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PERSPECTIVE

The Human Right to Science and the Regulation of Human Germline Engineering

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Abstract

There is currently no international consensus on how human germline engineering should be regulated. Existing national legislation fails to provide the governance framework necessary to regulate germline engineering in the CRISPR era. This is an obstacle to scientific and clinical advancements and inconsistent with human rights requirements. To move forward, we suggest that the human right to science is an ideal starting point for building consensus, at the national and international levels, on governing principles that promote responsible scientific and technological advancements. Regulatory frameworks must recognize the international nature of modern germline genome engineering research, the need for shared governance rather than tech-locked prohibitions, and the fact that humans are not their germline.

Introduction

The CRISPR revolution has created new opportunities for germline engineering. The prospect of clinical applications that modify the germline is exciting for many people, but also fraught with scientific, ethical, and political uncertainty.[1] In the past four years, international organizations, governmental bodies, and learned societies have released more than 60 ethics statements on germline engineering.[2] The most recent ones come from the National Academies of Sciences Engineering and Medicine (NASEM, 2017), the Organisation for Economic Co-operation and Development (2018), the Nuffield Council on Bioethics (2018), the Organizing Committee of the Second International Summit on Human Genome Editing (2018), and the Council of Europe (2018).[3,4] Yet, there is still no international consensus on how human germline engineering should be regulated.

News that the Chinese scientist He Jiankui had altered embryos for seven couples during fertility treatment, leading to the birth of twin girls with modified DNA, served as a red flag that stronger regulatory frameworks are needed to govern heritable gene editing. Bar the Oviedo Convention and the European Clinical Trials Regulation, there are no binding international legal instruments. To address the problem, scholars have called for activating deliberation processes to debate the possible effects of gene editing on future humans, ideally reaching international consensus on governing principles.[5,6] But we cannot ignore the fact that currently human germline engineering is imperfectly regulated by legislation at the national level. As often happens with disruptive technological breakthroughs, policy makers are struggling to keep up with the CRISPR revolution.

Here, we discuss the global governance of germline engineering by analyzing current national regulatory approaches by legislative initiatives or via policy or guidelines. We argue that some aspects of these approaches fail to meet human rights standards. International human rights standards should be central to the development of germline engineering law and policies for various reasons, especially that these rights are legally binding on states, at a minimum because they are written in treaties that have been widely ratified, or because they have become part of customary international law. No matter how technical or specific legislation regulating germline engineering is, governments cannot depart from their international human rights obligations when developing regulatory frameworks. It is not just a matter of legality. It is also a matter of legitimacy. International human rights standards are the legal articulation of widely

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agreed upon values. They are an expression of an internationally negotiated consensus.

Our analysis focuses in particular on the human right to science. Recognized, *inter alia*, in Article 27 of the Universal Declaration of Human Rights (UDHR) and Article 15 of the International Covenant on Economic, Social and Cultural Rights (ICESCR or Covenant), the right to science is the key source of more specific rights and freedoms to which all humans are entitled in relation to scientific progress and its applications. Embracing the call for a wider integration between policy development, ethics, and human right, we believe that the right to science—particularly where it creates an obligation ''to respect the freedom indispensable for scientific research'' and to ''recognize the right of everyone … to enjoy the benefits of scientific progress and its applications'' (ICESCR, Article 15.1 and 15.3)—should inform the development of policy at the national level and provide the framework within which any future international regulation should be placed.

Our legal analysis relies on data (to be published in full as a book[7]) from 18 countries. These countries were selected to reflect diversity in geography, legal systems, and commitment to science and innovation. Eight are members of the European Union (EU) and the Council of Europe (Germany, Belgium, Sweden Netherlands, Italy, Spain, and France). One European state is a member only of the Council of Europe (Switzerland). Three are in North America (Canada, the United States, and Mexico), four are in Asia (Japan, China, South Korea, and Singapore), and two are other ''Western countries'' (Australia and Israel). For each country, we recruited experts to write a country report and address the same issues at each step of the translational pipeline. We also looked at the European regulatory regime.

