CRISPR

'Broad societal consensus' on human germline editing

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CRISPR ('Clustered Regularly Interspaced Short Palindromic Repeats') is a new gene editing technique that can be used to change the genome of living cells by deleting, repairing or replacing genes.[1] This technology can be used to change somatic cells (i.e., body cells whose genomes are not transmitted to subsequent generations) or germ cells (i.e., sperm and eggs whose genomes are transmitted to subsequent generations). To date, no CRISPR-edited human cells have been transferred to humans. In the near future, the hope is to move to clinical trials using CRISPR-edited human somatic cells. In the distant future, there is the prospect of using CRISPR-edited human gametes or early human embryos for reproduction. The genetic modification of gametes or early embryos would result in germline editing, as the genetic changes would be passed on to offspring and subsequent generations.

At the time of writing, there is common knowledge of two basic science projects involving gene editing of early human embryos in a research setting. In April 2015, the journal *Protein & Cell* published work by a research group in China at Sun Yat-sen University in Guangzhou (led by Canquan Zhou and Junjiu Huang) that involved making genetic alterations to nonviable human embryos.[2] The research aimed to repair a genetic defect that causes beta thalassemia (a potentially fatal blood disorder). No genetically modified human embryos were transferred to initiate a pregnancy. More recently, in February 2016, the United Kingdom's Human Fertilisation and Embryology Authority (HFEA) approved a research license renewal application submitted by Kathy Niakan from the Francis Crick Institute. The license application was for human embryo research that would include knocking out the *OCT4* gene in healthy embryos to better understand embryonic development with the hope of eventually contributing to advances in pregnancy and fertility treatment.[3] The HFEA approval was subject to ethics approval "from an appropriately constituted research ethics committee".[4] At the time of approval, the HFEA underscored the fact that "as with all embryos used in research, it is illegal to transfer them to a woman for treatment."[5]

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The first of these two human embryo projects spurred considerable ethical debate and angst, as the research demonstrated both the potential to modify the human genome across generations, and the inherent risks in doing so. In the months preceding the publication of the research (and according to some 'in anticipation of the publication of the research'),[6] there were calls for a voluntary moratorium on modifying the human germline[7,8] to allow for careful deliberation on the risks and benefits of the technology and "the attendant ethical, social, and legal implications of genome modification".[9] In the ensuing debate, many argued that the research, though not intended for use in pregnancy, nevertheless crossed an ethical rubicon and would lead to the creation of 'designer babies' and the introduction of a new eugenics.

In response to this burgeoning debate, in December 2015, the U.S. National Academies of Science, the U.S. National Academy of Medicine, the Royal Society, and the Chinese Academy of Science hosted an International Summit on Human Gene Editing. At the close of the International Summit, the Organizing Committee of ten

scientists and two bioethicists (of which I was a member) issued a formal statement.[10] This statement – On Human Gene Editing: International Summit Statement – included four discrete conclusions.

In this article, I briefly outline each of the four conclusions. I then elaborate on the third conclusion which includes two clear thresholds for moving forward with human germline editing – namely, (i) evidence of safety and efficacy, and (ii) 'broad societal consensus'. Taken together, these two thresholds for acceptability create a potentially useful policy-making framework. Next, I move to a discussion of the fourth conclusion, which calls for an ongoing international forum – broadly inclusive of a diversity of nations, perspectives and expertise – to discuss the potential merits and harms of engineering humans. I suggest that such an ongoing forum is a *sine qua non* for achieving 'broad societal consensus', and then offer a model for decision-making by consensus. This model embraces work done by women activists in the 1980s and calls on scientists to support the consensus building process through honest brokering of policy options. In this way, this article begins the project of fleshing out whether and, if so, under what circumstances, human germline engineering might proceed.

International Summit Statement: four conclusions[11]

First, members of the Organizing Committee concluded that, in their view, there was no reason to curtail basic and preclinical research on human cells. Lab-based research could continue in accordance with "appropriate legal and ethical rules and oversight". In this way, the Committee endorsed laboratory research involving human somatic cells as well as human sperm, eggs and early embryos. This conclusion would have been reassuring to those involved in human embryo research, as they could interpret it to mean 'business as usual.' Conversely, those who object to any and all human embryo research would not have agreed with this conclusion. Further, among those who might otherwise cautiously support some human embryo research, there would be those who object to this conclusion on the grounds that it leaves the door open to possible misappropriation of genetically modified embryos to initiate a pregnancy. As well, depending upon the focus of the embryo research, disability activists would have had serious reservations about the ways in which specific research might reinforce flawed and harmful assumptions about what kinds of lives should be prevented.

