

An Ethical Pathway for Gene Editing

Julian Savulescu

Uehiro Chair in Practical Ethics

Director, Oxford Uehiro Centre for Practical Ethics

University of Oxford

& Visiting Professor in Biomedical Ethics, Murdoch Children's Research Institute

Peter Singer, AC

Ira W. DeCamp Professor of Bioethics

University Center for Human Values

Princeton University

& Laureate Professor,

School of Historical and Philosophical Studies,

University of Melbourne

Word count 1158

Ethics is the study of what we ought to do; science is the study of how the world works. Ethics is essential to scientific research in defining the concepts we use (such as the concept of "medical need"), deciding which questions are worth addressing, and what we may do to sentient beings in research.

The central importance of ethics to science is exquisitely illustrated by the recent gene editing of two healthy embryos by the Chinese biophysicist He Jiankui, resulting in the birth of baby girls born this month, Lulu and Nana. A second pregnancy is underway with a different couple. To make the babies resistant to HIV, He edited out a gene (CCR5) that produces a protein which allows HIV to enter cells. One girl has both copies of the gene modified (and may be resistant to HIV), while the other has only one (making her still susceptible to HIV).¹

He Jiankui invited couples to take part in this experiment where the father was HIV positive and the mother HIV negative. He offered free IVF with sperm washing to avoid transmission of HIV. He also offered medical insurance, expenses, and treatment capped at 280,000 RMB/CNY, equivalent to around \$40,000. The package includes health insurance for the baby for an unspecified period. Medical expenses and compensation arising from any harm caused by the research were capped at 50,000 RMB/CNY (\$7,000 USD).² He says this was from his own pocket.³ Although the parents were offered the choice of having either gene edited or unedited embryos transferred, it is not clear whether they understood that editing was not necessary to protect their child from HIV, nor what pressure they felt under. There has been valid criticism of the process of obtaining informed consent.⁴ The information was complex and probably unintelligible to lay people.

The most basic ethical constraint on research involving humans is that it should not expose participants to unreasonable risk.⁵ Risks should be the minimum necessary to answer the scientific question, and the expected benefits should be proportionate to expected harms.⁶ While the Declaration of Helsinki states that

research involving incompetent participants must be “minimal risk and minimal burden”,⁷ this is most plausibly interpreted as minimal *overall* risk or burden, where expected benefits match or outweigh expected harms. After all, children are exposed to trials of new toxic chemotherapeutic agents with significant risks.

In deciding whether a risk is reasonable, it is important to evaluate not only the probability of achieving a benefit, but also the extent of the benefit in question. A greater expected benefit is worth greater risk than a smaller expected benefit.

Avoiding HIV is certainly a benefit, but the probability that Lulu and Nana would have contracted HIV is low. In contrast, the unknown effects of the editing could cost them a normal life.

Given our ignorance of the full ramifications of changing a gene, what could justify taking the risk of a gene editing trial in humans? The answer is, if the embryo had a catastrophic single gene disorder. Several genetic disorders, such as BRAT 1, JAM3 and PHGDH, are lethal in the neonatal period, so for embryos with them, gene editing is potentially life-saving. (Thanks to Zornitza Stark for examples)

There is a risk of off-target mutations, but the expected harm of such mutations is arguably no worse than the fate of the unedited embryos.

The geneticist George Church has defended He's research on the grounds that HIV is a public health problem for which there is no cure or vaccine.⁸

Church is right to the extent that there is no problem in principle with editing out the CCR5 gene in the future. What he fails to take into account, however, is that Lulu and Nana are being used, at great risk, and without proportionate benefit, when there are more ethical experimental designs that would meet the need for greater knowledge of the effects of editing genes.

At the conference at which He presented his experiment, George Daley, the Dean of Harvard Medical School, indicated that Huntington's disease or Tay-Sachs might be suitable targets for gene editing.⁹

It is not clear whether Daley is endorsing these as first-in-human trials. Huntington's Disease is very different to Tay-Sachs. Babies with Tay-Sachs die in the first few years of life; people with Huntington disease have around 40 good years. Hence Tay-Sachs is a better candidate for early trials, as babies with that condition have less to lose. This mirrors the rationale for experimenting with gene therapy on babies with a lethal form of OTC deficiency rather than on adults with a mild form, such as Jesse Gelsinger who lost his life in a badly designed gene therapy trial in 1999.¹⁰

He Jiankui's trial was unethical not because it involved gene editing, but because it failed to conform to the basic values and principles that govern all research involving human participants.