What Is the Human Right to Science?

The right to science is an old right. Indeed, it is as old as international human rights. It was recognized first in 1948, in the UDHR, the keystone of the global international human rights regime, and in the American Declaration of Human Rights, the linchpin of the human rights system of the Americas.[8,9] Most importantly, the right to science has found further recognition in the ICESCR and in various legal instruments at the regional level. The Covenant and the regional instruments are treaties that bind those states that have ratified them (presently 169 for the Covenant). Here, the term ''right to science'' encompasses two distinct but interrelated sets of rights: the right of everyone to benefit from advancements in science and technology and the so-called rights of science (e.g., the right to freedom of scientific research, to intellectual property, to participate in learned societies and travel, etc.). States parties to the Covenant must ''respect, protect, promote, and fulfill'' the right to science. They must refrain from violating or interfering with the enjoyment of a right (respect); take active measures to prevent violation of the right (protect); advocate for, encourage, and otherwise support the advancement of the right (promote); and implement the affirmative measures that are necessary to realize fully the right (fulfill).[10] To discharge these obligations, state actions must be deliberate, concrete, and as targeted as possible.[11]

How these obligations relate specifically to the right to science is still partly unclear. This is because the right to science has been arguably the least known, discussed, and enforced of the rights recognized in the ICESCR, as evidenced, among others, by its occasional appearance in the country reports filed with the Committee on Economic, Social and Cultural Rights (CESCR).[12] After having neglected it for decades, however, the international legal community has started paying attention to this right after a group of experts who convened in Venice, under the auspices of UNESCO, issued a statement in 2009 sketching out its normative content. Since then, UN bodies have also taken various actions to ensure that the right to science is better defined, understood, and realized. The UN Human Rights Council took the first step in 2012 when it appointed Farida Shaheed as its Special Rapporteur in the Field of Cultural Rights.[13] She issued a report titled ''The Right to Enjoy the Benefits of Scientific Progress and its Applications.''[14] The second was the appointment in 2015 by the CESCR of two Rapporteurs (Mikel Mancisidor, initially, and Rodrigo Uprimny) to draft a General Comment on the Right to Science. The appointment of the two Rapporteurs is a significant step because of the authority of general comments for human rights treaties. Beside ''assisting the States parties in fulfilling their reporting obligations,''[15] general comments are commonly considered to be the official interpretation of a right on the part of the United Nations.[16] While a draft of this comment is not yet publicly available, remarks made by the Rapporteurs at various meetings shed light on its future content.[17,18] Scholars have also begun studying how the right to science can be applied to various science policy issues, including global genomic and clinical data,[19] open access to scientific knowledge,[20] citizen science,[21] and biomedical research funding.[22]

Even in the absence of a well-developed framework for the realization of the right to science, we find sufficient guidance about the normative content of the right from a textual analysis of Article 15 of the Covenant combined with a reading of the international legal instruments discussed above and related scholarly works.

Based on this analytical approach, the right has at least three main components: (1) the right of everyone to benefit from and contribute to scientific and technological progress (the ''right to science'' *sensu stricto*); (2) the right of scientists, for instance, to do research and push forward science and technology (the ''rights of science''); and (3) countries' duty to provide an enabling environment. This is the ''right for people to have a legislative and policy framework adopted and implemented which aims at making the benefits of scientific progress available and accessible—both through encouraging new scientific discoveries and through removing barriers for existing scientific knowledge to be used for public benefit.''[23] An additional component is the invitation to encourage international contacts and cooperation in the scientific and technological fields. It is important to note that state parties are also under the obligation to ensure that scientific and technological developments do not end up violating human rights.

