Introduction to the Special Issue on CRISPR

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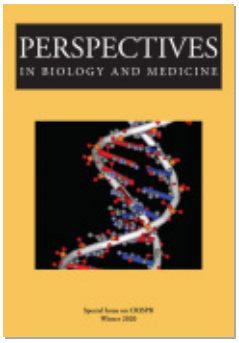

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As I was finalizing this introduction to the Special Issue on CRISPR genome editing for *Perspectives in Biology and Medicine*, news broke that the Chinese scientist He Jiankui had been sentenced in Chinese court to three years in prison for "illegal medical practice" for his role in the creation of the world's first genome-edited babies. This official reprimand reinforced the worldwide condemnation and censure that followed He's announcement in November 2018 that his team at the Southern University of Science and Technology in Shenzhen, China, had used the CRISPR-Cas9 genome-editing tools on human embryos created via in vitro fertilization. He produced and brought to term two babies (and later a third) carrying mutations in the CCR5 gene, a critical co-receptor for HIV, in hopes of rendering these babies immune to infection with the virus that causes AIDS. The work was criticized as premature practice of an unproven and controversial biomedical technology, and vilified for its flouting of widely promulgated international guidelines. Numerous expert committees that had called for restraint, further research to understand the potential risks, and wider social dialogue to determine which, if any, of the many possible genetic changes that could be introduced into the human germline might one day be

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deemed permissible. Scientists, bioethicists, and laypeople who had previously been at odds over whether genome editing of human embryos for the purpose of altering an individual's entire genetic constitution—and by virtue of passage through the reproductive germline, that of all of their offspring—should ever be practiced, were virtually united that the world's first experiment in human germline genome editing had been a gross violation of medical and bioethical norms. While the imprisonment of the first practitioner of human germline genome editing will likely dampen enthusiasm that might have been building in some quarters, an IVF clinic in Russia has boldly announced their intentions to create genome-edited babies, and application of this technology, however premature, may be inevitable. This volume is an important exercise in the critical dialogue that is essential if the potential application of this technology is ever to be managed for maximal benefit and minimal harm.

Gene editing is not a new technology, nor is the genome editing of humans a novel concept barely entertained prior to the discovery of the CRISPR-Cas9 genome-editing toolkit. For more than a century and a half, dating from the time of Mendel's discovery of the rules of heredity, the later definition of the gene as units responsible for the generational passage of hereditary traits, and ultimately the discovery of DNA as the molecular vehicle of such inheritance, farmers and scientists have been engaged—wittingly, or unwittingly—in the manipulation of genetic traits through selective breeding or experimental interventions. The potential that scientists might one day prove capable of altering and defining human traits either chemically or genetically in the context of in vitro fertilization and embryo manipulation has long been the subject of critical commentary and fiction. Perhaps most notable was the publication in 1932 by Aldous Huxley of *Brave New World*, a dystopian view of a future society in which highly mechanized in vitro embryo manipulation produced babies preordained into specific castes of social strata. The modern era of gene editing began, arguably, in the Stanford laboratory of Paul Berg, who in 1972 published the creation of the world's first hybrid DNA molecule, a link between genes of the monkey tumor virus SV40 and a virus that infects bacteria, called lambda phage (Jackson, Symons, and Berg 1972). A natural next step was injecting this novel gene construct into the bacterial host *Escherichia coli*, a denizen of the human intestine. But Berg deferred this experiment because of concerns about the potential risks of propagating a monkey tumor virus within the human gut, and together with other scientists, he advocated for restrictions on certain types of recombinant DNA research (such as inserting toxins, antibiotic resistance, or cancer genes into bacteria) until safety concerns could be better addressed. Berg and colleagues organized a conference of scientists to address ways to ensure the safe conduct of recombinant DNA research. Held in February 1975 at the Asilomar Conference Center in Monterrey, California, the meeting produced a set of recommendations predicated on biosafety containment practices that were commensurate with the predicted

risk of the experiments. Biosafety containment guidelines subsequently became widely adopted standards of practice for the worldwide community of molecular biologists, and arguably facilitated the revolution in biotechnology of the last five decades. Berg would win the Nobel Prize in Chemistry in 1980 for his "fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant DNA." One might argue that Berg is equally deserving of a Nobel Prize for Peace for his hugely influential advocacy for restraint, public discourse, and transparent self-regulation of emerging biotechnologies.

