The case for banning heritable genome editing

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A group of prominent scientists and bioethicists recently called for an international moratorium on heritable genome editing,¹ a position supported by National Institutes of Health (NIH) leadership.² The reports of unethical research by He Jiankui³ in attempting to edit the genomes of two children has fueled a certain urgency in addressing the ethical, social, and legal issues. But a moratorium is not sufficient. The strikingly unfavorable balance of social benefits of heritable genome editing versus the social burdens and risks argues for an international ban on this research and clinical applications. The central argument I offer here is that the value of genome editing to the small number of families potentially benefiting 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. A clear, firm stand on this question at the early stages of this technology is essential to establishing international standards. (My focus here is nuclear genome editing, not mitochondrial transfer therapies, which present a somewhat different set of considerations.)

A moratorium means that while heritable genome editing is not appropriate at this time, this assessment can be revisited periodically. A moratorium permits research, short of uterine transfer, to develop the techniques and to assess efficacy and safety. Brokowski recently reviewed 61 international ethics statements on germline gene editing and found that 54% concluded only that heritable genome editing was impermissible currently and 30% did not clearly express a position.⁴ Further, Brokowski notes that “Since then [the 2015 International Summit on Human Gene Editing] ... there seems to have been a subtle, though important, shift in opinion about the permissibility of heritable genome editing—from ‘impermissible as long as risks have not been determined’ to ‘permissible if risks are accurately determined.’” The American College of Medical Genetics and Genomics (ACMG) Board of Directors opinion stated in 2017 that “...genome editing in the human embryo is premature and should be subject to vigorous ethical debate and further refinement of technological issues.”⁵ A moratorium is designed to be temporary and arguably lacks any meaningful force or

authority if backed by such cautious, contingent conclusions.

In contrast, a ban on heritable genome editing is justified by concluding that either the methods used to pursue an otherwise worthy goal are not acceptable or that the goal itself does not warrant pursuit even if concerns like feasibility and risk to the child can be adequately addressed. It is primarily this latter set of considerations that justify a ban, although, as noted below, the ethical issues and social controversy over research methods are also important considerations.

The balance of benefits to certain couples of genome editing contrasted with the risks to the children created and costs and risks to society more broadly is the appropriate assessment, not the evaluation of risk alone. The potential utility of therapeutic heritable genome editing is remarkably small.^{1,6} Parents at risk of bearing a child with a genetic condition typically will have the ability to produce unaffected embryos that can be used to create a pregnancy. For example, parents who are carriers of autosomal recessive conditions will, on average, produce embryos of which 75% will not be affected, and couples with one member with an autosomal dominant condition will produce embryos of which 50% will not be affected. Why edit the genome of an affected embryo when an unaffected embryo can be transferred? To the extent that the in vitro fertilization (IVF) process is not successful for some couples, the most appropriate approach is to improve IVF, testing, and implantation techniques rather than attempt to manipulate affected embryos through genome editing.¹

The contexts in which this strategy will not work are couples for whom both members are homozygous for a recessive condition or one member is homozygous for a dominant condition. These situations are exceedingly rare. But further, we must posit that the genetic condition is both serious enough to warrant a highly technical and potentially risky approach to embryo manipulation, yet the condition would still permit the affected parents to raise a child. Conditions associated with high morbidity and early mortality in the parents are not good candidates for innovative technologies to enable family building. For example, relatively common autosomal recessive conditions in the United States

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are cystic fibrosis (CF) and sickle cell disease (SCD). Both of these conditions currently carry a life expectancy of between about 30 and 40 years.^{7,8} Health care for CF and SCD has improved substantially in recent decades; nevertheless, the later years or decades of life for affected individuals involve burdensome and debilitating complications and treatments. These conditions can be compatible with parenthood, of course, but the question at hand is whether society should create embryonic gene editing for the rare circumstance when *both* parents are afflicted with such serious conditions. For conditions with more limited morbidity or mortality, the rationale for embryo manipulation is even less compelling.⁹

However, as somatic genome editing develops, couples might present in which one or both parents have been effectively treated. Somatic gene editing will not correct their germlines in the foreseeable future so they will still be at risk of bearing affected children. Here a preferred approach is clearly the somatic genome editing of the person once born. The point is that couples who must have heritable genome editing to have a biologically related child will be extremely small in number and will be affected themselves by conditions that will either challenge their ability to experience parenting or be of more moderate health impact, meaning that complex and controversial efforts at genome editing of embryos are not warranted.