Second, the Organizing Committee concluded that gene editing involving human somatic cells could proceed in both a research and a therapeutic context, always with careful attention on the part of both the researchers and the regulators to the risks and potential benefits of such research. This conclusion would have been welcome news to researchers working to develop therapeutic interventions for identifiable patients, who feared that disproportionate attention to the controversy surrounding germline editing would negatively affect their ability to proceed with clinical trials. This conclusion would also have satisfied patients and patient advocacy groups eager for the science to move forward with a view to improving human health. Some disability rights activists, however, would have been concerned with this conclusion, which could reasonably be perceived as uncritical endorsement of a technology that would further contribute to both geneticization (understanding humans primarily in terms of their DNA)[12] and ableism (discrimination that favours able-bodied individuals).[13] As well, there could have been concerns about the ways in which this conclusion would further undermine important distinctions between normal variation and disability.[14] Lastly, some would have been concerned about the possible use of gene-edited somatic cells for enhancement purposes.

Third, the Organizing Committee addressed the use of gene editing technology in human gametes and early human embryos destined for reproductive use. Gene editing in these cells would result in genetic alterations to offspring and subsequent generations. The Committee concluded that "[i]t would be irresponsible to proceed with any clinical use of germline editing unless and until: (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application." Those who hoped for as wide as possible a *marge de manoeuvre* would have been pleased with this conclusion, as they could reasonably interpret it as a recommendation to 'proceed with caution'. On this view, the first three conclusions follow in step-wise fashion one from the other: first, do the lab work in human somatic and germ cells; second, proceed to clinical trials involving the transfer of gene-edited human somatic cells; and third, by the time there is sufficient evidence of safety and efficacy with the transfer of genetically modified somatic cells, expect public awareness and acceptance of the potential therapeutic benefits of germline editing to have shifted sufficiently as to provide a 'broad societal consensus' on human germline editing for therapeutic purposes. On the other hand, those who hoped for either a ban or a moratorium on human germline editing would have been disappointed with the Committee's failure to take a stronger stance in support of what might reasonably be described as a 'broad societal consensus' against this use of gene editing. Evidence of this consensus could be found in a number of countries with legislation or guidelines prohibiting human germline editing,[15] and in quasi-governmental and professional organizations' statements condemning human germline editing.[16] Either of these two mechanisms – a ban or a moratorium – would have served to temper the enthusiasm of researchers like George Church who is reported to have described his lab as "the center of a new technological genesis—one in which man rebuilds creation to suit himself".[17]

Fourth and finally, the Organizing Committee called on the sponsors of the Summit to create an ongoing forum for discussion to encourage thoughtful conversation among individuals with a wide range of knowledge, expertise, experience, and values. Participants in this conversation were to include "not only biomedical scientists, policymakers, regulators, research funders, and industry representatives, but also health-care providers, patients and their families, people with disabilities, ethicists, lawyers, social scientists, faith leaders, public interest advocates, and members of the general public".[18] Some would have been particularly pleased with this conclusion for at least two reasons. First, it clearly aimed to create a legitimate space for additional voices to contribute to the global discussion. Second, it arguably recognized that the work that needed to be done to flesh out the two threshold elements would benefit from discussion among persons with diverse perspectives. Others would have been deeply concerned about who ultimately would have authority to make what decisions.

A moratorium by any other name[19]

The claimed benefit of human germline editing is its potential to cure serious inherited diseases not only in individuals, but in their children and in subsequent generations. A second potential benefit, from the perspective of some, is the prospect of enhancing human traits and capabilities. The widely acknowledged potential harms of human germline editing include: the risk of introducing genetic changes with long-term harmful consequences for individuals, families, and future generations; the risk of exacerbating social inequalities; the risk that the technology might be used coercively; the risk of a new eugenics; and the risk of human enhancement. While some are ever so keen to co-author the human evolutionary story and thus see human enhancement as a benefit, others question the audacity of those who embrace volitional evolution in seeking to improve the human condition.