While safety was of primary concern at Asilomar, a subtext was the assumption that gene splicing might one day be applicable on human genes, in human cells and tissues, and potentially even in human embryos, conferring the ability to alter the human germline. However, with gene splicing technology in a most primitive state, such concerns were relegated to futuristic speculations—science fiction.

Experiments in molecular biology and genetics entail an understanding of how gene variation, which occurs naturally in populations or organisms, relates to traits, which for biomedical applications is most often concerned with the genetic underpinnings of human disease. The essence of molecular biology and genetics therefore depends not only on splicing genes but on altering their structure via creation of specific sequence alterations, or mutations, in cells, tissues, and model organisms to observe and interrogate the relationship between specific genetic mutations and disease. Driven by the enormous potential for using gene editing to create specific genetic alterations in *Mus musculus*, the laboratory mouse, Oliver Smithies of the University of North Carolina and Mario Capecchi of the University of Utah developed tools for altering genes in mouse embryonic stem cells that could be used to create genetically engineered strains of mice. Gene targeting, as developed in the mid to late 1980s, employed an intrinsic mechanism within cells called "homologous recombination," during which pieces of exogenous DNA with sequence homology to existing parts of the genome would spontaneously recombine, or exchange with the endogenous chromosome. Initially, homologous recombination was exploited to introduce foreign sequences between stretches of homologous DNA, thereby interrupting the endogenous gene, enabling scientists to observe the effects of gene deletion (loss-of-function, or "knock-out") on whole animal physiology. Ultimately this methodology was refined and extended to introduce smaller, more refined genetic alterations, enabling the creation of genetically engineered murine models of human disease that revolutionized biomedical research. Smithies and Capecchi, together with Martin Evans who first cultured mouse embryonic stem cells, shared the Nobel Prize in Medicine in 2007.

Despite the enormous potential of this early strategy for gene editing in mice, many technical barriers hindered its assimilation in other organisms, most notably the lack of equivalent embryonic stem cells and methods for creation of genet-

ically engineered strains that had been perfected in the mouse. Even with the eventual isolation of human embryonic stem cells in 1998, the prospect for using the methodology to introduce genetic changes in human embryos and human beings remained remote and unfeasible. The process of homologous recombination in mammalian cells via introduction of exogenous snippets of DNA was simply too inefficient and depended on commandeering the intrinsic pathways for DNA replication and repair. In the decades between 1990 and 2010, the heyday of gene targeting to create mouse models of disease, it would routinely take many months to years to engineer strains of mice, and more time to breed them to numbers suitable for experimental analysis. Experimental studies might consume the entirety of a four- to six-year graduate student or postdoctoral career. The evolution towards technology for editing human genomes would require major technological innovation.

It was known that recombination could be stimulated by creation of double strand breaks in the DNA of the target gene, provoking parallel efforts to harness nucleases to catalyze greater recombination efficiency. The critical challenge was engineering nucleases that would recognize specific target genes and induce highly sequence-specific breaks in DNA. Many classes of sequence-specific bacterial meganucleases had been characterized, but adopting them to recognize specific sequences among the billions of base pairs of DNA in mammalian genomes proved insurmountable for all but a small number of gene sequences. Growing understanding of the sequence-specific recognition motifs of various DNA-binding proteins, together with molecular evolution for altered DNA-binding specificity, has led to the creation of artificial sequence specific nucleases that combine sequence-directed DNA-binding domains with DNA cleavage domains. Indeed, virtually any DNA sequence can be targeted by highly specific zinc finger nucleases (ZFNs) or transcription activator effector-like nucleases (TALENs), and these entities have advanced in efforts to edit genomes in human somatic cells, most notably in an attempt to silence the CCR5 HIV co-receptor to induce resistance to HIV. Nevertheless, ZFNs and TALENs are themselves enormously challenging to refine for sequence specificity, and targeting of any new sequence requires months or even years of protein design optimization. Consequently, their potential for applications in human germline gene editing are remote and unlikely to scale across multiple applications.