A broader ethical and social policy question arises from the fact that the large majority of couples at risk for bearing children affected with a genetic condition have several options currently available.⁶ As noted, IVF followed by preimplantation genetic testing to select an unaffected embryo make possible a child biologically related to both parents. Sperm or egg donation will enable a child biologically related to one parent. Adoption will enable a family without a biological relationship between parents and the child. The drive to develop technologies like genome editing is entirely based on the desire of parents to have biologically related children. While this desire is understandable, the ethical and social policy question is how much shared capital should be invested to support this personal goal. Is it really necessary for society to make this investment or should we dedicate our support to the many other ways of building families?

This analysis also requires attention to the social burdens and risks. As Lander et al.,¹ the National Academies of Sciences, Engineering, and Medicine (NASEM),⁹ the ACMG,⁵ and others have recommended, any research or clinical service using genome editing in human embryos to create a child should only occur after extensive research to address safety and efficacy and broad public engagement. What are not sufficiently emphasized or appreciated in this formula are the enormous costs entailed. A substantial investment of public resources and expertise would be necessary to support such research. Hundreds to thousands of human embryos would need to be created, manipulated, and destroyed to demonstrate feasibility. Careful evaluation and long-term follow-up of the children created would be necessary. Oversight mechanisms by the Food and Drug Administration

(FDA) and other organizations nationally and internationally would be essential, and extensive engagement of the public over time will be important.⁹ The question is then whether such expensive, complex, and extended efforts are appropriate given the benefits that may accrue to very few couples who have other options available today.

Pursuing therapeutic heritable genome editing also substantially increases the risks of misuse. If the ability to safely and effectively edit the genome of human embryos is demonstrated, however determined, the temptation to offer this same technology for enhancements will be ever-present, even if not biologically feasible for complex traits. In contrast to uses for therapeutic purposes, claimed possibilities for enhancements could be extensive, particularly if unethical technology vendors and edge-cutting scientists are not encumbered by the need for valid outcome data. The rapid emergence of the multimillion-dollar industry offering “stem cell treatments” is a stark illustration of the risks. The promise of an enhanced child might be very attractive to many parents, and how might we conclude that the resulting child is or is not “better” than he or she would have been otherwise? Genome editing of human embryos does not lend itself to randomized, placebo-controlled trials. Assessing efficacy for genome enhancements would be quite challenging in the absence of a controlled experimental design but, more to the point here, it would be equally challenging to conclude that enhancements *don't* work following the emergence of an international genomic enhancement industry.

This analysis suggests that the social benefits of heritable genome editing are insufficient to warrant the necessary resources and opportunity costs involved in technology development. There are other options available for families. Further, honoring the desire of a very few couples for genetically related children, in this context, will create substantial risks of the misuse of this technology—a door that will be difficult to close once opened. These concerns are in addition to the quite profound challenges of demonstrating sufficient safety to warrant first-in-human trials.

It bears emphasis that this analysis does not hinge on a position regarding the moral standing of human embryos. However, successfully developing heritable genome editing would entail research involving the creation and destruction of numerous human embryos purely for research purposes. This practice has been controversial for decades in the United States, largely in the context of stem cell research, and cannot be conducted with federal funding.¹⁰ Whatever one's beliefs regarding the moral status of the embryo, we need to recognize that supporting such research will be divisive in our society and should merit approval only when such research has compelling social value.

The NASEM report articulates ten essential criteria and structures that should be in place before any clinical trials of genome editing.⁹ They then note that “[...]those opposed to germline editing may even conclude that, properly implemented, the above criteria are so strict that they would have the effect of preventing all clinical trials involving germline genome

editing.” Indeed, and as Director of the NIH Francis Collins stated, “...NIH will not fund any use of gene editing technologies in human embryos.” We should welcome the resolve from these positions and take a firm, clear stand—an international ban on heritable genome editing, including research leading directly to clinical applications. Our fascination with the technology is simply not justified by its utility and risks. Being pro-science should not mean a defensive advocacy of all science. A ban could entail a number of different legal and regulatory elements but should begin with a commitment by genetics and reproductive professionals to a professional standard that such manipulations should not be pursued. As professionals and as a society, there are many, many better ways to invest in the welfare of children and families.

DISCLOSURE

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