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Global Governance of Human Genome Editing: What Are the Rules?

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Abstract

Human gene editing, particularly using the new CRISPR/Cas9 technology, will greatly increase the capability to make precise changes to human genomes. Human gene editing can be broken into four major categories: somatic therapy, heritable gene editing, genetic enhancement, and basic and applied research. Somatic therapy is generally well governed by national regulatory systems, so the need for global governance is less urgent. All nations are in agreement that heritable gene editing should not proceed at this time, but there is likely to be divergence if and when such procedures are shown to be safe and effective. Gene editing for enhancement purposes is not feasible today but is more controversial with the public, and many nations do not have well-developed regulatory systems for addressing genetic enhancement. Finally, different nations treat research with human embryos very differently based on deeply embedded social, cultural, ethical, and legal traditions. Several international governance mechanisms are currently in operation for human gene editing, and several other governance mechanisms have been proposed. It is unlikely that any single mechanism will alone be effective for governing human gene editing; rather, a polycentric or ecosystem approach that includes several overlapping and interacting components is likely to be necessary.

1. INTRODUCTION

Genome editing is already being applied across a variety of domains, including human health, animal and plant breeding, environmental applications, and basic biomedical research, with much greater use of gene editing projected across each of these domains in the future (18). The discovery and recent development of CRISPR (clustered regularly interspaced short palindromic repeats), for which the 2020 Nobel Prize in Chemistry was recently awarded (25), has greatly accelerated the use of genome editing across all these domains. This review focuses on human genome editing, and in particular current efforts and proposed future strategies for the global governance of this technology. Governance includes traditional government regulation by legislation, regulation, and treaties, as well as more informal oversight and guidance by nongovernmental entities such as industry groups, professional associations, civil society organizations, journals, funders, and other third-party entities (20, 75).

This review begins with a brief description of genome editing technology and its existing and potential applications to humans, and then identifies safety and ethical concerns raised by different types of human genome editing and how those concerns are being addressed by national regulatory bodies around the world. It then focuses on global governance, addressing three questions: What are the arguments for and against global governance of human genome editing? What mechanisms of international governance of human genome editing currently exist? And what additional mechanisms of international governance have been proposed or may be needed?

2. OVERVIEW OF HUMAN GENOME EDITING

Genome editing is a procedure in which the DNA sequence of an organism is altered (edited) at a specific site. Unlike forms of DNA engineering that randomly insert DNA sequences into a genome, genome editing is able to make precise changes by using a short sequence of RNA or protein that binds at a specific site, and then using a DNA-cutting protein known as a protease to cut the DNA double helix at or near the binding site (40, 41, 94). The cut DNA is then repaired using one of the cell's several own DNA repair mechanisms and, under the right conditions, manipulated to add or delete nucleotides (or even longer stretches of DNA) or to alter the original DNA sequence to change one or more nucleotides (94).

The initial gene editing systems—such as zinc-finger nucleases and transcription activator–like effector nucleases (TALENs)—used specially designed protease proteins to bind to and cut the appropriate DNA sequence (94). Much effort and skill was required to design proteins that would bind to and cut a specific DNA sequence. CRISPR, the newest gene editing technology, uses a guide RNA molecule rather than a protein to bind to the target DNA sequence, which is combined with a DNA-cutting protease such as Cas9 (41). This CRISPR system evolved in bacteria as a quasi–immune system to cut and destroy the DNA of invading bacteriophages (9). CRISPR/Cas9 makes genome editing easier, more accurate, less expensive, and more useful, in part because a guide RNA can be created for any particular DNA sequence much more easily and quickly than creating a protein that would bind at the target site (94). Moreover, it can be used to make a variety of genetic manipulations, from point mutation edits, to full gene knockouts, to inserts of new DNA sequences, to combinations of several simultaneous genetic changes, as well as serving other functions, such as diagnosis and modifying gene expression (18, 94).

While genome editing can be used for any type of organism, the focus of this review is on human genome editing, which can be categorized into several different types of applications. The least controversial human application is to treat somatic cells of patients with existing genetic diseases. Government-approved clinical trials of somatic gene editing are underway in jurisdictions

such as the United States, China, and Europe to treat patients with cancer, sickle cell disease, and genetic eye conditions, among others (36, 40).

A much more controversial human application of genome editing is germline or heritable gene editing. This application would involve genome editing a fertilized egg or early embryo, or cells that will develop into gametes, with the objective of modifying every cell in the resulting child. As discussed below, no jurisdiction currently approves of heritable gene editing. In November 2018, a rogue Chinese scientist named He Jiankui shocked the world by announcing that he had gene edited at least two human embryos that resulted in live births in an attempt to confer resistance to HIV (33, 36, 50); the birth of a third gene-edited child was also later confirmed (90). These cases of heritable gene editing were universally condemned as unethical and in violation of numerous national and international guidelines and norms (4, 17, 65). Dr. He lost his job and was put under house arrest, fined, and eventually sentenced to three years in jail by Chinese authorities (36, 86).

While somatic therapy and heritable editing are the two human applications that have received the most attention, there are other potential human applications to note. One is for nontherapeutic enhancement purposes, such as gene editing an existing person or a future person (i.e., heritable editing) for improved abilities, performance, or other qualities. As discussed below, such enhancement applications are problematic from both a scientific and ethical perspective at this time.

The final application of human genome editing is for research purposes. Several countries permit gene editing research on embryos under 14 days of development that will not be used for implantation, as well as research on various other in vitro human cell types, including gamete-producing cells. The purposes of such research are to better understand the development of normal embryos and the early manifestations of genetic diseases, as well as various aspects of human fertility biology (82).

3. SAFETY, ETHICAL, AND REGULATORY ASPECTS OF HUMAN GENOME EDITING

While human genome editing brings enormous potential and promise for treating and preventing human genetic disease, it also presents serious and novel safety and ethical risks. The risks, concerns, and regulatory approaches differ significantly among different categories of human genome editing.

