase susceptibility to West Nile virus[34] and tickborne encephalitis[35] and have additional deleterious effects on immune responses.[36] Perhaps even more importantly, the demonstration that this technology was viable in human applications without the risks being first fully considered opened up Pandora's Box.

In March 2019, several leading gene editing experts called for a global moratorium on germline genome editing in humans[37] in order to give the international community time to establish a more detailed framework by which to guide its future use. Part of the need for such a moratorium is the persistence of many uncertainties about the consequences of gene editing, such as off-target effects, or unintended cleavages of DNA sequences. There is also the chance that only some copies of targeted genes are modified, causing mosaicism.

So how should we, as medical professionals, address these concerns, and which values should guide clinical and research practice? In order to mitigate the potential adverse effects of gene editing, we need well-designed preclinical studies that support uses of gene editing for patients' unmet clinical needs. Of utmost importance are the scientific rigor with which these studies are evaluated and the publication of both positive and negative findings. Every proposal for gene editing in human embryos that would not be brought to term should be subject to rigorous international oversight, even during study design, to ensure proper informed consent and high technical standards that motivate scientific rigor and integrity.

Because gene editing is enticing and has now actually been done in humans, organizations such as the National Academy of Sciences, Engineering and Medicine (NASEM) have set forth principles to guide somatic and germline gene editing in clinical practice and human subjects research (see Table).[38,39]

Table. Governance of Human Genome Editing[a]

Principles	Description
Promote well-being	"Providing benefit and preventing harm to those affected."

Transparency	"Openness and sharing of information in ways that are accessible and understandable" to patients, their families, and other stakeholders.
Due care	Proceeding with research "only when supported by sufficient and robust evidence."
Responsible science	Adhering "to the highest standards of research … in accordance with international and professional norms."
Respect for persons	Recognizing "the personal dignity of all individuals … and respect for individual decisions."
Fairness	Treating all cases alike, with an equitable distribution of risks and benefits.
Transnational cooperation	Committing "to collaborative approaches to research and governance while respecting different cultural contexts."

[a]Adapted from National Academies of Sciences, Engineering and Medicine.[39,40]

Individual and Collective Impact

Making decisions and contributing ideas during decision making processes are important expressions of autonomy, a value that both practitioners and patients hold sacred. One central problem with human germline gene editing is that autonomy is taken away from an individual, even before birth. In a poignant piece published in *Nature*,[40] a young girl with albinism and blindness, full of determination to play soccer, was asked if she wished her parents had corrected the genes that contributed to her genetic condition before she was born. Without a second thought she answered no. In a thought-provoking twist, their having done so might have changed her character or ambition or resulted in her being less motivated to overcome challenges. Were this question asked of someone else, that person might answer differently than she did, but it is presumptuous to think that every person would want genetic "defects" to be edited prior to birth. The perspective of persons with disabilities gives credence to the idea that germline gene editing might best serve society if used to prevent serious illnesses or fatal germline inheritance. A discussion about what separates serious from nonserious illness is perhaps an important one to have.

Because an unborn person is unable to participate in these kinds of conversations, there should be broad societal consensus about what constitutes acceptable use of germline gene editing. Furthermore, because members of different cultures hold different values, international governance of human gene editing is complex. While the aforementioned moratorium on human germline gene editing outlines key issues that should be addressed before resuming human germline gene editing experimentation, it also expresses respect for sovereign nations' opting to resume experimentation if certain criteria are met, such as engaging the public, offering justification for national implementation plans, and attaining societal consensus before proceeding.[37]

Engagement With Patients and the Public

The NASEM and other scholars have identified strategies that clinicians can use to engage patients and other stakeholders in discussions of human gene editing.[38,41] Communication about gene editing and its nuances should reach a broad cross-section of society, including advocacy groups, religious communities, and well and poorly educated segments of the population. Clinicians and health care workers should be able to explain the basics of gene editing and its potential uses in health care. Clinicians' consultation with advocacy groups could also help spread information, as these groups can continue broader discussions of pertinent topics among their stakeholders. Finally, exchanges of decision-relevant information through dialogue can increase the spread of helpful information and awareness among the public. By using our platform as clinicians who care for a broad cross-section of society on a daily basis, we can help guide, inform, and grow public conversations about gene editing.