As often happens in science, technological and intellectual breakthroughs surface from unpredictable inquiries into basic biological mechanisms, and the emergence of the CRISPR-Cas9 toolkit can trace its earliest origins to a most elegant series of experiments interrogating how bacteria evolve to survive infection by bacteriophage viruses. During the first decade of this century, several laboratories determined that bacteria harbor clustered regularly interspaced short palindromic repeats (CRISPR) that carry copies of DNA whose sequence matches that of bacteriophage, and researchers had hypothesized they might be involved

in response to bacteriophage infection. However, it was food scientists working for the French firm Danisco who made the first definitive experimental demonstration of the role of CRISPR and the CRISPR-associated protein 9 (Cas9) as a mechanism of acquired immunity to bacteriophage. Rodolphe Barrangou and Philippe Horvath led a team that wished to understand why some *Streptococcus thermophilus*, an essential player in the fermentation process of cheese and yogurt production, could survive phage attack, which would otherwise plague manufacture. They showed that resistant bacteria integrate phage sequences into CRISPR arrays within their genome, which together with Cas9 function as an adaptive immune system to stave off the next wave of phage infection. Subsequently, several groups—but perhaps most notably those of Virginijus Siksnys, Emmanuelle Charpentier, and Jennifer Doudna—illuminated the molecular choreography responsible for the ability of CRISPR-Cas9 to digest invading phage sequences, filling in the various pieces of the puzzle by demonstrating that RNAs expressed from the CRISPR array (crRNAs and trans-activating crRNA, or tracrRNA) act to guide Cas9 to target DNA for cleavage at specific sequence locations. Importantly, and arguably the innovation that most effectively facilitated the rapid adoption of the CRISPR-Cas9 toolkit for gene editing, Charpentier and Doudna's labs showed that crRNA and tracrRNA could be fused into a single synthetic guide RNA, greatly facilitating the efficiency and application of CRISPR-Cas9 for genome editing.

The adaptive immune system in bacteria known as CRISPR-Cas9 derives from the capacity of bacteria to integrate copies of the invading virus into their own genome to serve as a memory of prior infection, then to produce an RNA copy that binds to future invading phage and recruits a phage-gobbling nuclease to silence the infection. While the elucidation of this elegant biological mechanism is in and of itself a remarkable testament to curiosity-driven research, in my estimation it was the epochal paper published in 2012 by Charpentier and Doudna (Jinek et al. 2012) that conceived and reduced to practice the prospect of an RNA-directed programmable nuclease, rendering remarkably facile and effective the capacity to target DNA breaks with the ease of designing a gRNA, thereby revolutionizing our capacity to perform genome editing. Importantly, the groups of Feng Zhang and George Church performed essential optimizations and demonstrations of genome editing in mammalian cell systems, including human cells (Cong et al. 2013; Mali et al. 2013). Remarkably, within a year of the first reduction to practice of RNA-guided DNA editing by Charpentier and Doudna, Zhang collaborated with Rudolph Jaenisch to produce the first genetically engineered strains of mice edited via CRISPR-Cas9 (Wang et al. 2013). Within two years, the group of Jiahoa Sha had generated gene-targeted cynomolgus monkeys (Niu et al. 2014). Those of us in the biomedical community, watching in wonder at this dizzying pace of progress, imagined that it would only be a matter of time before genome editing would be applied to human embryos.

