Taylor & Francis
Taylor & Francis Group

The American Journal of Bioethics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/uajb20

Preparing for the Next Generation of Ethical Challenges Concerning Heritable Human Genome Editing

Robert Klitzman

To cite this article: Robert Klitzman (2021) Preparing for the Next Generation of Ethical Challenges Concerning Heritable Human Genome Editing, The American Journal of Bioethics, 21:6, 1-4, DOI: 10.1080/15265161.2021.1913894

To link to this article: https://doi.org/10.1080/15265161.2021.1913894

THE AMERICAN JOURNAL OF BIOETHICS
2021, VOL. 21, NO. 6, 1–4
https://doi.org/10.1080/15265161.2021.1913894

Taylor & Francis
Taylor & Francis Group

GUEST EDITORIAL

Preparing for the Next Generation of Ethical Challenges Concerning Heritable Human Genome Editing

Robert Klitzman

On September 5, 2020, the International Commission on the Clinical Use of Human Germline Genome Editing, established by the U.S. National Academy of Medicine (NAM), the National Academy of Science, and the British Royal Society, with members from 10 countries, issued its Report, recommending caution in future uses of heritable human genome editing (HHGE) (National Academy of Medicine, the National Academies of Sciences and the Royal Society 2020). The report carefully considered a range of key issues, and marks a significant and impressive achievement, but also raises and highlights several additional crucial ethical challenges that various stakeholders will likely confront and that also need attention.

The Commission was established in November 2019, following Dr. He Jiankui's announcement that he had transferred edited human embryos into a uterus, producing twin girls. In response, the World Health Organization (WHO) similarly created an Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, which has recently also released additional documents about its deliberations (WHO 2020).

BACKGROUND

HHGE lets researchers alter the genes of embryos and thus future individuals and their descendants, but poses ethical concerns related to potential unknown effects, needs for subsequent longitudinal follow-up of edited individuals and their offspring (Niemiec and Howard 2020; Jonlin 2020), possible therapeutic misconception, potential uses for human enhancement or eugenics (e.g., wealthy individuals choosing socially-desirable traits) (Brokowski 2018; Cwik 2020b; Greely 2019; Niemiec and Howard 2020), and needs for broad societal consensus and empowerment (Baylis 2019). Questions emerge regarding how exactly to differentiate between medical *vs.* nonmedical, and somatic *vs.* germline uses, and different types of germline use (Cwik 2020a) and whether this research represents the best allocation of limited resources (Niemiec and Howard 2020).

Following He's announcement, many scientists called for a moratorium on all HHGE (Lander et al. 2019) or bans on research toward HHGE (Botkin 2020), and for the establishment of the Commission, "tasked with addressing the scientific considerations that would be needed to inform broader societal decision-making." This task involved "considering technical, scientific, medical, and regulatory requirements, as well as … societal and ethical issues." While scholars had discussed several of these issues, many hoped that the Commission could resolve or address many of these dilemmas.

THE COMMISSION'S RECOMMENDATIONS

The Commission (National Academy of Medicine, the National Academies of Sciences and the Royal Society 2020) recommended that pregnancy "should not be pursued unless the precise genomic changes can be made without undesired changes," "extensive societal dialogue" occurs, and use "proceed[s] incrementally … Preclinical evidence of safety and efficacy should be based on the study of a significant cohort of edited human embryos," biopsies of blastocysts should show no unintended edits, and "long-term follow-up of resulting children and adults" should occur. "Initial uses of [HHGE], should a country decide to permit them, should be limited" to certain circumstances: for "serious monogenic diseases" that cause "severe morbidity or premature death," in which parents "have no option for having a genetically-related child without the disease" or "the expected proportion of unaffected embryos" would be <25%, and the parents have had one unsuccessful trial of Pre-implantation Genetic Diagnosis (PGD). An International Scientific Advisory Panel should assess scientific safety and efficacy

CONTACT Robert Klitzman rlk2@cumc.columbia.edu 1050 Riverside Drive Mail Unit #15 New York, NY 10032.

and an international mechanism should address any concerns about deviations from these standards.