These rights are not absolute. States can limit them ''by law,'' but only ''in so far as this may be compatible with the nature of these rights,'' and the aim is ''to promote the general welfare in a democratic society'' (ICESCR, Article 4). However, these limitations can never be preemptive of science and must be based on scientific facts, as they must be balanced against scientists' freedom of research and everyone's right to benefit from their research as well as ''general welfare in a democratic society'' (ICESCR, Article 4; see below). For now, we turn to current approaches followed at the national level to regulating germline engineering and their limitations.

Regulating the Translational Pipeline

To understand how human germline engineering is regulated, it is expedient to break it down into the different stages of the translational pipeline: basic research, clinical research, and clinical applications (see Box 1 for definitions).

Basic research with human tissue

Basic research involving germline genome modifications of human tissue entails primarily working *in vitro* or *ex vivo* on embryos and gametes. Typically, regulatory frameworks impose requirements for tissue procurement and research oversight. Before tissue can be used in research, scientists must: (1) show that the source of that tissue consented to its use in research, and (2) have their research protocol approved by an oversight body—whether at the institutional level (i.e., Institutional

BOX 1. Definitions

Consistent with the traditional conceptualization of biomedical research in basic and clinical research, as well as the distinction between research and practice, we define basic research, clinical research, and clinical applications in the context of human germline engineering as follows. Basic research involves *in vitro* or *ex vivo* studies of germline tissue of humans, animals, or of the two in combination, to understand the biological mechanisms of germline genome modification. Clinical studies are studies involving a living person whose germline tissue (gametes or embryos) is genetically modified *in vivo* or who receives germline tissue that was modified *ex vivo* (i.e., by transferring a modified embryo in the uterus of a research participant) to test the safety and efficacy of germline genome engineering. Clinical applications involve the provision of germline engineering services in a clinical setting that are ''designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success.''[24]

Our definitions are useful to conceptualize the regulation of germline genome engineering, but they suffer from two limitations. First, the boundaries between the different stages are not as neatly separated as we imply. However, we believe that a reliable dividing line can be drawn between basic and clinical research when a living human being is involved in research directly as a research subject. Second, as the Belmont Report notes, the distinction between research and practice is blurred partly because both often occur together. Clinical research may result in a therapeutic benefit for research participants, thus presenting aspects of preventive treatment or therapy that are typical of the practice of medicine, and the safety and efficacy of therapies may be evaluated using formal research protocols.

In line with the Belmont Report, we consider ''research'' to be any activity that aims at developing, or contributing to, generalizable knowledge. Granted, apart from Dr. He's first use of CRISPR-Cas9 genome editing in human embryos, no germline clinical research has been undertaken so far. Drawing the contours of research is thus hypothetical and requires a degree of speculation. It is difficult, at this stage, to imagine germline genome engineering being tested on adult human beings.

Review Board [IRB]) or the national level (national ethics committee). Also, in some countries, specialized human embryo research oversight (EMRO) committees monitor ongoing research. Often, to do so, these bodies follow the 2016 guidelines of the International Society for Stem Cell Research.[25]

Germline basic research or certain aspects of it may be prohibited.[26] In Germany, Italy, and Switzerland, germline basic research is prohibited because research with embryos is prohibited *tout court*. In Australia, Canada, China, France, Japan, South Korea, Mexico, the Netherlands, and Spain, embryo research is not prohibited, but scientists can only use embryos that were created for reproductive purposes and that will not be used (so-called *in vitro* fertilization [IVF] supernumerary embryos). In a handful of countries (Belgium, Israel, Singapore, Sweden, the United Kingdom, and several states of the United States), scientists can create embryos for research purposes. However, a standard rule is that such embryos can only be studied during the first 14 days of their development *in vitro*. The regulation of research with gametes is much less detailed, partly because gametes do not raise the moral or ethical concerns that embryos do. For instance, *in vitro* gametogenesis is mostly unregulated, being neither prohibited nor expressly legalized. Manipulation of gametes is mostly regulated at the level of clinical applications.