Having anchored efforts on behalf of the International Society for Stem Cell Research (ISSCR) to establish professional and ethical guidelines for human stem cell research and its clinical translation, I was immersed in considerations of the professional responsibilities carried by researchers and clinicians. As a physician-scientist and translational researcher, I also had a deep concern for the risks involved in human clinical experimentation. I had witnessed over a decade of premature clinical trials using stem cells, which failed because of our ignorance of stem cell function in disease. Such trials were performed at times by well-intentioned but naïve practitioners, but often by charlatans peddling snake-oil cures to vulnerable patients over the internet. An unregulated industry emerged, and stem cell "clinics" proliferated. Some patients were injured. Some patients died. Seduced by the hype and unrealistic hope for miracle cures, many patients paid exorbitant prices for unproven interventions and, though not harmed physically, were exploited financially. My experience with the premature rush to clinical applications of stem cell medicines raised my concerns for applications of genome editing in a similarly unexamined manner.

In the fall of 2014, rumors began to circulate that two to three papers had been submitted to scientific journals demonstrating gene editing in human embryos. I knew these rumors to be true, as I had received two of the papers to review. As co-chair of the public policy committee of the ISSCR, I participated in a monthly call where the topic of genome editing of human embryos was raised. While the confidentiality of the review process precluded my disclosing the details of the specific manuscripts in question, I confirmed the existence of reports from Chinese laboratories of the application of CRISPR-Cas9 editing to human embryos, restricted to in vitro studies only. However, the tenor of the committee's discussion clearly reflected the feelings of urgency that the application of human genome editing of embryos and their use to induce a pregnancy could be imminent. The ISSCR would ultimately issue a statement in March 2015, calling for a moratorium on the clinical applications of human nuclear genome editing of the human germline.

Quite coincidentally, and largely because of my prior involvement in anchoring the ISSCR Guidelines task forces, in October 2014 I received an invitation from Jennifer Doudna to attend a small gathering of scientists and bioethicists to discuss the "bioethical issues raised by the explosion in new genomic editing methods." A small group of 16 or so met toward the end of January in Napa Valley. The meeting included three participants from the 1975 conference at Asilomar: Paul Berg, David Baltimore, and Dana Carroll. As at Asilomar, the discussions explored the risks of deleterious, "off-target" effects of genome editing for human clinical applications, whether for somatic cell repair or for engineering the human embryo and hence, the germline. Given the ease of practice of CRISPR-Cas9 genome editing, and the potential for overconfidence in its editing specificity, many of those assembled worried there would be insufficient barriers to

imminent clinical use in the context of IVF. Arguments against clinical use could be predicated on safety concerns alone, but unlike Asilomar, concerns for the safe application of genome editing were secondary to ethical considerations. There was a palpable urgency for making a statement admonishing the biomedical community against premature application of genome editing in human reproduction. In a perspectives piece published later that year in *Science*, we wrote: "Given the speed with which the genome engineering field is evolving, the Napa meeting concluded that there is an urgent need for open discussion of the merits and risks of human genome modification by a broad cohort of scientists, clinicians, social scientists, the general public, and relevant public entities and interest groups" (Baltimore et al. 2015). Further, the commentary went on to "strongly discourage any attempts at germline genome modification for clinical application while societal, environmental, and ethical implications are discussed among scientific and governmental organizations. . . . This will enable pathways to responsible uses of this technology, if any, to be identified." The piece ended with a call for convening a "globally representative group of stakeholders, developers and users of genome editing 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 further consider these important issues, and where appropriate, recommend policies."

Following the Napa meeting, appeals were made to leaders of the US National Academies of Science, Engineering and Medicine (NAS) to convene just such a "globally representative group of stakeholders," and the first such meeting, dubbed the "International Summit on Human Gene Editing: A Global Discussion," took place in Washington, DC, in early December 2015. Co-sponsored by the NAS, the Royal Society of the United Kingdom, and the Chinese Academy of Sciences, the summit entailed three days of presentations and discussions among a wide array of experts in biotechnology, gene therapy, reproduction, embryology, genomics, bioethics, history of science, law, and religion, as well as patient advocates and representatives from industry, academia, and multiple continents.