These recommendations are important, and reflect careful, and thoughtful discussion, but also reveal and underscore critical remaining challenges. The Report describes, for example, three potential uses of HHGE, providing disease examples that would justify use of germline editing: if one parent is homozygous for an autosomal dominant condition (e.g., Huntington disease [HD], neurofibromatosis or Marfan syndrome), if both parents are homozygous for an autosomal recessive condition (e.g., beta thalassemia, sickle cell disease, or cystic fibrosis [CF]), or if both parents are heterozygous for the same or different serous dominant diseases (e.g., HD, early-onset Alzheimer's, or familial adenomatous polyposis).

Yet, these situations pose key questions that have not yet been addressed. If both parents are homozygous for an autosomal recessive condition, they would both have the disease. But if they did so, and had reached reproductive age, and were able to have children, the disease would, therefore, be relatively treatable and not extremely severe and lethal to the degree that HHGE would necessarily be justified, given the risks involved. With new treatments for CF and bone marrow transplants for blood disorders, for instance, such homozygous patients are in fact able to reach reproductive age. But such treatment effectiveness also reduces the potential needs for HHGE. The Report, however, does not mention treatability. Early Onset Alzheimer's would not affect future children for decades, by which time effective treatments may exist. Homozygous individuals for an autosomal dominant condition (e.g., HD, neurofibromatosis, or Marfan syndrome) rarely reach reproductive age.

These scenarios are also exceedingly rare. The Report estimates, for instance, that for HD in the U.S. and Europe combined, only three couples are currently both heterozygous carriers, meeting this criteria for HHGE; and that in the U.S., for CF, in only 1–2 reproductive-age couples are both members homozygous, thus fitting these criteria. Yet these low prevalences may even be significantly less, given nonrandom mating (i.e., individuals choosing *not* to mate with patients with certain severe diseases). The only known cases of HD homozygosity or both parents being heterozygous for HD are in poverty-stricken isolated regions of developing countries (e.g., rural Venezuela), among individuals who are often unaware of HD genetics, and have very poor access to basic health care. Education about genetics could thus potentially help prevent such situations. Estimations concerning the potential needs for HHGE should also, arguably, reflect how countries might realistically decide to allocate relatively limited resources; and should also focus on regions where use of these technologies might realistically occur at some point in upcoming years.

Additionally, the Commission's definition of serious monogenetic disease as causing "severe morbidity or premature death" is very broad and open to interpretation, and can include conditions such as cardiomyopathy, various arrhythmias and cancer susceptibilities—all serious and causing premature death, if average death is around 60. Instead, the commission could have used more stringent criteria of infantile or childhood, rather than premature death.

The specific disease examples the Commission uses to legitimate HHGE are so extremely rare that they are, realistically, unlikely to be pursued, but could nonetheless serve to justify, and open the door to, other uses in less serious scenarios. Especially given widespread global reproductive travel and lack of effective global governance, the Commission's sanctioning of HHGE in these cases can serve to create a Trojan Horse, loophole or slippery slope: HHGE, once allowed in these rare circumstances, might then spread to other, more controversial uses. Indeed, Dr. He hoped to eventually establish a profitable offshore clinic to provide future offspring with socially desirable traits. The technological possibility of future such enhancement is unclear, but might nonetheless lure many customers. Instead, the Report could perhaps have framed these potential situations differently, highlighting these additional limitations and considerations regarding these proposed scenarios.

Challenges emerge, too, regarding the best interests of the future child and the abilities of parents in the three situations above to raise the resultant children well. HD, for example, causes severe psychosis, dementia, and violent behavior that can seriously impede parenting abilities. The Commission does not address these concerns or the best interests or rights of the unborn child to have an open future.

The Report concluded that "clinical use of HHGE raises not only scientific and medical considerations, but also societal and ethical issues that were beyond the Commission's charge." Yet the Commission's task was "addressing the scientific considerations," and "[t]his task involves considering … societal and ethical issues … " (National Academy of Medicine, the National Academies of Sciences and the Royal Society 2020). The document mentions social justice issues briefly, as a topic for possible future societal discussion, regarding "implications to exacerbate social inequities;"

but does not seek to integrate these ethical or social concerns into its scientific considerations, or explore the implications. The Report mentions financial costs only very briefly, in passing, but also does not weigh these in to probe, for example, how much to balance the enormous costs of HHGE research against competing global health needs. These questions are indeed large and complex and will require significant ongoing, focused deliberations.