Overall, the regulation of basic research is complex and unsettled. Three reasons are particularly challenging in this area. First, the law struggles with capturing the complexities of embryos as emerging biological entities. Legal definitions tend to be crafted digitally (i.e., an entity is or is not an embryo) rather than analogically to reflect the fact that these entities undergo various stages of development (from fertilization to the formation of the primitive streak). As a result, different legal systems draw the line at which point an embryo exists differently. In some cases, this line is drawn very early. This is the case in Germany, where an embryo is a ''human egg cell, fertilized and capable of developing, from the time of fusion of the nuclei, as well as any totipotent cell removed from an embryo that is capable of dividing and developing into an individual under appropriate conditions'' (Embryo Protection Act, Section 8.1); in Switzerland, where an embryo exists after pronuclear fusion has taken place (Federal Act on Medically Assisted Reproduction, Article 2); and in the United Kingdom, where legal references to an embryo ''include an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo'' (Human Fertilisation and Embryology Act 1990, Section 1). Other legal systems (e.g., Israel, Italy, and China) avoid the problem altogether by regulating embryo research without defining what embryos are.[27]

Second, the regulation of research using gametes is relatively underdeveloped. Very few rules apply specifically to the use of sperm and oocyte in basic research. Article 119 of the Swiss Federal Constitution is an exception, where it prohibits any ''interference with the genetic material of human reproductive cells,'' including gametes. In Singapore, regulations provide that research with oocytes must be treated in the same way as research with embryos. Protocols of research on oocytes are subject to the full ethical review and the preapproval of an IRB. None of the countries surveyed prohibits the *in vitro* modification of gametes for research purposes. This includes ''gametogenesis,'' the *in vitro* derivation of gametes from induced pluripotent stem cells using gene-editing techniques.

Third, most regulatory frameworks surveyed neither prohibit nor permit germline genome modifications expressly. They regulate research with embryos, but they are silent as to whether researchers can modify gametes and embryos. If one follows the general legal principle by which everything that is not forbidden is allowed, it can be concluded that since the regulators excluded *some* goals of germline engineering—particularly clinical research and applications—but did not exlude others, embryo and gamete modification for the purpose of conducting basic research is lawful.

In short, regulations of basic research with embryos is an area filled with prohibitions and restrictions, but also with uncertainties and gaps that make it unclear how they must be interpreted. Few countries permit the creation of research embryos, which are an essential resource to maximize the possibilities of basic research on the germline. In our judgment, this is the baseline for full respect of ''the freedom indispensable for scientific research'' (ICESCR, Article 15). In more restrictive regulatory frameworks, any limitation to research with gametes and embryos will have to stand the test of Article 4 of the ICESCR, which we will discuss later in the paper.

Clinical research involving humans

In contrast to basic research, clinical research on germline editing involves a living human being as a research subject (not merely as the source of tissue used in research). This research is currently prohibited in all jurisdictions we have studied. In some, the ban is absolute. In others, exceptions to the prohibition are contemplated expressly or are revealed by statutory interpretation.

The jurisdictions with blanket or absolute prohibitions are Canada, Japan, Singapore, South Korea, Switzerland, the United States, and the EU. In Europe, Article 90 of

the EU Regulation 536/2014 on Clinical Trials of Medicinal Products for Human Use provides that ''No gene therapy trials may be carried out which result in modifications to the subject's germline genetic identity.'' While the Regulation goes into effect in 2019, the prohibition to carry out clinical trials involving germline modification has been the policy of the EU since 2001 (Directive 2001/20/EC). It should be noted, however, that it is unclear what kind of gene therapy changes a subject's ''germline genetic identity.''[28] Similarly, the Swiss Therapeutic Product Act permits only clinical research on somatic cells. Absolute prohibitions can result also from indirect regulation.

In the United States, the Federal budget prohibits the Food and Drug Administration from even acknowledging applications to begin clinical research ''in which a human embryo is intentionally created or modified to include a heritable genetic modification.'' Although only temporary, this budget provision has been renewed year after year. In Singapore, the Bioethics Advisory Committee issued binding recommendations that prohibit IRBs from approving clinical trials involving genome modifications. In Canada, Section 5.1.f of the 2004 Assisted Human Reproduction Act prohibits clinical research involving genome modification that is ''capable of being transmitted to descendants.''