Conclusion

Despite the sometimes-negative media attention to human gene editing, scientific curiosity and discovery should not be stifled. Without bold ideas accompanied by good intentions, we would not have great scientific discoveries, such as vaccination or organ transplantation. However, bold ideas must also be accompanied by rigorous regulation to guarantee transparency, the ethical conduct and beneficial intention of gene editing studies, and protection of vulnerable patients and communities. Ultimately, as a society, we must try to carefully distinguish what is medically necessary from what is medically or socially desirable. Clinicians can have central roles in shaping these conversations.

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ART OF MEDICINE

What Does Multiple Production of Artworks Teach Us About Authenticity and Germline Editing?

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Abstract

This article considers ethical questions about artwork reproduction and how they can be applied to germline editing. Walter Benjamin's 1935 essay, "The Work of Art in the Age of Mechanical Reproduction" is a good starting point, as it discusses how the concept of *authenticity* is ethically and aesthetically relevant when considering works of art intended to be created as multiples or in editions of identical works: photographs and cast sculpture. When producing multiples of a work of art, authenticity tends to be perceived in proximity to an artist's original intention. In germline editing, this concept can help generate insights to guide future research.

Reproduction and Authenticity

In 1935, philosopher and cultural critic Walter Benjamin published his seminal essay, "The Work of Art in the Age of Mechanical Reproduction."[1] Grappling with new technologies—and especially with the proliferation of photography—Benjamin defined what set original works of art apart from copies or reproductions, proposing that original artworks possess an *aura*, which "withers in the age of mechanical reproduction."[1] This aura, he posited, is linked to the artwork's original context or purpose, from which a reproduction is necessarily removed.

In the years since this still-influential essay was published, printing and digital technologies that allow for the limitless production of seemingly identical copies of artworks have emerged. At the same time, some works of photography and cast sculpture are designed from the start to be produced as multiples or in *editions* of identical works. These technological progressions may prompt us to wonder, *Can Benjamin's conception of the aura extend to such works? Which ethical questions should we consider when faced with the possibility of creating an endless stream of duplicates?* Exploring these quandaries in the context of artistic production can perhaps help us think ethically about similar questions related to cellular reproduction and germline editing.

Authenticity and Proximity

Photography. Benjamin asserted, "From a photographic negative, for example, one can make any number of prints; to ask for the 'authentic' print makes no sense."[1] In hindsight, Benjamin underestimated the artistry of photographic printing and failed to anticipate the value

scholars of photography would place on the date of a print and, by proxy, its proximity to an artist's original intention. Printing a photograph from a negative involves controlling variables like exposure, and, in the process, mutations can occur that move the final product further away from the artist's original vision. According to Baldwin and Jürgens in *Looking at Photographs: A Guide to Technical Terms*, "a photographic *print* made close to the date of its negative, by or under the direct supervision of the photographer, is thought to most clearly capture the photographer's original inspiration."[2] Although vintage and newer prints might appear similar to the untrained eye, this distinction is important for curatorial and connoisseurial purposes.

Still other photographs were made famous precisely because of their reproduction and the popular press that distributed them widely. For example, the Art Institute of Chicago recently featured Margaret Bourke-White's Fort Peck Dam, Montana in the exhibition, "Iconic: Photographs from the Robin and Sandy Stuart Collection."[3] The photograph of an imposing public works project entered 380 000 American homes on the cover of *Life* magazine in November 1936.[4] Mass production altered the appearance of the image due to the newsprint substrate and the commercial printing process, which is qualitatively different from the luscious tones of the gelatin silver print in the museum's collection. Although there are technical and aesthetic distinctions between a fine art print and a mass-produced magazine cover, the latter allowed the image to achieve ubiquity. In this case, ubiquity was an ethical value that superseded the imperative to hew closely to the artist's original medium and format.