The WHO Committee differs from the Commission, examining issues of governance. One might, therefore, argue that the Commission can leave out of its considerations, and largely ignore ethical, legal, or social concerns. But the documents released by the WHO Committee thus far focus on articulating broad principles and processes—e.g., regarding needs for equity, fairness, social justice, inclusivity, transparency, citizen consensus, and appropriate ethics committees to evaluate the merits of any individual proposals (WHO 2020).

The challenges raised by the Commission's Report concern, however, not just issues of 'governance' *per se*, but *precisely how much* to weigh complex potential risks and benefits, costs and parents' and children's rights related to specific HHGE uses—quandaries regarding neither science alone nor processes of governance *per se* alone, but rather intricate balancing of competing ethical principles.

While the Report presents straightforward, binary, future scenarios in which preclinical efficacy and safety have been established, thus making these clinical uses permissible, policy makers, oversight committees, institutional review boards, physicians and others will at some point in the near future probably confront more complex and nuanced dilemmas, requiring delicate weighings of relative degrees of risks and benefits as well as ongoing uncertainties. Invasive medical procedures generally entail some risks. The odds are low that HHGE will be completely risk-free. Rather, preclinical data might suggest that HHGE is, say, 80% or 90% safe, occasionally causing some off-target effects, the long-term impacts of which may remain relatively unclear. Whether the procedure is sufficiently safe and effective in humans will remain unknown, unless it is in fact first performed, with long-term follow-up of the resulting children. When the first edited embryos are transferred to the uterus, many unknowns will likely persist regarding long-term safety and benefits, generating grayer, less black-and-white scenarios, and complex dilemmas of how much to consider these. In the not-too-distant future, individual governments, ethics committees, researchers, physicians, patients, and the public will probably have to address this next generation of specific HHGE use decisions. Clear guidance is therefore critically needed.

Perceived technological imperatives may fuel HHGE use—the notion that technology, if developed and available, should be used, resulting in "excessive and unnecessary application" of technology that becomes self-propagating (Hofmann 2002). The rarity of the Report's examples poses questions of how much HHGE-related expenditure is justified, and what is fueling the extraordinarily high levels of interest and investment in this area, given other current global health needs. The lure of using gene editing for other purposes, such as enhancement for socially-desirable traits, even if science does not fully support these, may in part be fostering this enormous attention.

Questions surface, too, regarding whether any limitations should exist on the rights of parents who meet the Commission's criteria to use HHGE. Arguably, prospective parents have certain rights to have children in these situations, but these rights need to be balanced against the potential harms to the children and to these offspring's descendants, social justice, and other societal concerns. Critics have argued that these broader ethical concerns outweigh these parents' rights (Botkin 2020). These prospective parents could also alternatively adopt a child or use donor gametes that would enable use of one parent's gametes, allowing at least one member of the couple to have some biological connection to the child. Parents may understandably prefer to avoid use of donor gametes, but this preference needs to be balanced against the risks to future children and broader societal concerns. The Report does not address exactly how much to weigh these parents' rights.

Ongoing increases in global reproductive travel make these concerns even more important. The U.S. and several other countries regulate the Assisted Reproductive Technology (ART) industry relatively little—36% of countries performing ARTs have no legislation regarding it (International Federation of Fertility Societies' Surveillance 2019). The American Society of Reproductive Medicine (ASRM) issues guidelines on several topics, but providers often fail to follow these, and have largely opposed any government regulations or lessened independence (Klitzman 2019). These regulatory differences drive global reproductive travel.

Patients and doctors interested in pursuing HHGE could therefore readily cross borders. In 2016, for example, a New York-based doctor used mitochondrial replacement therapy to alter the genes that would otherwise exist in embryos to create a child. Since the Food and Drug Administration bans this technology, the embryos were made in Massachusetts,

then transferred in Mexico, and the child was born in New York (Mullin 2017).

MOVING FORWARD

Policymakers will thus need to make complex and nuanced risk/benefit calculations regarding costs and extents of treatments, ages of onset, severity of symptoms, degrees of genetic penetrance, disease prevalence, future scientific benefits, research costs, appropriate allocations of limited resources, and questions of who should pay.