In the months leading up to the Summit, and at the Summit, there were prominent calls for a ban or a moratorium on human germline editing, not only from individuals[20,21] but also from professional organizations.[22] Notable among these was the statement issued by the International Bioethics Committee (IBC) of UNESCO on October 2, 2015, the same day as the public information gathering meeting hosted by the International Summit Organizing Committee. On that day, UNESCO released the "Report of the IBC on Updating its Reflection on the Human Genome and Human Rights". Taking into account the Universal Declaration on the Human Genome and Human Rights (1997), the International Declaration on Human Genetic Data (2003), and the Universal Declaration on Bioethics and Human Rights (2005), the IBC 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 treatments."[23] And, during the Summit, on December 2, 2015, the Council of Europe Committee on Bioethics issued a "Statement on Genome Editing Technologies"[24] in which it recalled the prohibition in Article 13 of the Convention on Human Rights and Biomedicine (commonly known as "the Oviedo Convention") on any intervention that would affect the germline.[25]

In very general terms, those who advocate a complete ban on human germline editing typically advance one or more of the following arguments. There are arguments about the inability of children born of genetically altered embryos to consent to such alterations and the resulting threat to their right to an open future. There are arguments about the difficulties of long-term follow-up given that the results of germline editing could not be fully analyzed for generations to come. There are arguments about unbridled hubris and the attendant risk of catastrophic irreversible biological consequences. And, there are arguments about unacceptable social consequences and inevitable human rights abuses resulting from new forms of eugenics, unfair discrimination and prejudice, and stigmatization. The purpose of a ban is to entrench a permanent prohibition.

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Meanwhile, those who advocate a moratorium on human germline editing tend not to be troubled by arguments suggesting that consent on the part of children born of genetically altered embryos is required. Rather, they typically worry that the risk of failure may be too great to warrant proceeding, or that the anticipated benefits may be too few to warrant proceeding, or that preferable alternatives may be available (or in the offing). In this context, some focus narrowly on harmful biological or medical consequences, others worry about negative ethical and social consequences – including a new kind of bottom-up eugenics shaped by dominant economic, social, and political forces. The hope with a moratorium is for a stay to allow for careful reflection, discussion and debate (during which time, available facts and social mores inevitably will change). The worry with a moratorium, which essentially 'stops the clock', is that it might nonetheless function like a ban – as when a temporary prohibition becomes 'frozen in time'.

The Organizing Committee did not endorse a ban, and it eschewed the language of a moratorium in favour of language that clearly communicated 'not now'. Why 'not now'? Because of serious concerns about safety and efficacy, and because of lack of agreement on legitimate (ethically sound) goals for the use of this technology.[26]

Importantly, these two reasons for the 'not now' pronouncement/verdict (i.e., for the 'actual, but not so-called, moratorium') form the basis of a policy-making framework that allows for moving forward (i.e., 'not now' but 'maybe later'). The framework is simple insofar as it only includes two threshold elements: (i) demonstrated safety and efficacy (taking into consideration risks, potential benefits and alternatives); and (ii) broad societal consensus about acceptable uses of the technology. Paradoxically, the framework is also quite complicated because the substance (meaning and the scope) of each of these elements is unclear and very likely to be contested. As the science of human gene editing continues to develop, we may be able to negotiate a common understanding of appropriate standards for safety and efficacy for human germline editing, but this will not be without considerable (and perhaps vociferous) ethical and policy debate. For example, is 'reversibility' – whatever that might mean – a facet of safety? In any case, regardless of how easy or difficult it will be to agree on appropriate standards for safety and efficacy, in all likelihood it will be more difficult still to negotiate agreement on what is required for 'broad societal consensus'. What could this mean? And, more importantly, what should this mean?

'Broad societal consensus'

If 'broad societal consensus' is to be a meaningful criterion for moving forward

with science for the benefit of humankind, we need a clear and robust answer to the normative question, "What should this mean?" Notably, the Organizing Committee's fourth conclusion calls for an ongoing international forum for discussion. Helpfully, this sets the stage for continued learning about the science of human germline editing. It also sets the stage for continued deliberation about the meaning of 'broad societal consensus', and about how such consensus might best be achieved. Here it is worth recalling Ruha Benjamin's caution that we not create a forum for discussion that appears public, but really only serves to insulate science from criticism.[27]

In the summer of 1983, thousands of women camped out at Romulus, in Seneca County near the Seneca Army Depot to stop the deployment of Cruise and Pershing II nuclear missiles to Europe. These women – participants in the Seneca Women's Peace Encampment – stood together in opposition to violence and oppression. As part of this collective effort, the women developed a statement on decision-making by consensus which they included in their Resource Handbook. This statement is reprinted below in its entirety:

Consensus does not mean that everyone thinks that the decision made is necessarily the best one possible, or even that they are sure it will work. What it does mean is that in coming to that decision no one felt that her position on the matter was misunderstood or that it wasn't given a proper hearing. Hopefully, everyone will think it is the best decision; this often happens because, when it works, collective intelligence does come up with better solutions.