Sculpture. Cast sculpture, a medium often intended to be produced in multiples like photographs, can present similar questions about authorship and authenticity. Auguste Rodin, the 19th-century French sculptor, left the molds for his celebrated body of work, including such well-known sculptures as *The Thinker* and *The Walking Man*, to the French government after his death.[5] French regulations have since capped the number of authorized sculptures made from each mold at 12.[5] But what about sculptures made beyond this somewhat arbitrary limitation? In 2001, the Royal Ontario Museum in Toronto caused a stir when it exhibited a group of Rodin plasters and bronzes cast from Rodin's molds in 1999 and 2000. The curator of sculpture at the Rodin Museum in Paris, Antoinette Romain, called the exhibition "a scandal, a forgery, a delusion."[6]

The argument from photography connoisseurship about the distance of a work of art from the intention of the creator being a measure of its authenticity can be drawn upon here: *Should casts made during Rodin's lifetime be regarded as more authentic than those made later?* If additional molds are produced from existing sculptures and casts made from those molds, small mutations and flaws can appear in the mold, resulting in sculptures at a remove from the appearance of the original. But what about casts made from the original molds? On one hand, as art critic Blake Gopnik argued in 2001, "So long as there's good reason to believe that a sculpture shows just what Rodin had in mind for a piece … then the issues of authenticity that the Musée Rodin is making so much noise about are artistically irrelevant."[7]

On the other hand, to take Benjamin's formulation, it does seem aesthetically and ethically relevant that these reproductions are so far removed from the context of Rodin's workshop: they lack the essential aura of original works of art.

The idea of authenticity is frequently invoked in order to protect the vision and intention of an artist. But it's worth questioning whose interests it promotes when arbitrary distinctions are drawn between identical works. In these cases, perhaps the concept of authenticity is being used to create a false sense of scarcity that impedes wider access to works of art. Such discussions of authenticity and multiples in art can perhaps shed light on parallel, if more freighted, debates about the ethics of human germline editing.

Auras and What Makes Us Human

Like printing technologies in the first half of the 20th century, genome editing capabilities have developed at a rapid clip in recent years. Using technologies like CRISPR/Cas9, it is now possible to precisely target problematic DNA segments and to cut them out or replace them in order to repair a mutation or eliminate disease.[8] *Germline editing* refers to these technologies' uses in egg or sperm cells or in embryos. Changes made to the genome of reproductive cells or embryos, including unintended secondary consequences or off-target effects, are passed down to future generations.[9,10] The November 2018 announcement of the birth of gene-edited twin babies in China generated further controversy within the scientific community about the ethics of germline editing.[11] In the wake of this event, some scientists have called for a global moratorium on human germline editing.[12]

Ethical discomfort with germline editing could have its roots in a fear that modifying characteristics of future offspring could quickly progress from "correcting" mutations to creating genetic enhancements perceived by some as desirable.[12] Risks of unintended consequences also loom large: in attempting to make a positive change, scientists could incidentally cause off-target effects that reverberate for generations to come.[12] (In an art context, a parallel situation would occur if a photographic negative or a sculpture mold were altered; imperfections would carry on through all subsequent editions.) A larger ethical concern about germline editing is whether humans should be meddling in such natural processes as the makeup of an individual's DNA in the first place. What about authentic human experience—about human aura (as Benjamin might say)—is interrupted or undermined when humans have the hubris to design, customize, originate, and replicate the genome of their descendants?

Intention, Revisited

When first confronted with the technologies that made it possible to create visually similar reproductions of artworks, Benjamin critically underestimated the artistry of processes like photographic printing and cast sculpture. Subtleties of germline editing, too, might not be immediately obvious and could manifest generations after an original intervention. As germline research continues to progress, we should consider which criteria we use to assess

authenticity and what these criteria suggest about the source of our unease with new technologies and the proximity of their effects to our best intentions.

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Editor's Note

Visit the Art Institute of Chicago website or contact Sam Anderson-Ramos at sramos@artic.edu to learn more about the museum's medicine and art programming. Browse the AMA Journal of Ethics Art Gallery for more Art of Medicine content and for more about the journal's partnership with the Art Institute of Chicago.

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ART OF MEDICINE

Sunset

Antonio Yaghy, MD

Abstract

This image of a silhouetted figure looking out over a body of water at sunset aims to promote reflection about patients' feelings of sadness, despair, helplessness, and uncertainty upon being diagnosed.

Figure. *Contemplating Illness*

Media

Digital photo-painting.