In other countries, clinical research bans and moratoria are not absolute. The most interesting case is Israel, where during the debates that amended the 1999 Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law, Parliament clarified that the Minister of Health could authorize, through regulations, clinical research on and clinical use of genetically modified germline cells, as long as it does not violate human dignity and may have therapeutic benefit.

Elsewhere, statutory language may present gaps and ambiguities that open the door to some clinical research. In South Korea, as the Bioethics and Safety Act prohibits clinical research with a therapeutic goal, one could argue that clinical research without a therapeutic goal (e.g., enhancement or aesthetic reasons) is allowed. In Japan, although clinical research using germline genome editing is largely prohibited, editing that does not involve ''the administration of a gene or cells'' is not prohibited. This could be done if editing is performed using a messenger RNA rather than by inserting a plasmid harboring a gene of template DNA.

In Australia, Section 15 the Prohibition of Human Cloning for Reproduction Act 2002 prohibits genome alterations if, ''in altering the genome, the person intended the alteration to be heritable by descendants of the human whose cells was altered.'' This prohibition extends to clinical research when the alteration is tested for safety and efficacy on a research subject with the intention to modify the genome in a way that *could* be inherited is present. However, these provisions can be read as permitting clinical research where modified gametes are not fertilized or where the research protocol foresees implantation followed by termination of the pregnancy.

In China, clinical trials involving germline modifications seem to fall in a legislative vacuum, and therefore there is some uncertainty as to what is prohibited. Research with human subjects is subject to the Guiding Principles for Human Gene Therapy Research and Quality Control of Preparation, which regulate somatic but not germline genetic therapy. It is thus unclear whether the Guiding Principles allow gene therapy on human embryos and whether germline genome modifications can be clinically tested on humans. In the wake of He Jiankui's controversial revelations, the Chinese regulatory and funding agencies and various professional bodies issued statements condemning Dr. He's actions and asserting the principles that clinical research is prohibited in China. For instance, the investigating task force set up by the Health Commission of China in Guangdong Province released a preliminary report on January 21, 2019, stated that He had violated government bans. However, a regulatory gap exists.

The laws of Belgium, Italy, and Mexico permit germline interventions that are therapeutic, that is, clinical applications that have a positive therapeutic effect for the embryo. Thus, one could reasonably argue that clinical research involving testing clinical applications that are beneficial to the embryo is permitted too. The French Civil Code includes an exception to the ban on clinical research, allowing for research activities aimed at preventing or treating genetic diseases but not at modifying the genetic traits of a person.

In the United Kingdom, the key statute does not address clinical research involving germline modifications. However, it is possible that British regulators will adopt the same approach used for mitochondrial donation using a pronuclear transfer (due to the matrilineal nature of the inheritance of mitochondrial DNA, modifications made on female offspring are heritable). If this is the case, proposals of clinical research involving germline modification will be permitted and possibly authorized under the strict oversight of the agency, provided that researchers apply for permission for each patient and monitor patients' health scrupulously in follow-up sessions.[29,30]

We should note that many jurisdictions have adopted blank or absolute bans of clinical research involving human genome germline modifications. These bans preclude considering translational pathways to germline editing. This has important implications for the obligations to respect, protect, and fulfil the human right to

science. In fact, as we will discuss later in the article, absolute bans are incompatible with everyone's right to ''benefit from scientific and technological progress,'' even when taking into account that the right is not absolute but may be limited under certain conditions.[31]

Clinical applications

Clinical paths involving CRIPSR techniques include generating gametes *in vitro* with subsequent fertilization, *in vitro* or *ex vivo* modification of embryos with subsequent in uterus transfer, and *in vivo* modification of embryos. These clinical paths have a reproductive goal: the successful completion of a pregnancy and the birth of a newborn whose genome embeds the modifications imparted to parental germline cells. Since, with exception of Dr. He's actions, no clinical application has been developed to date, the list of applications is rather speculative.