3.1. Somatic Genome Editing

The least controversial human application is somatic genome editing to treat existing disease. This application is quite similar to somatic gene therapy, which has been approved for hundreds of clinical trials worldwide (49). Genome editing is likely a safer procedure than traditional gene therapy, because it involves a more precise editing of the genome rather than, for example, the random insertion of DNA segments into the genome, as occurs with many existing gene therapy protocols. Several jurisdictions have therefore approved somatic genome editing attempts under the same regulatory authority they have used to approve gene therapy clinical trials (82).

While existing national regulatory frameworks can and are being adjusted to include somatic gene editing, this application does still raise some unique safety and ethical concerns (40). Because gene editing is not completely accurate, there is a risk of errors occurring at the site of editing (on-site errors) or from unintended edits at sites elsewhere in the genome (off-site errors) (56, 94). There are two major approaches to somatic gene editing, depending on the target tissue (82). Some tissue types, such as blood cells, can be removed from the body and edited in vivo, and the transformed cells can then be grown in vitro and tested for the accuracy and errors of the

editing process before being transplanted back into the body (82, 94). For many other tissues, the cells cannot be safely removed and edited, so the gene editing mechanism must be delivered to the target cells inside the body, using a virus or some other vector (7, 40, 94). This results in less control of the editing process, since editing errors cannot be easily detected and the affected cells cannot be removed from the body (7, 56).

Regulatory approval of somatic gene editing in various countries focuses primarily on safety, with requirements that include preclinical testing, an initial approval to commence testing in humans, and then several phases of clinical testing that evaluate safety and efficacy (82). Several such somatic genome editing studies have been approved in the United States, China, and the European Union, although these studies are still in the initial phase of clinical testing (40). Significant benefits have been reported from these early gene editing attempts for diseases such as cancer and sickle cell disease, and no adverse effects have been reported (40).

While national regulatory systems generally have similar and well-settled premarket approval systems for somatic gene editing (82), one issue that remains somewhat unsettled is consent (38). An exotic new technology such as genome editing carries the risk that proponents will overstate its potential or that patients may have unrealistic expectations about its potential, either or both of which could distort the informed consent process (46). The open question is whether some extra type or intensity of consent is required for gene editing given the novel nature of this technology, as well as consent for longer-term monitoring of genome-edited patients for unexpected effects (38, 56).

3.2. Heritable Genome Editing

There is likely to be more diversity of national responses to heritable gene editing than there is to somatic gene editing, although no nation has yet approved heritable gene editing. The ethical concerns about potential human heritable modification have long been debated (37, 44), but the advent of CRISPR creates more immediacy and urgency in the debate now that there is a realistic technological approach to achieve such modifications (87). Accordingly, much of the focus of concern relating to CRISPR human gene editing focuses on germline or heritable gene editing.

Heritable gene editing presents more serious safety and ethical concerns than somatic editing. Every cell in a heritable edited offspring will contain the gene edit (assuming there is no mosaicism from incomplete editing of only some of the cells in a multicell embryo) (82). If the gene edit causes any adverse effects, then the consequences will be more severe (because every cell in the person has that edit) than they are in somatic editing (where only a small percentage of the total cells in the person are transformed). Moreover, the descendants of a person who receives heritable editing will also carry the edited genes, and it may take several generations before the adverse impacts of the editing become clear, at which point dozens of people may be affected (27). Proving that heritable modification of embryos is safe is a long way into the future, if it is even possible (56, 70, 82, 110).

In addition to the greater safety concerns, there are other ethical concerns about heritable genome editing. Heritable editing may create eugenic concerns, in that parents could be enabled to add selected traits to their offspring. The vast majority of parents known to be at risk of producing children with a serious genetic disease could avoid such an outcome by using in vitro fertilization and preimplantation genetic diagnosis to select only healthy embryos for implantation (56), and heritable gene editing would therefore only be needed to prevent genetic disease in a very small number of couples (34, 56). The more likely applications would be to try to add in new characteristics, such as disease immunity or enhancement traits.

Moreover, the attempt to edit out certain genetic disease conditions may send a message to existing people with those same conditions that their lives are less valued (6, 26, 27). Heritable gene

editing could also present distributional and access concerns, in which the wealthy and powerful get unequal access to these expensive interventions, and poorer people do not have access (27, 87). Given the multigenerational impacts of heritable editing, this distributional impact has the potential to continue and even expand over the long term (104).

Heritable gene editing also raises ethical questions about the right for individual people or nations to permanently alter the human genome, which, according to some ethical statements, is the common heritage of all people (102). Another ethical issue has to do with consent, given that future people have no opportunity to consent to procedures that may significantly affect their health and welfare, such as heritable genome editing (27, 28). On the other hand, parents make decisions all the time on behalf of their existing or future children that could affect their health and welfare (52).

Given these serious and currently unresolved issues about the safety and ethics of heritable genome editing, there is a strong consensus today that such editing should not be attempted at this time (8, 56, 66, 82). Where there is genuine disagreement, however, is whether heritable gene editing should be prohibited forever, on which a range of positions have been expressed (14). Some scientists, ethicists, and nations seek to permanently ban human heritable gene editing, asserting that even if the safety issues can somehow be overcome, such modification of the human genetic pool is inherently unethical (13).

Others, however, take the position that if and when the safety concerns can be satisfied, human heritable editing can be ethical and should be permitted to proceed, at least in certain circumstances (53, 82, 88). For example, two different committees established by the US National Academy of Sciences (and in one case cosponsored by the UK Royal Society and the US National Academy of Medicine) have taken the position that if human heritable editing is to proceed, it should be limited (at least initially) to restoring wild-type (normal) function in prospective children with serious, monogenic genetic diseases (56, 82).