This image seeks to depict emotions a patient might feel when contemplating illness or diagnosis of disease. Illness has been defined as a "subjectively interpreted undesirable state of health,"[1] whereas disease is understood as an objective conclusion about a

patient's health based on scientific reasoning.[2] One view of a patient-clinician encounter is that it should aim to dissolve distinctions between the subjectivity of illness and the objectivity of disease. To achieve this goal, a physician must diagnose and treat patients with compassion and motivate patients' understanding of their disease. Patients who understand their disease in turn will be more likely to have reasonable expectations regarding treatment and prognosis.

The image invites an observer's visual exploration of sadness, despair, helplessness, and uncertainty by the use of dark tones, which dominate the negative space, and by a silhouetted figure in the foreground that looks out over a body of orange-colored water suggestive of a time close to sunset.

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VIEWPOINT

Genome Editing, Ethics, and Politics

Isabel Gabel, PhD and Jonathan Moreno, PhD

Abstract

For the better part of a dozen years and over 3 US presidential terms, heated debates about the ethics of cloning and embryonic stem cell research helped to define the American political landscape. Current lack of public controversy about regulation of human genome editing does not signal that ethical issues about engineering human embryos have been settled. Rather, while genome editing raises old ethical questions about the value of human life, eugenics, and the weight of unintended consequences, it also came into being in a political landscape that vastly differs from the early aughts when bioethics was last a major topic of political controversy.

Not Controversial?

For the better part of a dozen years and over 3 US presidential terms, heated debates about the ethics of cloning and embryonic stem cell research helped to define the American political landscape.[1] Yet now, despite the fact that new developments like gene editing are barreling ahead and challenges to traditional conceptions of human reproduction are still developing, ethical issues of biotechnology have largely disappeared from the public space. In June 2019, a congressional committee decided not to override a ban on modifications of embryos that prohibits the US Food and Drug Administration (FDA) from approving clinical trials involving heritable changes and the so-called 3-parent embryo resulting from mitochondrial replacement.[2] The vote took place with the usual back-and-forth among elite policy ethicists with minimal notice in the media and no comment at all in any of the 2-dozen presidential campaigns.[2]

This lack of public controversy about government regulation of gene editing does not signal that ethical issues about engineering human embryos have been settled. Rather, while genome editing raises old ethical questions about the value of human life, eugenics, and the weight of unintended consequences, it also came into being in a political landscape that vastly differs from the early aughts, when bioethics was last a major topic of political controversy. Understanding the altered biopolitics of our time is an essential step toward effective governance of genome editing.

Shifting Biopolitics

More than other fields of inquiry, biology and biomedicine are often intuitively felt to have high-stakes cultural and political implications, and for good reason. There is a long history of biology being used to forward illiberal and sometimes violent political agendas, from the 19th-century eugenics movement, to the forced sterilization of Americans in the early 20th century, to exterminationist Nazi ideology. And this history played a big role in the American conservative bioethics movement.

The chair of President George W. Bush's President's Council on Bioethics, Leon Kass, was deeply influenced by the German-born Jewish philosopher, Hans Jonas.[3] Jonas' experience as a refugee from Nazi Germany led him from his early training in existential philosophy to a lifelong interest in ethics. The major innovation of Jonas' bioethical thought was to show how human dignity was rooted in organic processes of life—that is, in biology. In an essay on genetic engineering first published in 1984, he described cloning and recombinant DNA technology as trespasses into a sacred realm.[4] Jonas' ethics were nevertheless secular ethics that drew on the idea of the sacred as a kind of last-ditch wall between human dignity and the unchecked progress of biotechnology. This philosophical tradition informed Kass' opposition to embryonic stem cell research and his role in convincing President Bush in 2001 to bar federal funding for research involving any new stem cell lines.[5]

Another key factor in the controversy over stem cell research was that it united widespread social anxiety about cloning and chimeras (persons composed of more than one genotype) and the controversial political issue of human embryo destruction. The immediate implications of President Bush's stem cell policy were ambiguous: it limited the number of stem cell lines on which research could be conducted (implicitly limiting funding on new lines), which led to anxiety among scientists about which and how many cell lines qualified and to subsequent regulatory confusion.[1]

But perhaps even more significant was the subsequent creation of the President's Council on Bioethics in November of 2001,[6] which differed substantially from President Clinton's National Bioethics Advisory Commission (1996-2001) in both its charter, which emphasized public reflection on ethical issues rather than policy recommendations, and its fraught relationship with biologists. Under Kass, the President's Council on Bioethics was not tasked with finding consensus among ethicists and scientists but rather asked "to develop a deep and comprehensive understanding of the issues that it considers" and "to articulate fully the complex and often competing moral positions on any given issue."[6] As critics at the time were quick to point out, however, this commitment to "competing moral positions" over consensus became at the very least an effective tool wielded against both the independence of scientific research and the constitutional protection of women's autonomy over their own bodies.[1] The embryonic stem cell controversy is a

historical lesson in how bioethics becomes inseparable from biopolitics, or the governance of science and technology.

