The Dubious Benefits of Germline Editing

Jennifer Mara Gumer*

Keywords: germline editing, CRISPR-Cas9, CRISPR, clinical, human embryos,

INTRODUCTION

This past summer, humankind took one step towards a Gattaca-like future in which human beings may be genetically engineered before birth. As trumpeted by the headlines, researchers at the University of Oregon became the first American scientists to genetically alter human embryos using CRISPR-Cas9 (CRISPR).[1] CRISPR is a naturally occurring bacterial immune response that can recognize and destroy the DNA of invading viruses.[2] In 2012, Berkeley scientist Jennifer Doudna and team demonstrated that CRISPR could be reprogrammed to target and alter ostensibly any gene of any organism on earth.[3] Although not the first gene-editing tool to be discovered, CRISPR is much more precise and cost-effective than its predecessors.[4] Consequently, Doudna's discovery unlocked a plethora of unprecedented gene-editing applications including, but not limited to, the treatment of human disease, the study of human development, the more reliable creation of plants and animals with certain desirable characteristics, and the ability to alter the genomes of human embryos.[5] It is this last application of CRISPR that researchers at the University of Oregon explored when they reportedly eliminated the gene responsible for hypertrophic cardiomyopathy, a leading cause of death among young athletes, from viable human embryos last summer.[6] Although the researchers assert that these embryos were not intended for implantation—a move that would violate current law[7] — the experiment may be a harbinger of things to come.

ANALYSIS

If made clinically available, this particular application of CRISPR may be used to alter human genomes in heritable ways, a practice known as germline modification. However, such alterations carry numerous, well-publicized risks.[8] For example, researchers have identified several technical issues associated with the technology such as off-target edits, mosaicism (i.e., the uneven uptake of edits in embryonic cells),[9] and, more recently, the possibility of causing cancer.[10] These risks, however, arguably constitute just the tip of the iceberg when it comes to the potential harms related to germline editing. Even if the technology can be made sufficiently effective from a technical standpoint, our relatively superficial understanding of the human genome renders attempts to modify the germline extremely risky.

For instance, most diseases and disabilities are caused by a complex interplay of numerous genes[11] - an understanding of which still eludes us. Without complete comprehension of these interactions, we are unable to predict what effect changing just a few genes will have on the expression of others.

* Jennifer Mara Gumer, MS, JD

We also lack a clear understanding of the multiple functions that individual genes play, such that the removal of a so-called "bad" gene could inadvertently impact beneficial pathways and processes.[12] Such outcomes are particularly problematic given the heritability of germline edits and their potential to affect countless unborn individuals.

Germline editing also presents risks to society as a whole. For instance, the technology could be used to create children that conform to problematic societal ideals born from a history colored by discrimination and prejudice[13]. Germline editing also has the potential to exacerbate problematic wealth and power disparities given the likely expense of the procedure. Finally, the technology may detrimentally impact familial relations and the psyches of children designed to meet parental preferences.[14]

While supporters of the technology claim that the medical benefits will likely outweigh these anticipated risks, surprisingly little has been done to parse out what these benefits may actually be. To address this lacuna, let's take a closer look at some of the technology's promised benefits against which its concomitant risks are to be weighed.

First, despite frequent overblown claims about the revolutionary medical potential of germline editing, it must be emphasized that the technology likely cannot prevent the vast majority of health conditions, which emanate from a myriad of genetic and environmental factors not yet understood.[15] There is, however, a relatively small subset of diseases caused by single genes (e.g., Huntington's and Tay Sachs), which are much better understood than polygenetic conditions and therefore constitute the best candidates for germline editing[1].[16]

In the overwhelming majority of cases, however, an embryo screening technique called Preimplantation Genetic Diagnosis (PGD) can be used to prevent inheritance of these conditions[17] —an essential fact downplayed or even omitted in the discussions surrounding germline editing. PGD allows prospective parents who undergo *in vitro* fertilization—a procedure that would also accompany germline editing—to sequence the genomes of their embryos to identify the presence of any single-gene conditions (or other genetic risks, e.g., BRCA genes). Given the rarity of single-gene diseases, most couples affected by such conditions can create some portion of healthy embryos that may be implanted to produce offspring. Consequently, PGD can be used in most instances to prevent inheritance of single-gene conditions without the help of germline editing.[18]

It is only in the *exceedingly unlikely* event that one reproductive partner carries two copies of a given disease gene while the other also possesses two copies—or one if the disease is dominant, i.e., only requires one copy of the gene to manifest—that the potential value of germline editing obtains is realized.[19] While such a couple could still raise healthy children by using third-party gametes (or, of course, via adoption), CRISPR could theoretically be used to edit the disease gene from the couple's embryos to afford them an unaffected child, genetically related to both parents. While no doubt a desirable outcome, the number of individuals who may be uniquely helped by germline editing is

[1] The application of germline editing to monogenetic conditions is also likely less ethically controversial than targeting genes such as BRCA 1 and 2 that signal a risk rather than a certainty that a given condition will develop. Edits to such genes arguably constitute something beyond treatment—namely a genetic advantage conveyed by eliminating even the predisposition to disease—in a way that makes a slide toward pure enhancement uses of the technology more plausible.

limited. The question thus remains: does this benefit outweigh the technology's many medical and social risks?

