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Human Genome Editing: Our Future Belongs to All of Us

And we should all have a say in how the technology is governed.

In late November 2018, the Chinese scientist He Jiankui ignited a media firestorm with the birth announcement of “healthy” twin girls, Lulu and Nana (pseudonyms), born following germline genome editing to provide resistance to HIV. This announcement was followed by swift and nearly unanimous condemnation. A common theme among the critics was He’s failure to respect international consensus.

As a strong and steady advocate of “broad societal consensus” as the threshold for ethically acceptable heritable human genome editing, I was intrigued by this response. What is this “consensus” whereof they speak?

A quick review of media reports and various commentaries chastising He for having violated international consensus suggests considerable equivocation about the scope and meaning of consensus. Some commentators referred to a perceived political consensus, others intuited a somewhat amorphous scientific consensus, and a few others complained of a failure to respect the call for broad societal consensus issued in December 2015 at the International Summit on Human Gene Editing.

Political consensus

Globally, the political consensus on heritable human genome editing—such as it is—inclines toward an outright ban, and if not a ban, at least a moratorium. Article 13 of the Council of Europe’s Convention on Human Rights and Biomedicine (the Oviedo Convention)—the first legally binding international text designed to prohibit the misuse of biological and medical advances—stipulates: “An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.” The Oviedo Convention, opened for signature in 1997, is legally

binding on the 29 countries that have signed and ratified it. In December 2015, on the occasion of the international gene-editing summit, the Council of Europe issued a press release reminding the world of the scope and import of Article 13.

A few months earlier, in October 2015, at a pre-conference in preparation for this summit, the UNESCO International Bioethics Committee (IBC) released the *Report of the IBC on Updating Its Reflections on the Human Genome and Human Rights*. This update called on states and governments to “agree 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 treatment.”

If we look beyond international statements to the international regulatory landscape, it appears that heritable human genome editing is mostly forbidden by law or research guidelines in those countries that have pertinent regulations. According to a 2014 survey of 39 countries, 25 countries have a legal ban in place, and four other countries have an explicit ban entrenched in guidelines. One country, the United States, has a de facto ban insofar as it is not possible to proceed with germline genome editing for reproductive purposes because of provisions in the Consolidated Appropriations Act. The act explicitly prevents US authorities from reviewing proposed clinical trials of heritable genome editing. The other nine of the 39 countries surveyed had ambiguous information.

Thus, if there is a political consensus of any kind, it is that heritable human genome editing should be prohibited, in which case there is little doubt that He violated the consensus.

Scientific consensus

Scientists disagree about the ethics and governance of human germline editing. Some scientists favor a moratorium; others want a pathway forward. This difference in perspective is not limited to genome editing, but also applies to technologies that aim to change the composition of mitochondrial DNA.

Until recently, there was agreement among members of the international scientific community that human embryos genetically manipulated in vitro should not be used to initiate a pregnancy. But then the scientific community in the United Kingdom broke ranks and spurred their government to make legislative changes to explicitly permit the transfer of some types of genetically manipulated embryos. In 2015, the UK Parliament adopted the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations. In December 2016, the UK's Human Fertilisation and Embryology Authority approved the use of mitochondrial donation to eliminate mitochondrial diseases transmitted through mitochondrial DNA.

Prior to this later action, news broke in September 2016 that a child conceived following nuclear genome transfer (also known as mitochondrial replacement and “three-person IVF”) had been born in Mexico in April 2016. The embryo was genetically modified in the United States at the New Hope Fertility Center in New York. The embryo transfer and birth

occurred in Mexico to avoid violating US federal legislation. At the same time, a child was said to have been born of this technology in China.

In 2017, there was another such birth in Ukraine at the Nadia Clinic in Kiev. This time the clinician-researcher used pronuclear transfer instead of maternal spindle transfer, and the goal was to treat infertility, not to avoid mitochondrial disease. Since then, there have been additional births in Ukraine and, in January 2019, a first pregnancy resulting from a Spanish-Greek collaboration was announced. As yet, there are no births following nuclear genome transfer in the United Kingdom. Today, it is not clear what the international scientific consensus on heritable modifications is (or might be). It is legal in the United Kingdom to perform nuclear genome transfer (and make heritable modifications) to treat mitochondrial disease. And in some jurisdictions this is a business opportunity for the treatment of infertility.

As concerns germline genome editing, the most prominent science policy documents are the 2017 US National Academy of Sciences and National Academy of Medicine (NASEM) report *Human Genome Editing: Science, Ethics, and Governance*, and the 2018 Nuffield Council on Bioethics report *Genome Editing and Human Reproduction: Social and Ethical Issues*. Both of these reports effectively conclude that heritable human genome editing “should be permitted” under certain circumstances. The guiding principles and the stipulated conditions enumerated in these reports vary considerably, however.

The NASEM report variously affirms that it would be ethically appropriate to proceed with germline genome editing “for serious conditions under stringent oversight,” “for compelling reasons under strict oversight,” and “for compelling circumstances subject to comprehensive oversight.” The report includes seven overarching principles—“promoting well-being, transparency, due care, responsible science, respect for persons, fairness, and transnational cooperation”—which are said to inform a 10-point “robust and effective regulatory framework.”