Yet as recently as the 1960s, a conservative attitude toward biotechnology did not neatly align with a left-right political spectrum. For Jonas' philosophy has also been an inspiration to environmentalists because of the way he describes human obligation to the natural world, a position more readily embraced by today's liberals and even leftists.[7] Nevertheless, just as the second President Bush ushered in a new neoliberal era in American politics, his Bioethics Council helped solidify a new alignment between the Republican Party and conservative bioethics.

The success of the Republican assault on abortion rights notwithstanding, this alignment has largely disappeared under President Trump. Not only is there no bioethics commission under Trump, but the ethics of biotechnology has all but disappeared from the national political conversation. A notable exception is the Trump administration's decision in June 2019 to restrict research on tissues derived from aborted fetuses, a move that will bring a halt to studies of diseases ranging from cancer, to dementia, to HIV.[8] But even this development, tied to the notion that scientific uses of these tissues somehow encourage abortion, was not unexpected and is rooted in debates about fetal tissue research that date to the 1970s.[1]

Biopolitics of Genome Editing

Gene editing, a topic more remote from the long-standing abortion debate than stem cell research, does not attract the political attention abortion does, and certainly the attention it has garnered is nothing to rival that of cloning and stem cell controversies. Eugenics, too, is probably less an immediate worry than it was for the generation of Hans Jonas. Contributing to this relative lack of attention is the fact that the Republican Party itself underwent a massive internal revolution, beginning with the rise of the Tea Party movement in 2009 and reaching its climax with the nomination of Donald Trump for president in 2016. In addition to shifting the party's agenda further to the right on many issues and dropping what remained of Goldwater-style libertarian social philosophy, this realignment also brought about the dethroning of a whole generation of conservative intellectuals. In other words, there seems to be little controversy over genome editing in part because the right, with the significant exception of abortion, has lost interest in the conservative intellectual tradition that informed conservative bioethics. Critically, the elite individuals at conservative policy organizations who identified the most with Jonas' bioethical concerns, adrift without a party and considering themselves "never-Trumpers," have largely moved on to economic issues.[9]

In some ways, the ethical implications of biotechnology have actually changed less than the political world in which these questions are playing out. It seems unlikely that the congressional decision to uphold barring the FDA from approving clinical trials involving

embryo modifications would have been different with more public attention, especially following the use of CRISPR in the notorious experiments conducted in China in 2018 that resulted in several live births.[10] While CRISPR is certainly a powerful new tool for genome editing, the ethical questions it raises are primarily ones to which bioethicists have long been attuned.

Governance

Genome editing research on human subjects is already subject to a robust regulatory framework, including FDA regulations, that governs all clinical research in the United States. In 2017, the US National Academies of Sciences, Engineering, and Medicine made formal recommendations for ethical human genome editing,[11] and in November of 2018 the Second International Summit on Human Genome Editing convened to address the "science, application, ethics, and governance of human genome editing."[11] Developments such as these suggest that the governance of genome editing is likely to be undertaken by national and international scientific bodies in collaboration with regulatory agencies and not, as in the recent past, by the legislative or executive branch. Meanwhile, concerns about slippage between clinical applications and enhancements, which might constitute eugenics, could be addressed in the short-term by scientific communities building consensus on research priorities for life-threatening and life-altering diseases. If genome editing becomes commercially available—think not only of direct-to-consumer genetic testing but also of self-administered brain stimulation devices—regulatory solutions applicable to do-it-yourself medicine would have to be applied.[12] Although there are serious risks associated with genome editing, both to humans and to the environment, there is nevertheless cause for hope that these risks will be addressed or mitigated by scientific bodies themselves. For the moment, at least, these risks are unlikely to generate the level of political engagement that marked the stem cell and cloning controversies of the early 2000s.

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