While no nation has yet authorized heritable gene editing, national regulatory systems take more or less restrictive approaches to such procedures (5, 11, 69). Discerning the regulatory restrictions on heritable editing across nations is difficult because countries have previously adopted restrictions on related practices (such as human reproductive cloning, stem cell applications, heritable gene therapy, and in vitro reproduction) that, depending on the precise wording of the specific measure, may or may not extend to heritable gene editing (60).

Nevertheless, it is clear that many nations have adopted restrictive legislation or regulations that permanently ban any clinical use of heritable gene editing (11). For example, most (but not all) of the European Union members have ratified the Oviedo Convention, which prohibits heritable modifications (11, 31). Individual nations in the European Union and elsewhere have adopted prohibitions in their national statutes on heritable modifications of human embryos, including Germany, Canada, and Australia (11, 60, 69).

Other jurisdictions have adopted a more intermediate or temporary prohibition of heritable gene editing, such as the congressional spending rider adopted in the United States that prohibits the Food and Drug Administration from exercising its regulatory authority to consider or approve clinical applications that involve heritable editing (62). That rider must be reauthorized on an annual basis to stay in effect (21). Without the rider, the Food and Drug Administration's regulatory authority does not expressly prohibit heritable gene changes, but the requirements to show safety and efficacy would be de facto prohibitions at the present time (21). The United States also prohibits federal funding of research that may involve the creation or destruction of embryos, and the director of the National Institutes of Health has stated that the National Institutes of Health will not fund any research on human heritable gene editing (28).

Finally, there are more permissive regulatory systems that do not expressly prohibit heritable gene editing, but approvals of specific requests would be required to proceed, and no such approvals have been granted. Such countries do, however, permit research and experimentation that involve the modification of embryos, gametes, or gamete precursor cells but do not result in implantation of modified embryos. Examples of such jurisdictions include China and the United Kingdom (60).

In conclusion, while national regulatory systems are uniform today in not approving heritable gene editing attempts, there is no assurance that international harmonization will continue into the future given the different regulatory approaches of various countries, likely reflecting divergent social, political, historical, and ethical norms in each nation (82).

3.3. Enhancement

Genetic enhancement has been debated for decades (47, 80), but as is the case with heritable modification, the advent of human gene editing generates more immediacy and reality in the enhancement debate (87). While human genomic editing has focused almost exclusively on health applications, it could be applied to nonhealth issues in the future, specifically genetic enhancement. The potential for genetic editing for human enhancement raises several issues.

The first is feasibility. Most discussion of genetic enhancement focuses on traits such as intelligence, athletic ability, appearance, or personality. However, the past two decades of genetic discovery have revealed that these types of traits have complex etiologies that involve multiple genes in combination with the environment (82, 92). As a result, it will be difficult to achieve meaningful enhancement of these major traits through editing of one or even a few genes (34). The most likely scenario for human gene editing for enhancement is in competitive sports (101). There has been a long history of professional and Olympic athletes using illegal doping to try to obtain a competitive edge (93). Those same incentives would apply to gene editing of enhancement in sports, which has already been declared illegal by the World Anti-Doping Agency (105). Some genes have been identified that may influence athletic ability, and even if the effect of a single gene edit is small, any competitive edge is likely to be pursued if it can be achieved, legally or illegally (101).

Related to feasibility is the concern about risk–benefit balance. Genetic enhancement could potentially occur in either somatic or heritable applications. Like gene editing for therapeutic purposes, gene editing would create risks of unintended effects, with the risks much greater in heritable than somatic applications, but with even somatic editing presenting nonnegligible risks. In some cases, the risks may be sufficiently reduced and managed to justify therapeutic gene editing, given the potential life-saving benefits of such applications in treating or preventing serious diseases. But for enhancement applications, the benefits are much more uncertain and marginal and are less likely to be worth taking any risks for (82). In addition, public opinion is particularly strong against gene editing uses for enhancement in many countries, although it is more sympathetic to enhancement in some Asian countries (12, 74, 96).

Another important issue with respect to enhancement is the difficulty of clearly distinguishing therapeutic from enhancement uses of a medical intervention (35, 79, 87). Many conditions run a continuum of severity—addressing that condition at one extreme, where the person may be physically or mentally disadvantaged by their atypically low or high measurements, may be therapeutic, while at the other end of the spectrum, where the person is well within the normal range of variation, such interventions may be enhancement. In addition, definitions and perceptions of disease are context specific and socially determined, so a condition that is seen as pathological in one time or place may not be perceived as a disease in another time or place. For example, there has been

discussion of gene editing to make people incapable of experiencing pain—which in a normal person may be classified as enhancement (however ill advised), but which in a terminal cancer patient experiencing uncontrolled pain may be therapeutic (95). The lack of a clear line between therapy and enhancement not only creates a challenge for regulatory distinctions between the two types of interventions but also creates a risk that approval of gene editing for some conditions may create a slippery slope for the same application to be used in other patients for enhancement purposes (8).

While no country has authorized or approved human gene editing efforts for enhancement purposes, many jurisdictions do not have existing regulatory systems in place to address enhancement. One exception is for the European signatories to the Oviedo Convention, which prohibits genetic enhancement (32). In a handful of other countries (e.g., Chile, Columbia, Mexico, and Panama), express prohibitions of genetic enhancement are in place (56, 82). Many Asian countries tend to be more positive toward human enhancement, but none have expressly indicated support for genome editing enhancement (74). Otherwise, most existing regulatory systems instead focus on approval of products for diagnosing, preventing, or treating diseases. It is uncertain how or whether an enhancement technology fits within these existing regulatory systems.

3.4. Basic and Applied Research

The fourth human application of human genome editing is research. Research on somatic cell editing is generally noncontroversial and is not raising any unique regulatory or ethical concerns. Research on embryos or gametes is more controversial and is being regulated differently by different countries based on preexisting regulatory constraints on embryo research (11, 18, 60, 82). Genome editing research using human embryos could be preparing for possible future heritable editing, or it could also be undertaken to better understand the basic biology of human reproduction, early embryo development, and the progression of various genetic diseases (82).