Clinical applications are regulated primarily as assisted reproduction techniques. This makes a comparative analysis of regulatory frameworks challenging because assisted reproduction laws vary significantly from jurisdiction to jurisdiction, with countries taking very different positions on critical issues such as surrogacy, gamete donation, and mitochondrial replacement.[32–34] Nonetheless, some indications emerge from our comparative analysis. No legal system expressly permits germline genome engineering for reproductive purposes. Importantly, germline engineering therapies in a clinical setting are prohibited in Australia, Canada, France, Germany, Israel, Japan, the Netherlands, South Korea, Spain, Sweden, Switzerland, and the United Kingdom.

Other countries have achieved the same result through regulatory mechanisms. For instance, in Singapore, clinical research and applications are not allowed as a result of a moratorium issued by the Bioethics Advisory Committee in 2005. In China, a technical specification of standards for assisted reproduction, issued in 2003 by the Ministry of Health, prohibits ''the use of gene manipulation of human gametes, zygotes or embryos for reproductive purposes.'' In the United States, while no federal law expressly prohibits clinics from providing germline editing services, the federal legislature has prohibited the federal agency from accepting applications to begin clinical research. This also means that no gene editing applications can be offered to patients in a clinical setting, since the regulators' pre-market approval is a prerequisite to offering clinical applications.

In Belgium, Italy, and Mexico, the rules are vague and fail to provide clear guidance as to what is allowed. A liberal reading of these rules leads to the conclusion that in some cases, germline genome engineering might be used in a clinical context. In these countries, the law makes it clear that embryos must not be ''harmed'' during research. Along these lines, interventions that improve the well-being of the embryo can be considered lawful: clinical applications that benefit an embryo are permitted. However, this interpretation of the Belgian, Italian, and Mexican statutes has not been tested in courts. The liberal interpretation is intriguing, but it might create false hopes.

A major problem we have identified is the use of the adjective ''heritable'' to identify the applications that are prohibited. The term ''heritable'' is never defined with precision, leaving the door open to interpretation as to *when* germline modifications become heritable. Is it when any germline modification takes place, even *in vitro* or *ex vivo*? When gametes and/or embryos are modified *in vitro* or *ex vivo* with the intent of making it heritable by transferring the modified cells in the uterus? When modified germline cells are transferred to the uterus? When the transfer in uterus leads to a successful pregnancy? When the newborn reaches reproductive age and could or does transfer the genes to the next generation? The vagueness concerning the term ''heritable'' is problematic, given the consequential nature of its use. All in all, it provides a weak basis to demarcate the line between lawful and unlawful activities.

Tensions Between the Regulation of Human Germline Engineering and the Human Right to Science

To discharge the duty to respect, protect, promote, and fulfill the right to science, countries must, among other things, respect scientists' ''freedom indispensable for scientific research'' and realize the right of everyone to benefit from scientific and technological progress. Scientific *freedom* and the right to benefit from *scientific* and technological progress are not absolute rights and can be restricted. However, states that intend to do so must conform with the conditions set by Article 4 of the ICESCR, according to which restrictions must be determined ''by law,'' be ''compatible with the nature of these rights,'' and ''solely [intended] to promote the general welfare in a democratic society.'' Many of the regulatory frameworks we have surveyed do not meet the requirements conditions set by international human rights law. In this section, we will assess the consistency of existing regulations with two of those conditions: legality and proportionality.