As one of the few physicians on the organizing committee for the summit, I was assigned the unenviable task of presenting the plausible medical applications of germline genome editing, as applied to human embryos during IVF or on gametes produced in vitro for the purposes of human reproduction. Such a topic was sure to inspire vigorous debate and opposition from those who believed any attempt to engineer the human germline was a Rubicon moment, the crossing of which would take humanity down a path towards dehumanization and enable misbegotten efforts at eugenics and human enhancement. However, as a physician committed to relief of suffering, and as (at the time) Director of the Stem Cell Transplantation program at Boston Children's Hospital and the Dana Farber Cancer Institute, I had seen numerous families devastated by genetic diseases for

which bone marrow transplantation offered hope but no guarantee of cure, and typically meant suffering severe toxicity and potentially long-term disability. Following principles of medical triage, I presented a hierarchy of disease indications that might represent a gradation of medical necessity, and thus permissibility. I argued that the most compelling use of gene editing of embryos might be to allow families already burdened by a child with debilitating and often fatal genetic disease to have a healthy child, and to rid future generations of their family of the scourge of genetic disease. Furthermore, I argued that only the most devastating, terminal, painful, and disabling conditions would qualify for the earliest first-in-human attempts at gene editing, and only after sufficient research to optimize the methodology and reduce the risk of deleterious off-target mutation and incomplete editing (mosaicism).

I listed conditions like Tay-Sachs and sickle cell anemia, which are transmitted with an autosomal recessive pattern of inheritance requiring inheritance of two flawed copies of a gene, one from each parent who are asymptomatic carriers. While alternatives exist for such couples in the form of pre-implantation genetic testing and selection of embryos that lack two flawed gene copies, I cited evidence that such procedures are notoriously inefficient and unsuccessful. Moreover, I posed the interests of a couple, both of whom suffer from genetic disease, and cited the unfortunate individual who happens to carry two copies of an autosomal dominant disease gene like Huntington's. In these cases, genome editing was the only means of conceiving a healthy, genetically related child. These cases are indeed rare, but I argued that rarity of a medical condition has never precluded nor obviated the application of medical technology to alleviate suffering. Indeed, much of the current progress in gene therapy owes to perseverance in attempts to treat ultra-rare conditions like immunodeficiency and bone marrow failure syndromes. I gave less weight to the use of gene editing for repair of gene variants that merely convey or modify the risk of a particular medical condition, such as the risk of breast cancer, heart disease, or resistance to HIV. In such cases, the correction of risk variants carried a less compelling ratio of benefit when weighed against the risk of the unknown, but that ratio might shift with time, as more knowledge emerged about specific gene variants. At the other end of the spectrum of medical necessity, I argued that the use of gene editing to modify variants unrelated to human suffering but rather aimed at enhancing human potential—learning, memory, strength, beauty—was the most problematic and bound to stoke concerns for further exacerbations of social inequalities. It was this last category that served as the foundation for much concern, and the very justification for the summit. While preventing disease might one day be a permissible use of genome editing, it was the corrupting possibility of employing genome editing for human enhancement, and that such advantage would accrue only to the privileged, that warranted restriction.

In a summary statement following the 2015 summit, the organizing committee concluded that there was a need for further basic and preclinical research, including on human embryos, to determine the feasibility and fidelity of genome editing. Progress towards clinical applications of genome editing of somatic tissues for the treatment of disease was enthusiastically endorsed, using current oversight mechanisms for ensuring the safety and ethical use of somatic gene therapy. However, the committee stated that "it would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application." Most forcefully, the statement concluded "these criteria have not been met for any clinical use." Finally, the committee recognized the need for oversight and further refinement of principles of governance, and called for an ongoing forum to explore and refine these issues further.