Several nations have permitted human genome editing of human embryos for research purposes, including China, the United States, the United Kingdom, and Sweden. For example, studies reported from China (63, 71) and the United States (73, 110) attempted to correct genetic diseases using CRISPR in viable or nonviable human embryos. Embryonic genome editing studies in the United Kingdom have focused on studying the reproductive process and possible approaches for addressing human fertility (43). Other countries prohibit research on human embryos, and these restrictions apply to any genome editing experiments on human embryos (11). Examples include Italy, Germany, and France (11).

The diversity in national regulations on human embryo genome editing research is further complicated by the lack of clear and agreed definitions of some key terms, such as human embryo and germline (60). The variation in national embryo research laws, deeply embedded in each nation's history and culture, makes it unlikely that regulations governing human editing in embryo research can be fully harmonized among nations (23, 46, 56). Nevertheless, there may be other objectives of international coordination, such as creating a consortium of nations that can proceed with embryo research to share resources, methodologies, and results among themselves and with nations prohibited from conducting such research themselves (91).

4. INTERNATIONAL GOVERNANCE

The divergent national positions and unresolved questions about human genome editing oversight have generated many calls for international governance of this technology. This section first addresses whether, why, and how international governance of human gene editing is needed. Next, it

reviews existing mechanisms of international governance of human gene editing. The final section discusses proposed new mechanisms or initiatives for international governance.

4.1. International Governance: Whether, Why, and How?

There have been many calls for international approaches to human genome editing governance (30, 46, 54, 56, 59, 77, 88, 91). Yet the case for international governance is not inevitable, and there are arguments against it (75). Nations have their own distinct cultural, political, economic, and ethical values that are relevant to human genome editing, and these different values may support different regulatory approaches and preferences (82). Moreover, attempts to negotiate international governance agreements take an enormous commitment of time, energy, and resources, which might be better applied to national regulation, especially in less wealthy nations. Even if efforts to negotiate an international agreement are successful, such agreements often have poor compliance, because there is usually no enforcement body with requisite authority. Finally, allowing each nation to experiment with its own oversight approach would provide a living experiment to test and compare different regulatory approaches that regulators and regulatory experts can learn from.

Notwithstanding these arguments against international governance, there is a strong case for international governance of gene editing. More than 10 different rationales for international governance of technologies have been identified, but only some of these rationales apply to any given technology (75). An example of a rationale that would not apply to human gene editing is to use international standards to reduce trade disputes and barriers, which may be a problem for gene-edited plants and animals but not for human gene editing, since there is generally not expected to be much international trade of goods related to human gene editing.

Several rationales for international governance are, however, applicable to human genome editing. For example, one problem that arises from discordant national regulation is that patients might travel from a restrictive regulatory jurisdiction to a more permissive regulatory location to undergo medical procedures that may be prohibited in the patient's home nation (56). This problem of medical tourism has already been experienced with other comparable medical procedures, such as stem cell treatments and mitochondrial replacement, and there is concern that it will also happen with human genome editing (19, 22, 56, 72). This can be problematic if medical tourism allows citizens to travel abroad to undertake gene editing procedures that their own home country has determined are unsafe or unethical, and it also creates the possibility that under- or unregulated facilities in other countries will try to exploit desperate patients with unrealistic or unproven claims of miracle cures (22, 72). A related problem is that this dynamic may create a race to the bottom or ethics washing, where some nations try to engage in regulatory arbitrage by intentionally underregulating a medical procedure (such as human genome editing) to entice well-paying foreign patients to come to their country for treatment, putting patient safety at risk for economic gain (11).

A second argument for international governance of human gene editing is protection of global human rights and medical ethics (75). While nations are generally free to determine their own political, economic, and legal systems, when an act violates fundamental human rights or important principles of medical ethics, it becomes a matter of concern for all nations and peoples. We all care when people are tortured, deprived of basic freedoms and political rights, or subjected to risky and unethical medical procedures, such as unproven genome editing attempts.

Third, international technology governance is warranted when the asset being protected is the common property of all humankind (75). The classic examples are from the global ecosystem, such as the stratospheric ozone layer or climate change, where all nations have a claim to common

ownership of the asset, and each country must contribute to protecting that common asset. The same argument could be made for the human gene pool, that this is the common property of all humankind, and therefore any attempt to permanently alter that common good should be the joint decision of all nations and peoples (56, 102).

A fourth rationale for international governance of human genome editing is fairness (75). If some nations allow the use of genome editing for enhancement purposes, while others do not, it could create an unfair competitive advantage for those who permit enhancement in activities such as sports. Stronger international governance mechanisms may be able to detect, enforce against, and prevent such unfairness.

Finally, there is a practical argument for international governance (75). International deliberations provide opportunities for collecting and sharing ideas, perspectives, experiences, and results from around the world (56). These shared resources can weave together a shared vision for the future of human genome editing, while also reducing the need for every country to do all the work itself and in a duplicative way.

Given these rationales for international governance, what would the international governance seek to accomplish? One goal would be to try to harmonize regulatory requirements whenever possible. As discussed above, the unique social, cultural, political, and economic histories of different nations have already translated into divergent approaches to human genome editing research. Such differences are also likely to result in divergent approaches to heritable gene editing in the future, although no nation has yet approved heritable editing, and there may be an opportunity for at least short-term or even medium-term international agreement on the inappropriateness of heritable genome therapy, at least until it has proven to be safe and effective (82). Most nations have not developed nuanced regulatory approaches for gene editing enhancement, since genetic enhancement has not been a realistic undertaking until now. So there may be an opportunity for coordination on regulatory approaches to enhancement. Most countries that have authorized or are considering authorizing somatic human gene editing have in place similar premarket approval mechanisms to regulate safety and efficacy, but some additional coordination may be possible there as well to address some of the unique issues raised by gene editing discussed above relating to consent or disease prevention.