Restrictions not conforming with the condition of legality

The condition of legality is codified in Article 4 of the ICESCR (limitations to scientific freedom must be ''determined by law'') and is recognized by and can be found in the legal system of several, if not all, ''civilized

nations.'' In broad terms, it means that any limitations to the rights recognized in the Covenant ''should have a basis specifically in domestic law consistent with the Covenant; the law must be adequately accessible; the relevant domestic law must be formulated with sufficient precision,'' and the law must not be ''arbitrary, unreasonable, discriminatory or incompatible with the principle of interdependence of all human rights.''[35]

For the most part, restrictions considered in our study fail the test because they are embedded in regulatory frameworks that are unnecessarily vague and obsolete, not allowing a reasonable person to regulate their conduct. Examples of unreasonably vague regulatory frameworks are those that regulate research with gametes and embryos but neither expressly prohibit nor permit gametogenesis and other forms of germline genome modifications. Other examples are the regulatory frameworks of Belgium, France, Italy, and Mexico, which open the door to some germline engineering clinical applications but neither prohibit nor permit clinical research to study the efficacy and safety of those clinical applications.

Vagueness is particularly problematic in countries that criminalize certain activities connected with using human gametes and embryos and/or modifying the human genome (i.e., Australia, Canada, China, France, Germany, Israel, Italy, Mexico, the Netherlands, South Korea, Spain, Sweden, Switzerland, and the United Kingdom). Criminal prohibitions often lack clarity and precision. Granted, one could argue that what is not prohibited is permitted, and thus, unless research or clinical activity is expressly prohibited, it is lawful. Loopholes abound. Nonetheless, given the risk of facing a penal sanction, which also has reputational costs, scientists are unlikely to take advantage of loopholes and move ahead with innovative research.

Obsolete regulatory frameworks cannot be reconciled with the principle of legality either. Many laws and regulations were drafted, debated, and enacted well before the advent of CRISPR. Only Japan has adopted a regulatory framework in recent times (in 2014). A handful of other countries (e.g., France, the Netherlands, South Korea, Sweden, and the United Kingdom) have undertaken formal policy discussions on germline engineering in the past five years. However, all the other countries surveyed have laws that were drafted, debated, and enacted in the 1980s, 1990s, and 2000s—well before 2012 when CRISPR-Cas9 first appeared in the scientific literature. To wit, Mexico adopted its key statute regulating basic research on germline engineering in 1982, revised in 2002; Germany in 1991; China adopted various instruments between 1993 and 2003; Switzerland in 1998 and 2003; Australia and the Netherlands in 2002; Canada, France, Italy, and South Korea in 2004; and Spain in 2007. Definitions and substantive provisions are rarely updated, and new advancements are not expressly regulated, as in the case of *in vitro* gametogenesis, which has the potential to revolutionize human reproduction. For the most part, regulatory frameworks are made of ''inherited'' rules.[36] As often happens with disruptive technological breakthroughs, lawmakers are struggling to adjust the regulatory frameworks with scientific and technological developments.

To be sure, scientific freedom is not an absolute right, and restrictions on scientific freedom to protect research participants are acceptable. This is the case when the research participants are human beings. Germline engineering regulations require that gamete and embryo donors properly consent to participation, and their interests must be protected throughout the research process (International Covenant on Civil and Political Rights, Article 7). Also, some countries have legitimately reinforced these protections by adding a second layer of oversight specifically tailored to embryo research. However, when provisions protect solely gametes and embryos rather than human beings, they fall short of human rights standards.

In our judgment, vagueness and obsolescence make many regulatory frameworks fail to meet the requirements set by Article 4 of the ICESCR. We believe that in regulating heritable gene editing, legislative measures must guarantee, as a default, scientists' freedom to use CRISPR, and any other gene-editing tools that might be invented in the future, to create and modify human gametes and embryos, and identify reasonable opportunities for translational pathways of therapies to cure heritable genetic disorders. Limitations must be spelled out in statutory and regulatory instruments that are sufficiently clear to allow scientists to regulate their conduct based on those provisions. Obsolescence raises issues of whether restrictions are truly aimed to protect the ''general welfare in a democratic society,'' considering they were envisioned, debated, and democratically adopted before the CRISPR revolution, that is, before we possessed the actual technological capacity to engage in germline engineering. At a minimum, the restrictions on basic research on germline cells must be revisited through engaging democratic debates of some form (legislative debates, public discussions, expert consultations, referenda) considering the state of evolving technology.