To answer the question affirmatively places an enormous amount of importance on having a biological child that is almost tantamount to asserting a right to do so. While the concept of procreative liberty does indeed bestow certain rights on prospective parents, such as the negative right to enjoin the state from preventing a woman from conceiving or carrying a pregnancy to term, no American court has found an affirmative right to have a biological child.[20] It is also essential to note that enabling more people to have biological children for reasons unrelated to sterility is arguably a social, rather than a medical, benefit. Consequently, it must be asked whether this social benefit outweighs the related social risks discussed above.

If the costs of germline modification may outweigh the benefits, then why do we continue to pursue the technology? Perhaps the answer is that we are pushing forward simply because we can. If that is indeed our approach to technological advancement, however, we may be headed for trouble.

CONCLUSION

Given the rapidity with which technology is evolving, we will likely find ourselves in a future that poorly reflects our shared values as a society and species if we pursue every technological enhancement possible. To ensure that our powerful scientific capabilities help build a fair and inclusive world, we must instead engage in honest discussions regarding the true risks and benefits of a given technology before it is pursued. In the case of germline editing, that means proponents need to be more forthcoming about the technology's limited medical benefits. Only then we will be able to responsibly decide whether and how to proceed with germline editing in a way that takes us closer to a future of our choosing.

---

[1] Heidi Ledford, "CRISPR Fixes Disease Gene in Viable Embryos," *Nature*, August 2, 2017, https://www.nature.com/news/crispr-fixes-disease-gene-in-viable-human-embryos-1.22382.

[2] Jennifer A. Doudna and Samuel H. Sternberg, *A Crack in Creation*, (Houghton Mifflin Harcourt, 2017), 34-59.

[3] Ibid.

[4] National Academies of Sciences, Engineering, and Medicine. 2017. *Human Genome Editing: Science, Ethics and Governance*. Washington, DC: The National Academies Press 1-8, accessed July 31, 2017 https://doi.org/10.17226/24623.

[5] Ibid.

[6] H. Ma et al., "Correction of a Pathogenic Gene Mutation in Human Embryos", *Nature* (2017), accessed June 8, 2018, doi:10.1038/nature23305.

[7] Consolidated Appropriations Act of 2016, Public Law 114-113 (adopted December 18, 2015).

[8] Patrick Skerret, "Experts debate: Are we playing with fire when we edit human genes?", *STAT*, November 15, 2017, https://www.statnews.com/2015/11/17/gene-editing-embryo-crispr/.

[9] H. Ma et al., "Correction of a Pathogenic Gene Mutation in Human Embryos", *Nature* (2017), accessed June 20, 2018, doi:10.1038/nature23305.

[10] Haapaneimi et al., "CRISPR-Cas9 Gene Editing Induces p53-mediated DNA Damage", *Nature Medicine* (2018), accessed June 20, 2018, https://doi.org/10.1028/s41591-018-0049-z; R. Ihry et al., "P53 Toxicity is a Hurdle to CRISPR/CAS9 Screening and Engineering in Human Pluripotent Stem Cells", *bioRxiv* (2017), accessed June 20, 2018, https://doi.org/10.1101/168443.

[11] "Frequently Asked Questions About Genetic Disorders", National Human Genome Research Institute, accessed July 31, 2017, https://www.genome.gov/19016930/faq-about-genetic-disorders/.

[12] See e.g., Moises Velasquez-Manoff, "The Upside of Bad Genes", *New York Times*, June 17, 2017; "Protective Effect of Sickle Cell Trait Against Malaria-Associated Mortality and Morbidity", CDC.gov, accessed June 20, 2018, https://www.cdc.gov/malaria/about/biology/sickle_cell.html; Sheri E. Gabriel et al., "Cystic Fibrosis Heterozygote Resistance to Cholera Toxin in the Cystic Fibrosis Mouse Model", *Science* 266 (1994): 107-109; L. Kivela et al., "Presentation of Celiac Disease in Finnish Children Is No Longer Changing: A 50-Year Perspective," *J Ped* 167 (2015): 1109-1115, accessed July 31, 2017, doi: http://dx.doi.org/10.1016/j.jpeds.2015.07.057.

[13] See e.g., Jackie Scully, "Disability Bioethics: Moral Bodies, Moral Difference", (Rowman & Littlefield, 2008), Chapter 2.

[14] Michael Sandel, "The Case Against Human Perfection", *The Atlantic*, April 2004.

[15] "Frequently Asked Questions About Genetic Disorders", National Human Genome Research Institute, accessed June 25, 2018, https://www.genome.gov/19016930/faq-about-genetic-disorders/.

[16] Hank Greely, "Of Science, CRISPR-Cas9, and Asilomar", *Stanford Law and Science Blog*, April 4, 2015, https://law.stanford.edu/2015/04/04/of-science-crispr-cas9-and-asilomar/.

[17] Ibid; E. Lander, "Brave New Genome", *New England Journal of Medicine* 2015, accessed June 8, 2018, DOI: 10.1056/NEJMp1506446.

[18] Ibid.

[19] Ibid.

[20] *Meyer v. Nebraska*, 262 U.S. 390 (1923); *Pierce v Society of Sisters*, 268 U.S. 510 (1925); *Farrington v. Tokushige*, 273 U.S. 284 (1927); *Prince v. Massachusetts*, 321 U.S. 158 (1944); *Wisconsin v. Yoder*, 406 U.S. 205 (1972).