Traditionally, harmonization of national regulatory requirements was achieved by treaties (75). That remains an option for human gene editing, and indeed, as discussed below, there is already at least one existing treaty that applies to heritable genome editing. Generally, though, international governance has moved away from treaties as the primary instrument of harmonization, due to the major commitments of time, resources, and efforts needed to negotiate, implement, and enforce treaties (51, 75). A variety of other instruments, such as principles, codes of conduct, private standards, guidelines, public–private partnerships, and certification requirements, have been used across a wide variety of technologies and industries; these instruments are collectively referred to as soft law, because unlike treaties and statutes, they are not directly enforceable by governments (20, 51, 75).

This shift to soft law has been accompanied by an expansion of the entities that may be involved in oversight, beyond the traditional regulation model where only government regulators are involved in enacting and enforcing substantive requirements. The new model of oversight is often referred to as the governance model, in which other entities in addition to government regulators share responsibility for creating and overseeing performance, including industry organizations, civil society groups, think tanks, international organizations, insurers, journals, and funders (20, 75).

There has also been a shift in the ultimate goal of international governance (75). Instead of harmonization of identical requirements, adopting less formal goals characterized by terms such as

synchronization, alignment, coordination, or cooperation may be more feasible and useful (46, 97). Such softer harmonization goals would recognize and respect the expression of national cultural, historical, political, and economic differences, while agreeing on common core principles and procedures. An even more informal mechanism is the creation of and adherence to nonspecified international norms (20), which also play an important role in human genome editing governance, as discussed below.

While harmonization (or less formal or complete manifestations of harmonization, such as coordination or cooperation) is a primary objective of international governance, it is not the sole objective. International governance can establish scientific findings, ethical recommendations, or best practices, even if such recommendations are not adopted universally. International governance can also be used to generate data, tools, standards, and registers that national governments and scientists in the field can utilize (46, 91). It can also deter or ostracize rogues, such as He Jiankui in China, who violate international conventions and norms (20). Even something as simple as internationally agreed definitions of key terms such as embryo and germline would be helpful in coordinating and understanding national governance approaches (60). As discussed below, all these international governance strategies have been attempted or proposed for human genome editing.

4.2. Existing International Governance Approaches

A variety of international governance approaches already exist for human genome editing. These run the gamut from treaties, to soft-law instruments such as professional guidelines, to norms.

4.2.1. The Oviedo Convention. The Council of Europe's Convention on Human Rights and Biomedicine, known as the Oviedo Convention, expressly prohibits heritable modification and genetic enhancement. Specifically, article 13 provides that "[a]n 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" (31). Although enacted in 1997, in the pre-CRISPR era, this convention increased in relevance as CRISPR and gene editing have made genetic enhancement and heritable modification more feasible. It entered into force in 1999. Thirty-five member states of the Council of Europe have signed the convention, and 29 have ratified it (32). Of the 29 ratifying nations, 6 have expressed reservations about certain provisions, so only 23 European nations have agreed to fully comply with it (32). While the Oviedo Convention imposes a binding prohibition of heritable and enhancement editing for its signatories, it is limited to only some European nations, and the rest of the world has shown no interest in signing on to it.

4.2.2. International conferences and reports. Prominent quasi-governmental international conferences and reports, while having no binding regulatory effect, contribute to technology governance both by providing a forum for discussion and debate and by providing a sense of any emerging consensus on appropriate applications and safeguards for an emerging technology. Perhaps the most famous example was the Asilomar Conference on Recombinant DNA in 1975, which set forth initial guidelines for recombinant DNA research. In the context of human genome editing, the initial prompt for such a conference was an ad hoc meeting of scientists and legal scholars in January 2015 that called for an international multidisciplinary conference to deliberate on the ethics of various applications of human genome editing (8).

This call led to the convening of the first International Summit on Human Gene Editing in Washington, DC, in December 2015, which was jointly convened by the US National Academies

of Sciences and Medicine, the UK Royal Society, and the Chinese Academy of Sciences (30). After three days of presentations and panels involving multiple perspectives, disciplines, and stakeholders, the organizing conference issued a summary statement endorsing basic research and somatic gene editing under appropriate existing regulatory oversight, but concluded that it would be "irresponsible" to proceed with heritable genome editing unless the procedure had been demonstrated to be safe and effective and a broad social consensus to proceed had been achieved (30, p. 7). The statement also called for an ongoing international forum "to discuss potential clinical uses of gene editing; help inform decisions by national policymakers and others; formulate recommendations and guidelines; and promote coordination among nations" (30, p. 7).

The first international summit also marked the launch of a study committee convened by the US National Academies of Sciences, Engineering, and Medicine, consisting of experts from eight nations, which issued its report in February 2017 (82). The report concluded that it was appropriate to proceed with basic research and somatic gene editing under applicable regulatory oversight in nations that choose to proceed with such activities. The report recommended that heritable gene editing should not proceed at the present time given the lack of proven safety and efficacy, but could possibly be appropriate in the future if 10 specific criteria are met, including that the editing be limited to restoring a wild-type genotype in prospective children who would otherwise suffer from a serious single-gene disease. It also recommended against any pursuit of enhancement uses of genome editing at this time, given the strong public opposition to such uses and the unfavorable risk–benefit balance. It recognized that complete international harmonized regulation would be impossible given the national differences that exist, but called for international agreement on seven overarching principles, consisting of (*a*) promoting well-being, (*b*) transparency, (*c*) due care, (*d*) responsible science, (*e*) respect for persons, (*f*) fairness, and (*g*) transnational cooperation (82).