Further into the future, if gene editing can be done without off-target mutations, it could be used to address genetic dispositions to common diseases such as diabetes or cardiovascular disease. These involve tens or hundreds of genes. In principle, gene editing could be used to accurately modify many genes. Gene editing has been successfully employed to remove 62 porcine endogenous retroviruses from a kidney cell line.¹¹

It is notable that the first human gene edited babies were enhanced to have resistance to a disease, not to treat an existing disease. In future, perhaps gene editing will be used to engineer super-resistance to infectious threats.

At the Second International Summit on Human Genome Editing, where He revealed his research, the National Academies of Science, Engineering and Medicine called for a "translational pathway to human germ line gene editing." In our view, to be ethically justifiable, such a "translational pathway" should be: catastrophic single gene disorders (like Tay-Sachs), then severe single gene disorders (like Huntington's Disease) then reduction in the genetic contribution to common diseases (like diabetes and cardiovascular disease), then enhanced immunity and perhaps even delaying ageing.

Should the translational pathway extend to enhancing normal traits, such as intelligence? This has been the subject of almost twenty years of debate.^{12,13} One approach to enhancement has been to ban it. Many jurisdictions including most in Europe and Australia ban Pre-implantation Genetic Diagnosis (PGD) for non-disease traits. However, one US company recently announced the use of polygenic risk scores for low normal intelligence in PGD. They admitted the same techniques could be used to predict high normal intelligence and believe such a step is inevitable.¹⁴

Further into the future, gene editing could be used for enhancement of the genetic contribution to general intelligence. China is currently funding research that is trying to unravel the genetics of high intelligence.¹⁵ Perhaps the best we can hope for is harm reduction and a regulated market to make important enhancements, such as resistance to disease or the enhancement of intelligence (should it ever be possible), part of a basic health care plan so that the benefits of gene editing are distributed equally.

1. Marchione M. Chinese researcher claims first gene-edited babies. AP News. 2018;
2. He J. Informed consent. Version: Female 3.0. Available from: <http://www.sustc-genome.org.cn>. Accessed 26 November 2018.
3. Lucas L, Liu N. Chinese scientist defends controversial gene-editing experiment. Financial Times [Internet]. 2018 Nov 28; Available from: <https://www.ft.com/content/766c4824-f2f6-11e8-ae55-df4bf40f9d0d>. Accessed 10 December 2018.
4. Schaefer GO. Rogue science strikes again: The case of the first gene-edited babies. The Conversation. 2018;
5. Savulescu J, Hope T. Ethics of Research. In: The Routledge Companion to Ethics. 2010. p. 781–95.

6. World Medical Association . World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. JAMA [Internet]. 2013;310(20):2191–4. Available from: <http://www.cairn.info/revue-journal-international-de-bioethique-2004-1-page-124.htm>. Paragraphs 16 and 17.
7. World Medical Association . World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. JAMA [Internet]. 2013;310(20):2191–4. Available from: <http://www.cairn.info/revue-journal-international-de-bioethique-2004-1-page-124.htm>. Paragraph 28.
8. Cohen J. 'I feel an obligation to be balanced.' Noted biologist comes to defense of gene editing babies. Science [Internet]. 2018; Available from: <http://www.sciencemag.org/news/2018/11/i-feel-obligation-be-balanced-noted-biologist-comes-defense-gene-editing-babies>
9. Cyranoski D. CRISPR-baby scientist fails to satisfy critics. Nature. 2018;
10. Savulescu J. Harm, ethics committees and the gene therapy death. J Med Ethics. 2001;27(3):148–50.
11. Yang L, Güell M, Niu D, George H, Lesha E, Grishin D, et al. Genome-wide inactivation of porcine endogenous retrovirus or other sequences in the pig genome endogenous retroviruses (PERVs). Science [Internet]. 2015;350(6264):1101–4. Available from: <http://dx.doi.org/10.1038/34749>
12. Kass L. Beyond Therapy: Biotechnology and the Pursuit of Human Improvement [Internet]. The President's Council on Bioethics. 2003. Available from: <https://bioethicsarchive.georgetown.edu/pcbe/background/kasspaper.html>
13. Savulescu J, Bostrom N. Human Enhancement. Oxford: Oxford University Press; 2009.
14. Wilson C. Exclusive: A new test can predict IVF embryos' risk of having a low IQ. New Scientist [Internet]. 2018 Nov; Available from: <https://www.newscientist.com/article/mg24032041-900-exclusive-a-new-test-can-predict-ivf-embryos-risk-of-having-a-low-iq/>
15. Yong E. Chinese project probes the genetics of genius. Nature [Internet]. 2013;497:297–299. Available from: <https://www.nature.com/news/chinese-project-probes-the-genetics-of-genius-1.12985>