The Nuffield Council report endorses two cardinal principles for permissible heritable genome editing: the welfare of the future person, and social justice and solidarity. It concludes that uses of the technology could be ethically acceptable if they are “intended to secure, and are consistent with, the welfare of a person who may be born as a consequence,” and if they do “not produce or exacerbate social division, or marginalize or disadvantage groups in society.” The report calls for “a legitimate and effective regulatory procedure” subject to “broad and inclusive societal debate.”

Although there are important differences between these two reports, clearly He did not satisfy the conditions set out in either of them. Evidence of promoting well-being, or welfare of the person, was absent. Transparency and transnational cooperation clearly were lacking. Serious questions about due care and responsible science have arisen. As well, there are serious doubts about He's respect for persons, fairness, and social jus-

tice. And for those scientists who would have the consensus be a moratorium—He’s actions would most certainly be in violation of this.

Societal consensus

At the close of the 2015 International Summit on Human Gene Editing, the organizing committee issued a concluding statement that included an elegant ethics framework. The committee affirmed: “It would be irresponsible to proceed with any clinical use of germline editing unless and until: (i) the relevant safety and efficacy issues have been resolved, based on an appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application.”

In learning of He’s experimentation and the birth of the world’s first gene-edited humans, Feng Zhang, a researcher who helped develop the gene-editing CRISPR technology that He used, wrote: “In 2015, the international research community said it would be irresponsible to proceed with any germline editing without ‘broad societal consensus about the appropriateness of the proposed application.’” Similarly, David Baltimore, the chair of the international summit, affirmed: “It would be irresponsible to proceed with any clinical use of germline editing unless and until the safety issues have been dealt with and there is broad societal consensus.”

Despite these clear strong statements in support of “broad societal consensus,” the concluding statement issued by the organizing committee for the Second International Summit on Human Genome Editing, held in November 2018, makes no mention of this, but rather calls for a “rigorous, responsible translational pathway.” This call is consistent with the 2017 NASEM report, and might be consistent with the 2018 Nuffield Council report, but most certainly is not consistent with the 2015 summit statement. And yet, prominent scholars refer to the 2015 statement as the international consensus, even after the publication of the 2018 summit statement. For example, in an article in *Nature Biotechnology* that listed 10 ways in which He Jiankui violated ethics, Sheldon Krinsky, who studies the links between public policy and technology, cited the 2015 summit statement when asserting, “A first problem is that He’s work is a violation of an international consensus on if, whether, or when the editing of human embryos should be permitted.” This writing suggests that there is consensus on the importance of broad societal consensus.

Others disagree. For example, R. Alta Charo, who was co-chair of the NASEM committee that issued the 2017 report on human genome editing and a member of the organizing committee for the 2018 international summit, writes: “Some critics [of the 2018 summit statement on human genome editing] weaponized the language of ‘broad social consensus’ used by the first summit’s organizers, calling for an indefinite moratorium until such consensus could be reached, without describing what that consensus might look like. Certainly, a global con-

sensus (by majority? calculated by polling? calculated by voting?) is simply impossible.”

The suggestion here is that broad societal consensus is an unattainable ideal. And yet, the many references to He having violated international consensus belie this claim. Moreover, this perspective ignores recent efforts to address the meaning and scope of broad societal consensus. From another perspective, it is plausible that the real objection to broad societal consensus is that it threatens self-governance by the scientific community insofar as it requires sharing decision-making authority with civil society.

Process matters most

A few weeks after the 2018 summit, the presidents of the two US national academies and the Chinese academy that organized the summit published an editorial in *Science* eschewing broad societal consensus. Instead, they called for broad *scientific* consensus. They acknowledged the importance of forging a broad agreement that would include “not only the scientific and clinical communities, but also society as a whole.” But the agreement they referred to was not agreement about whether to proceed with heritable modification, but rather agreement on how best to do so—that is, what criteria to put in place for proceeding with human germline genome editing.

It is important to educate and to engage the public in discussions about the ethics and governance of heritable human genome editing. It is also important, however, to move beyond education and engagement to empowerment. This starts with setting aside what the editor of *Nature* called “the assumption that future germline editing is a foregone conclusion.” Instead of trying to assuage the public with assurances that heritable germline genome editing will proceed only subject to “strict independent oversight, a compelling medical need, an absence of reasonable alternatives, a plan for long-term follow-up, and attention to societal effects,” we should be asking the world’s citizens to identify their interests and ideas about how heritable human genome editing technology might make their lives go better, or not.

As a staunch proponent of broad societal consensus, I have tried to explain that this is not about unanimity, but that it also doesn’t collapse into majority rule. I have also made the point that what matters (and perhaps matters most) with broad societal consensus is the journey or the process. As people strive for consensus, they work together differently (some would say more productively) than is the case when some inside an inner circle overtly wield power and others on the outside clamor to be heard.

My bottom line is that the human genome, metaphorically speaking, belongs to all of us. We should all have a say in whether to proceed with heritable genome editing.

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