A second international summit was held in Hong Kong in November 2018, which happened to coincide with the disclosure that He Jiankui had edited the heritable genomes of at least two live-birth babies in China (83). The He controversy was the focus of much of the conference, with most experts heavily criticizing He's actions as irresponsible (36). The concluding statement from the conference noted that somatic gene editing was proceeding as appropriate, but that human heritable editing was not safe or appropriate at this time. The statement indicated that "germline genome editing could become acceptable in the future if these risks are addressed and if a number of additional criteria are met. These criteria include strict independent oversight, a compelling medical need, an absence of reasonable alternatives, a plan for long-term follow-up, and attention to societal effects. Even so, public acceptability will likely vary among jurisdictions, leading to differing policy responses" (83, p. 7). The summit statement also suggested that "it is time to define a rigorous, responsible translational pathway toward such traits" (83, p. 7).

Following up on the suggestion to create such a translational pathway for heritable genome editing, the US National Academies of Sciences and Medicine joined with the UK Royal Society to create the International Commission on the Clinical Use of Human Germline Genome Editing to study such a pathway (56). The commission issued its report in 2020, and although it did not address whether heritable editing should proceed, it set forth a responsible scientific and regulatory pathway for clinical use of heritable gene editing should any nation decide to permit its use (56). It concluded that such heritable editing should not be attempted until the safety and efficiency of the procedure had been established, and that these criteria have not yet been met (56). It also recommended that extensive societal dialogue should be undertaken before a country makes a decision to proceed with heritable genome editing (56). If such genome editing is eventually approved, it should be restricted, at least initially, to couples who cannot have genetically

healthy children due to monogenic heritable risk, and only a small number of couples worldwide meet these criteria.

The Organisation for Economic Co-operation and Development (OECD) has also convened international meetings of stakeholders on gene editing that have issued reports calling for coordinated global governance (46, 97). Finally, the World Health Organization (WHO) has established an Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, which is expected to issue its report on an international governance framework for human genome editing in 2021.

These various summits and reports provide a public forum in which the full range of scientific, policy, legal, and ethical dimensions of human gene editing are aired and debated before the technology is implemented, which is especially important for its most controversial applications, such as heritable and enhancement edits (104).

4.2.3. International statements and declarations. In addition to the quasi-governmental conferences and reports discussed above, a variety of nongovernmental international organizations have issued statements on human genome editing, and although they have no binding effect, these statements do affect the public and expert acceptability of genome editing approaches. For example, the Hinxton Group, an international consortium of experts from various disciplines on biomedical advances, has issued a statement on human genome editing that emphasizes the importance of considering both scientific aspects of risk and moral considerations and concludes that morally acceptable uses of heritable genome editing may exist once safety and efficacy concerns have been addressed (54).

The United Nations Educational, Scientific, and Cultural Organization (UNESCO) International Bioethics Committee also issued a statement calling on nations to "[a]gree on a moratorium on genome engineering of the human germline, at least as long as the safety and efficacy of the procedures are not adequately proven as treatments" (103, p. 3). In addition, it called for the development of national and international "rules, procedures, and solutions" for the modification of the human genome (103, p. 3).

National ethics bodies have also issued statements supporting international convergence on key ethical principles relating to human gene editing. The Nuffield Council on Bioethics has issued two reports on the ethics of gene editing (87, 88). In the most recent report, from 2018, the authors concluded that they could "envisage circumstances in which heritable genome editing interventions should be permitted" (88, p. 154) but that such actions must not produce or exacerbate social divisions of the marginalization of disadvantaged groups. A joint statement by the ethics councils of France, Germany, and the United Kingdom noted that, given the absence of any international authority that could put into effect enforceable legal controls, it was up to each nation to ensure that appropriate regulatory controls were in place to prevent unethical genome editing experiments (29). The three councils agreed that heritable genome editing should not be attempted until safety had been demonstrated but could not agree on whether there should be a blanket prohibition on all genome editing for enhancement purposes (29).

The impacts of these international statements and declarations are cumulative, and the more statements that converge on the same positions, the greater the moral force and influence those positions have. The impact of these international statements is also buttressed by the significant number of concurring reports, positions, and statements by national organizations.

4.2.4. Professional society guidelines. Various professional societies have adopted restrictions and guidance on human gene editing in their professional guidelines (45, 57, 89, 98). These guidelines can have significant influence on the scientists and clinicians responsible for genome editing

attempts, since they affect their professional standing and credibility. For example, the International Society for Stem Cell Research (ISSCR) supported a moratorium on heritable editing in a 2015 statement (57) and included a prohibition on heritable editing that involved implantation of a modified embryo in its 2016 guidelines (58). Although not legally binding, these professional guidelines often have enforcement procedures, including calling for journal editors, grant agencies, and peer reviewers to ensure compliance with the guidelines (58). As discussed in the next section, leading scientific journals have agreed to enforce the ISSCR guidelines for human embryo research considered for publication (84).

4.2.5. Scientific journals. Scientific journals can and are playing an important international governance role in human genome editing (54). Leading journals, such as the *Nature* family of journals, require compliance with appropriate ethical standards before publishing human editing research involving human embryos (85). *Nature* specifically recommends compliance with the ISSCR guidelines and requires researchers who submit manuscripts involving genetic modification of embryos to also submit an ethics statement; the journal then sends the manuscript for review by an ethics consultant to ensure compliance with relevant ethical guidance, such as the ISSCR guidelines (84). Since scientists seek the recognition and prestige of publishing their work in such prestigious journals, this gatekeeping role by scientific journals can be a powerful governance tool.

4.2.6. Norms. Regardless of what other national and international mandatory restrictions apply, there will always be the potential for mavericks to undertake unethical or unacceptable genome editing experiments, perhaps exploiting jurisdictions with lax or nonexistent regulations (85). International norms can be an effective approach for restricting unethical actions (20). An example of such a norm is provided by the 14-day rule against experimenting on human embryos after 14 days of development (55). This rule was originally developed by ethical advisory committees as a recommendation and has been written into the laws of 12 nations (55). But beyond those mandatory restrictions, the 14-day rule has been recognized as an ethical norm in many other nations without a legally enforceable provision, and in that role it has been described as "tremendously successful" (55, p. 170). The emergence of this international norm represented the "convergence of deliberations of various national committees over decades," reinforced by "[h]undreds of medical and scientific associations submit[ting] recommendations" and "dozens of public forums" (55, p. 171).