Responsibility: Participants are responsible for voicing their opinions, participating in the discussion, and actively implementing the agreement.
Self-discipline: Blocking consensus should only be done for principled objections. Object clearly, to the point, and without putdowns or speeches. Participate in finding an alternative solution.
Respect: Respect others and trust them to make responsible input.
Cooperation: Look for areas of agreement and common ground and build on them. Avoid competitive, right/wrong, win/lose thinking.
Struggle: Use clear means of disagreement – no putdowns. Use disagreements and arguments to learn, grow and change. Work hard to build unity in the group, but not at the expense of the individual who are its members.[28]

What is perhaps most noteworthy about this particular understanding of consensus is that it does not set the impossible standard of unanimity, nor does it reduce consensus to majority rule (which clearly would be ethically suspect in this context). Rather, it spells out clear responsibilities for all interested and willing participants in a democratic decision-making process. All are to assume responsibility for active, principled, respectful, and cooperative engagement. The consensus building process does not rely on hierarchy, does not privilege elites, and does not denigrate different types of knowledge. As different perspectives are discussed and debated, participants are enjoined to look for common ground on which to build consensus. When there is no common ground to be found, participants are to critically examine their contributions to discussion and debate, and, as appropriate, to recognize when they are an outlier. If they have had a fair hearing and others have not been swayed by their arguments, then they ought to recognize their own fallibility and step back instead of blocking emerging consensus for personal as contrasted with principled reasons. In this way, the consensus building process valorizes compromise as evidence of commitment to procedural fairness (which is necessary in a democracy), but eschews compromise that results in an erosion of personal moral integrity, leaving the individual with the experience of having 'been compromised'. This is the difference between compromise as a conciliatory process and outcome, and compromise as betrayal.

As an important feature of the consensus building exercise on human gene editing is broad-based participation by persons from around the world with a range of perspectives and interests, an important question arises as to the proper role of scientists in the deliberations. Roger Pielke Jr. outlines four discrete idealized roles for scientists vis-à-vis policy-making.[29] These are: (i) the Pure Scientist who is narrowly interested in knowledge production and who takes no responsibility for how policy-makers do or don't use the knowledge produced; (ii) the Science Arbiter who stands ready, willing, and able to answer questions policy-makers deem relevant (having no particular interest in the values or priorities informing the questions asked); (iii) the Issue Advocate who is committed to a particular policy option and who accordingly tries to inform the preferences of policy-makers; and (iv) the Honest Broker of Policy Alternatives who provides policy-makers with an informed overview of a wide range of policy options and who trusts the policy-maker to make worthy science-informed policy choices.

According to Pielke, the first two of these idealized roles – that of Pure Scientist and Science Arbiter – rest on an outdated linear model of science according to which science moves along a (mythical) continuum from basic research, to applied research, to development, to application, to societal benefit. On his view, if the linear model of science has any purchase, it is in allowing scientists to present themselves as Pure Scientists or Science Arbiters while effectively taking on the role of stealth Issue Advocates. These are scientists who, unlike their *doppelgangers*, have a clear interest in 'helping' policy-makers to 'see' which policy alternatives they 'prefer'. [30] Contrastingly, in an ideal world, scientists would pride themselves on being Honest Brokers of Policy Alternatives – persons committed to expanding the policy options and empowering decision-makers.

Conclusion

In closing, courtesy of the Organizing Committee of the International Summit on Human Gene Editing, we have a potentially useful policy-making framework for human germline gene editing that has two threshold elements – evidence of safety and efficacy, and 'broad societal consensus'. The framework is simple in terms of structure, and complex in terms of substance. As we set about exploring this complexity, I propose that we: (i) endorse an understanding of consensus building that, at minimum, is grounded in a commitment to the principles of responsibility, self-discipline, respect, cooperation and struggle; (ii) we enjoin scientists to embrace the role of honest brokers of policy alternatives, and (iii) work together towards a common understanding of the science and the ethics of human germline editing.