The ISSCR had in fact been responding to the need for a more detailed articulation of the standards for oversight and review of stem cell research, which had evolved and progressed considerably since the prior sets of professional guidelines had been issued in 2006 and 2008, and had grown to encompass many forms of human embryo experimentation. In a major revision and update of the ISSCR Guidelines for Human Stem Cell Research and Clinical Translation (2016), our task force recommended the extension of Embryonic Stem Cell Research Oversight (ESCRO) to include all forms of research on human embryos—Embryo Research Oversight (EMRO). The guidelines supported "laboratory-based research that entails modifying the nuclear genomes of gametes, zygotes and/or preimplantation human embryos, performed under a rigorous EMRO process" but also concluded that "until further clarity emerges on both scientific and ethical fronts, the ISSCR holds that any attempt to modify the nuclear genome of human embryos for the purpose of human reproduction is premature and should be prohibited at this time."

The NAS also took up that charge and convened a committee of experts who deliberated for the better part of a year, ultimately releasing a comprehensive accounting of the scientific, social, and ethical considerations for clinical applications of human germline genome editing. In a report issued in February 2017, entitled "Human Genome Editing: Science, Ethics, Governance," the NAS panel wrote: "Given both the technical and societal concerns, the committee concludes there is a need for caution in any move toward germline editing, but that caution does not mean prohibition" and further recommended "that germline editing research trials *might* be permitted, but only after much more research to meet appropriate risk/benefit standards for authorizing clinical trials" (emphasis added). A year later, another convocation of experts under the auspices of the Nuffield Council on Bioethics released a report in July 2018 entitled "Genome

Editing and Human Reproduction," proposing a potentially more permissive stance towards some applications of genome editing, writing: "We can, indeed, envisage circumstances in which heritable genome editing interventions *should* be permitted" (again, emphasis added).

During the period between 2015 and 2018, considerable progress was made in refining the technology of genome editing, with a dizzying array of new approaches and several new CRISPR-like systems harvested from various bacteria. The papers submitted in late 2014 and early 2015 that had spurred the original rumors about genome editing of human embryos were eventually published, and laboratories around the world—though small in number—began actively investigating the fidelity of embryo editing, which remained challenging and suboptimal for human clinical application. Moreover, more than 60 ethics statements released by various international bodies agreed with both the NAS and the Nuffield Council panels that any clinical applications of genome editing for human reproductive purposes should be prohibited at present (Brokowski 2018). Nevertheless, the articulate treatises composed by these latter two groups provided sound ethical rationales for the potential future limited use of human germline genome editing under a set of highly specific and regulated circumstances, setting the stage for the Second International Summit on Human Genome Editing at the end of November 2018. Originally planned to be held in China and to be co-sponsored again by the triumvirate of the NAS, the Royal Society, and the Chinese Academy of Sciences, negotiations with the Chinese organizers broke down around restrictions on the size and press access for such a conference. The venue was moved to Hong Kong, with co-sponsorship by the Academy of Sciences of Hong Kong. The organizing committee of this meeting, of which I was again a member, anticipated a robust, multifaceted discussion and debate around the clinical use of genome editing, but we also envisioned that an evolution had taken place since 2015, based on greater comfort with the precision of CRISPR-Cas9 genome editing and the statements of influential study groups like the NAS and the Nuffield Council that genome editing in certain circumstances *might* or even *should* be permissible.