In the same way, a strong international norm has developed against heritable genome editing at the present time, at least while the safety of such a procedure is unproven. Dozens of advisory committees, national bodies, expert opinions, and professional societies have converged on the need for much more proof of safety before heritable genome editing should be considered (20). The He Jiankui controversy in China illustrated the consequences of breaking this norm: The unanimous moral condemnation of He's premature attempts at heritable editing, and the personal and professional repercussions and punishments that He incurred, are a strong warning and deterrent against additional attempts at heritable editing at the present time (3, 33, 36, 50). While there is no consensus against undertaking heritable editing if and when safety has been demonstrated, the current international norm against such experiments is probably the strongest governance tool currently in place, notwithstanding its informality.

4.3. Proposed International Governance Approaches

Beyond the existing international governance mechanisms, there have been many proposals for additional governance approaches and mechanisms, as summarized below.

4.3.1. Moratorium or ban. A number of organizations and experts have called for an international moratorium or ban on heritable genome editing (13, 14, 48, 57, 66, 67, 103). Although less discussed to date, an international moratorium or ban might also be considered for genetic enhancement. The proposals for a ban or moratorium generally do not specify who would implement and enforce such a restriction, but presumably an international organization such as the United Nations would be tasked with the responsibility to adopt and enforce a ban. The history of adopting such bans or moratoria on biomedical interventions through international organizations such as the United Nations is not encouraging. For example, in the early 2000s, there was a concerted effort to adopt a ban on human cloning through the United Nations that ultimately floundered over questions such as defining the precise procedures to be banned and how the ban would be enforced (16, 51). The Council of Europe's Oviedo Convention is a pre-CRISPR treaty that bans heritable modification and genetic enhancement, but it has only been ratified by some European nations and no nation outside of Europe (32).

The central argument for a ban is that "the value of genome editing to the small number of families potentially benefitting from this technology does not warrant the risks to the edited children, the burdens to society for development and oversight, and the risks to society through its misuse" (13, p. 487). A permanent ban is a drastic remedy that has been applied in only a few circumstances involving highly unethical products or activities, such as biological weapons and land mines. Many nations and scientists, while opposing any use of heritable gene editing at this time, have not indicated a commitment to support a permanent ban of such procedures (64, 66).

A moratorium differs from a ban in that it is not permanent, but can be reconsidered at one or more times in the future. A time-limited moratorium is more in line with the existing consensus that human heritable editing should not be attempted at this time. Many professional societies have called for a voluntary moratorium by scientists (45, 57, 89, 98), but implementing such a moratorium would require determining how long it will last and/or under what criteria it will be lifted, and on these issues there is likely to be less consensus. If the moratorium were established for a fixed period of time, then the situation may be no different when it expires; conversely, the reasons for the moratorium may dissolve before the scheduled end date arrives. Alternatively, the moratorium could last until specified criteria are achieved, but this may require designating some body to make that determination, which could be difficult and controversial (2).

Some critics have opposed a moratorium or ban as lacking credibility or enforceability, even if the goals are worthy (2, 3, 24, 39, 64, 87). Other critics contend that a moratorium or ban is not needed and that a better governance approach is to specify the criteria that would have to be met before heritable editing could proceed, and to avoid using the loaded words moratorium or ban, which have historically been associated with unduly restrictive policies (3, 20, 24). This was the approach taken by the two international summits (30, 83) and the National Academies of Sciences, Engineering, and Medicine report (82).

4.3.2. Global governance framework. A number of experts and entities have called for a global governance framework for developing scientific and ethical standards for human genome editing and approving permissible gene editing translational pathways (48, 56, 77). The WHO expert committee is scheduled to issue its final report on a global governance framework for gene editing in 2021. In an interim statement, the committee stated that it plans to propose a governance framework that can do the following:

(i) Identify relevant issues, a range of specific mechanisms to address them, and be developed in collaboration with the widest possible range of institutions, organizations and peoples.

(ii) Be scalable, sustainable and appropriate for use at the international, regional, national and local levels.
(iii) Work in parts of the world where there is traditionally weaker regulation of scientific and clinical research and practice, and where genome editing may not yet be pursued or invested in with great intensity.
(iv) Provide those with specific governance roles for human genome editing with the tools and guidance they need. (106, p. 2)

One proposed model is a global framework inspired by the UK Human Fertilisation and Embryology Authority, in which researchers must propose and obtain approval for specific research or clinical heritable gene editing proposals (85). All researchers or clinicians who propose such gene editing would be required to adhere to a code of conduct that includes specific ethical principles that must be followed (85). The global framework may also include "legal strategies for the prevention and penalization of unacceptable research" (85, p. 145).

Proposals for a global governance framework have generally been silent or ambiguous about the institutional home of such a framework, but they generally envision some type of formal entity that goes beyond the existing informal and ad hoc governance system (56). One option would be an existing international organization, such as the WHO, although the WHO is more advisory than regulatory and does not have international enforcement authority. Nevertheless, the WHO could set forth a scientific and ethical framework for permissible genome editing, which could be updated over time and which would set a standard of care and guidelines for nations and scientists contemplating human genome editing. The WHO has created similar nonenforceable but nonetheless influential governance frameworks for other health technologies, such as xenotransplantation (53). Other options for existing international bodies to provide a home for this international genome editing governance framework include UNESCO and the OECD (56).