Restrictions not conforming with the condition of proportionality

Under Article 4 of the ICESCR, only restrictions that are ''solely [intended] to promote the general welfare in a democratic society'' are acceptable. When promoting

the general welfare of society, limitations must be proportional or adequate to this goal. They must be the result of a careful balancing of interests and be ''the least intrusive instruments amongst those, which might achieve the desired result.'' Total bans and other forms of absolute prohibitions violate this condition. Two prohibitions are particularly troubling: the prohibition to create research embryos and the prohibition to conduct clinical research.

The prohibition against creating research embryos deprives scientists of an essential tool. Research on supernumerary IVF embryos is only a second best because of the limited number of embryos available and because a considerable percentage of those have not been implanted, since they are either not viable or affected by various disorders. Modifying the genome of embryos is better than modifying the genome of gametes, as the chances of off-target mutations and mosaicism are reduced.

Considering that research embryos are essential to advancing our basic understanding of heritable gene editing and that this form of gene editing provides an ideal method to correct inherited disorders, it is difficult to claim that total bans of the creation of research embryos promote general welfare. Also, these bans fail ''to respect the freedom indispensable for scientific research and creative activity'' (ICESCR, Article 15). Using research embryos is indispensable to understanding certain basic mechanisms of germline modification. They are ''indispensable'' to study gene editing ''at earlier stages and with fresh oocytes and embryos.''[37] Scientific freedom is fully respected only when scientists can create and study research embryos.

In Canada, Japan, Singapore, South Korea, Switzerland, the United States, and the EU, there are blank prohibitions to conduct clinical research involving human genome germline modifications. In our judgment, they cannot be reconciled with everyone's right to have access to ''the benefits of scientific progress and its applications science'' (ICESCR, Articles 2.2 and 15.1.b). This provision speaks to the right to access scientific knowledge, the material results of scientific research, and the means to access knowledge and results. In the context of biomedical research, the right to science demands that basic knowledge is translated into applications to let everyone enjoy the benefits of scientific progress.

The prohibition to test new cures, or methods to prevent deadly or severely impairing diseases that are otherwise incurable, can hardly be said to ''promote the general welfare in a democratic society.'' Make no mistake: we are not advocating a liberalization of clinical trials. Instead, in line with the statements issued by the NASEM and the Nuffield Council on Bioethics, we contend that legal systems must contemplate translational pathways to germline editing. While it would be premature to do germline genome editing with the intent of bringing a genetically modified child to birth, as the rogue attempt by He Jiankui demonstrated, total prohibitions inhibit a conversation about what clinical research will look like, and whether it should be carried out to promote the ''general welfare in a democratic society.''[38] As Cwik persuasively argued, ''it's important to consider seriously what would be required for the conduct of ethically sound clinical trials of [gene editing]. Human germline gene editing raises a new set of ethical issues that are extremely difficult to resolve by current ethical guidelines and regulations.''[39]

We believe Israel offers the model of a more balanced approach to regulating clinical research. There, the law prohibits clinical research but leaves the door open to cases in which testing germline engineering may be warranted. The power to authorize clinical trials under exceptional circumstances is given to the Minister of Health, who can adopt a regulation greenlighting experimenting germline engineering on humans.

Conclusion

The CRISPR revolution has reinvigorated interest in germline genome engineering. The laws and regulations in place in the 18 jurisdictions we studied fail to ensure the governance framework necessary to regulate germline engineering in the CRISPR era. For the time being, most national regulatory frameworks entail obstacles to scientific and clinical advancements. Any actual and future regulatory approach must be based on the recognition of the international nature of modern germline genome engineering research, the need for shared governance rather than tech-locked prohibitions, and the fact that humans are not their germline.

We believe that the human right to science offers an ideal starting point for building international consensus on governing principles that promote responsible scientific and technological advancements.

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