What transpired at the Hong Kong meeting was surreal and shocking. A few days before the conference, as I and the other organizers were making the long trek to Hong Kong, some members of the committee were alerted by He Jiankui that he wished to be given the opportunity to announce his work on the creation of human pregnancies with embryos edited to inactivate the CCR5 gene. When we landed in Hong Kong, we set about anticipating the effects on the course of the meeting and the potential for issuing a strong statement of concern, while not yet knowing the full extent of the scientific readiness of He Jiankui's team, the degree of ethical review and oversight of his scientific and clinical protocols, and the outcome of the pregnancies. We, like the rest of the world, awaited He's presentation with fervent anticipation. The atmosphere in the auditorium

was electric, and as He walked slowly across the stage to assume the podium, the cacophony of camera shutters from the hundreds of media gathered was deafening. Indeed, the clicking continued as He began speaking, requiring the session chairperson Robin Lovell-Badge to issue warnings to the assembled media to cease their photography. Despite such admonishment, the media remained defiant, with calls of "freedom of the press." Fortunately, enough pictures were snapped that He could eventually proceed with his description of the preclinical data from his laboratory, the recruitment of couples affected by HIV who wished to have a baby resistant to the virus, and the procurement of informed consent using documents approved through a process of institution review and oversight. I, like many in the audience, was underwhelmed by the rigor and fidelity of the preclinical evidence for a highly faithful gene-editing procedure, and highly skeptical of the process of ethical oversight and informed consent. The mere fact that dozens of international groups had proclaimed clinical application as premature, that no international consensus on potentially permissible indications had yet been achieved, and that the experiments were conducted covertly flouted all norms of professional conduct. Following He's presentation and questions from Dr. Lovell-Badge and Matthew Porteus, an expert in genome engineering from Stanford and another member of the organizing committee, David Baltimore rose as the chair of the organizing committee and took to the podium to roundly condemn the experiments as irresponsible. It was an historic moment.

At the meeting's end, the organizing committee issued a strong summary statement that included the following highlights:

> At this summit we heard an unexpected and deeply disturbing claim that human embryos had been edited and implanted, resulting in a pregnancy and the birth of twins . . . the procedure was irresponsible and failed to conform with international norms. . . . While we, the organizing committee of the second summit, applaud the rapid advance of somatic gene editing into clinical trials, we continue to believe that proceeding with any clinical use of germline editing remains irresponsible. . . . the scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germline editing at this time. . . . progress over the last three years and the discussions at the current summit, however, suggest that it is time to define a rigorous, responsible translational pathway toward such trials.

In the aftermath of the second summit, the international response has included the empanelment of at least two major committees to determine next steps. The World Health Organization has convened an advisory committee to develop global standards for the governance and oversight of human genome editing. Co-chaired by Margaret Hamburg, former Commissioner of the US Food and Drug Administration, and Justice Edwin Cameron of South Africa, it is certain to be guided by strong standards of regulatory science and rigorous oversight.

An international panel has been convened by the NAS and the Royal Society to develop a framework for interested stakeholders to follow in assessing potential for clinical applications of human germline genome editing to inform the possible development of clinical applications, should a broader consensus emerge that such heritable genetic manipulations are deemed permissible. Both panels are slated to provide further guidance this year or early next.

With the sentencing of He to prison, we now know that the Chinese court system judged his experiments as not only outside the ethical norms articulated by the international community, but illegal as well. The deliberations and debate over which, if any, and when potential uses of germline genome editing might be permissible must and will continue. This volume is meant to inform readers of many critical perspectives on this debate. Essays include critical analyses of the existential and eugenic risks, biosecurity concerns, and the ethics of human enhancement. Others probe deeply into the fuzzy distinctions between therapeutic applications and enhancement, and the fact that simplistic sorting into somatic and germline applications cannot alone be used to distinguish good from bad. Yet others refocus the discussion around social exclusion and social justice, or address the approach to genome editing with the cautious expertise of human embryology and assisted reproduction. And perhaps most important, we hear the voice of patients and other stakeholders affected by disease, or by conditions like deafness that challenge the categories of disease and disability. These personal accounts bring us back to the consideration that, at its core, human germline genome editing impacts families, individuals, and their offspring, and as such is deeply personal. As for many potentially controversial emerging biotechnologies, the rights and autonomy of the individual must be weighed against broader societal concerns. This volume adds to the rich corpus of ideas and arguments that will inform a technology bound to influence generations to come.

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