Alternatively, a de novo institutional structure could be established, perhaps as the administrative body for a framework convention on human genome editing, similar to what has been created for tobacco or proposed for nanotechnology (1, 99). A third possibility would be a self-regulatory approach, such as the Helsinki Declaration principles for research subject ethics pronounced (and periodically updated) by the World Medical Association, which does not directly enforce its principles but instead relies on national governments, professional societies, and medical professionals to do so (109). This model would be less interactive than the other two because it does not provide for two-way dialogue with researchers and regulators about specific proposals or approaches.

4.3.3. International advisory panel. A somewhat similar but less powerful concept is the creation of an international advisory panel to advise nations on human genome editing (20). This advisory panel could provide scientific advice, ethical and policy recommendations, or both. The International Commission on the Clinical Use of Human Germline Genome Editing recommended the creation of an International Scientific Advisory Panel with a diverse, multidisciplinary membership to assess the scientific evidence on the safety and efficacy of genome editing and associated assisted reproductive technologies (56). This advisory panel might be based on international scientific advisory panels that address climate change and biological diversity (68, 100).

4.3.4. Public and stakeholder engagement mechanisms. There have been various proposals for a different type of international governance mechanism that does not so much set and enforce rules or guidelines on genome editing as facilitate greater public and stakeholder engagement on genome editing governance. Virtually every expert report on human genome editing has called for ongoing public engagement and dialogue to establish a broad social consensus before various

genome editing approaches are attempted (30, 46, 54, 77, 82, 83, 97). Given the stakes and interests of all humans in the application of such technology, such public participation in deciding uses of human genome editing is imperative, but implementing this imperative is more challenging (2, 11, 82). First, there are no good precedents for global public engagement mechanisms. An oft-cited example of successful public engagement is the approval of mitochondrial DNA replacement in the United Kingdom after an extensive public engagement process (24, 56), but applying such a process globally would be more problematic (51). A second challenge is that complete global consensus will of course never be possible, especially given the significant cultural, ethical, historical, and legal differences among countries (20, 46, 82) and the major differences in public opinion among and within nations on various gene editing applications (74, 78).

Notwithstanding (and indeed, to actively take on) these challenges, a number of innovative proposals for stakeholder and public engagement on genome editing have been put forward (10). One initiative that has actually already been launched is the Association for Responsible Research and Innovation in Genome Editing, a global nonprofit organization that seeks to promote the responsible global governance of genome editing through the involvement and interaction of a broad range of stakeholders (81). Another idea that has been proposed is to create a global consortium of 10–15 organizations that would be charged with connecting people with the science and policy debates around human genome editing (15). Another proposal is to create a "global observatory" on human gene editing that would consist of a network of scholars and organizations that would be "dedicated to gathering information from dispersed sources, bringing to the fore perspectives that are often overlooked, and promoting exchange across disciplinary and cultural divides" (61, p. 436). Yet another proposal put forward is to create a "global citizens assembly" (42, p. 1435) consisting of a representative sampling of people from around the world to deliberate and give input on genome editing governance. The idea of a Governance Coordinating Committee has been suggested as a mechanism for various stakeholders to communicate and coordinate with each other (76). A key ingredient missing from all of these proposals is an institution that would fund and host the initiative.

4.3.5. Genome editing registry. Another governance mechanism that has been proposed is an international registry of all experiments and research programs that involve human genome editing (85). The registry would provide information on the ethical approval of the study and the objective of the study, as well as identifying the researchers, institution, location, and proposed dates of the study (85). Before completing its final report, the WHO expert committee on gene editing issued an interim recommendation that the WHO establish a trial registry of all somatic and heritable human gene editing clinical trials (107), and the WHO accepted this recommendation and has already begun piloting such a registry (108).

4.3.6. Reporting mechanism for unethical activities. The revelation that several scientists and ethicists in the United States had advance notice of He Jiankui's unethical heritable editing attempts in China but did not blow the whistle has been blamed at least in part on the lack of any mechanism for such whistleblowing (23, 36, 50). The International Commission on the Clinical Use of Human Germline Genome Editing has called for the creation of an international mechanism by which concerns about gene editing research or conduct that deviates from accepted practices can be received, conveyed to relevant national authorities, and made public (56).

5. CONCLUSION

International technology governance is not easy. Unlike national law, there is no authority with the power to adopt and enforce binding rules at the international level. Accordingly, in the context

of human genome editing, like so many other technologies, national laws have and will continue to have the primary role in ensuring safe, responsible, and ethical applications (29). International governance can nonetheless play a critical secondary rule in encouraging harmonization and coordination and in facilitating beneficial practices such as providing and sharing information about national policies.

Of the four applications of human gene editing, additional international governance is less needed for research and somatic gene editing. These are the two applications of human gene editing now being actively pursued in some nations, and existing domestic regulatory programs already exist. Somatic gene editing, where it is occurring, is being regulated under existing gene therapy regulations, which are very similar among nations and are effectively addressing most of the relevant concerns, leaving little need or room for international governance. For research, there are important differences in national laws and policies, and these differences are likely resistant to any international efforts of harmonization, given the deeply entrenched cultural, historical, ethical, and political rationales for each nation's policies (46). No nation currently approves of using gene editing for heritable modifications or enhancement purposes. However, this consensus is unlikely to last, and international governance can put in place some substantive and procedural guardrails when national policies and practices begin to diverge, including a commitment to international transparency.

While some have called for a new international treaty or a ban or moratorium, such hard-law governance approaches are unrealistic and unlikely to occur. Rather, the governance of global human genome editing will likely continue to rely on a mixture of soft-law mechanisms, including additional conferences, reports, and statements at the national and especially international levels; one or more nonbinding governance frameworks by international organizations, such as the WHO or OECD (with the latter's efforts perhaps being expanded to include China and developing nations); professional society guidelines; public engagement processes; journal and funding agency policies; and the development of norms—in other words, a "polycentric" (64, p. 505) or "ecosystem" (20, p. 980) approach to global governance. In global technology governance, as in many other areas of life, the perfect is the enemy of the good.

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