Future efforts should thus consider examining scientific and ethical challenges in closer conjunction, not separated off, and bring together the respective strengths of the Commission's and of the WHO Committee's approaches. The WHO Committee includes broader stakeholders, but does not yet appear to have drawn conclusions regarding such specific medical and scientific scenarios (WHO 2020). These two groups' respective memberships also differ in instructive ways that can mutually inform future deliberations. Among the Commission's 18 chairs and members, only two appear to work primarily in ethics or policy; the majority are scientists (National Academy of Medicine, the National Academies of Sciences and the Royal Society 2020). In contrast, the WHO Committee includes two chairs and 16 members, with both chairs and the majority of members working primarily in ethics, policy or law (WHO 2020). ASRM and other countries' relevant professional organizations should also stipulate that physicians and healthcare professionals should not be involved in any way in the care of patients using germline editing abroad.

The Commission's Report thus provides valuable insights and guidelines, but multiple stakeholders will likely soon confront additional, complex dilemmas involving interplays of both science and ethics that also need urgent attention.

DISCLOSURE STATEMENT

The author has no competing interests to declare.

FUNDING

This work was supported by the National Center for Research Resources [grant UL1 RR024156], The Greenwall Foundation, and the Guggenheim Foundation.

DATA AND MATERIALS AVAILABILITY

All data are available in the manuscript.

REFERENCES

Baylis, F. 2019. Human genome editing: Our future belongs to all of us. *Issues in Science and Technology* 35 (3): 42–44. https://www.geneticsandsociety.org/article/uman-genome-editing-our-future-belongs-all-us.

Botkin, J. R. 2020. The case for banning heritable genome editing. *Genetics in Medicine* 22 (3):487–9. doi:10.1038/s41436-019-0696-6.

Brokowski, C. 2018. Do CRISPR germline ethics statements cut it? *The CRISPR Journal* 1 (2):115–25. doi:10.1089/crispr.2017.0024.

Cwik, B. 2020a. Responsible translational pathways for germline gene editing? *Current Stem Cell Reports* 21:1–8. doi:10.1007/s40778-020-00179-x.

Cwik, B. 2020b. Revising, correcting, and transferring genes. *American Journal of Bioethics* 20 (8):7–18. doi:10.1080/15265161.2020.1783024.

Greely, H. T. 2019. CRISPR'd babies: Human germline genome editing in the 'He Jiankui affair'. *Journal of Law and the Biosciences* 6 (1):111–83. doi:10.1093/jlb/lsz010.

Hofmann, B. 2002. Is there a technological imperative in health care? *International Journal of Technology Assessment in Health Care* 18 (3):675–89. doi:10.1017/S0266462302000491.

International Federation of Fertility Societies' Surveillance. 2019. Global trends in reproductive policy and practice. *Global Reproductive Health* 4 (1):e29. doi:10.1097/GRH.0000000000000029.

Jonlin, E. C. 2020. Informed consent for human embryo genome editing. *Stem Cell Reports* 14 (4):530–7. doi:10.1016/j.stemcr.2020.03.010.

Klitzman, R. 2019. *Designing babies: How technology is changing the ways we create children.* New York, NY: Oxford University Press.

Lander, E. S., F. Baylis, F. Zhang, E. Charpentier, P. Berg, C. Bourgain, B. Friedrich, J. K. Joung, J. Li, D. Liu, et al. 2019. Adopt a moratorium on heritable genome editing. *Nature* 567 (7747):165–8. doi:10.1038/d41586-019-00726-5.

Mullin, E. 2017. FDA cracks down on pioneering doctor who created a three-parent baby. MIT Technology Review, September 10. Accessed March 31, 2021. [https://www.technologyreview.com/2017/08/07/68027/fda-cracks-down-onpioneering-doctor-who-created-three-parent-baby.

National Academy of Medicine, the National Academies of Sciences and the Royal Society. 2020. *Heritable human genome editing: International commission on the clinical use of human germline genome editing.* Washington, DC: The National Academies Press.

Niemiec, E., and H. C. Howard. 2020. Ethical issues related to research on genome editing in human embryos. *Computational and Structural Biotechnology Journal* 18: 887–96. doi:10.1016/j.csbj.2020.03.014.

WHO (World Health Organization). 2020. Human genome editing: a DRAFT framework for Governance. Accessed March 31, 2021. https://www.who.int/docs/default-source/ethics/governance-framework-for-human-genome-editing-2ndonlineconsult.pdf?ua=1.