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MOVING BEYOND ‘THERAPY’ AND ‘ENHANCEMENT’ IN THE ETHICS OF GENE EDITING

Bryan Cwik

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Abstract

Since the advent of recombinant DNA technology, expectations (and trepidations) about the potential for altering genes and controlling our biology at the fundamental level have been sky high. These expectations have gone largely unfulfilled. But though the dream (or nightmare) of being able to control our biology is still far off, gene editing research has made enormous strides toward potential clinical use. This paper argues that when it comes to determining permissible uses of gene editing in one important medical context—germline intervention in reproductive medicine—issues about enhancement and eugenics are, for the foreseeable future, a red herring. Current translational goals for gene editing research involve a different kind of editing than would be required to achieve manipulation of complex traits such as intelligence, and there are more pressing (and unresolved) questions that need attention if clinical use of gene editing in reproductive medicine ever becomes a possibility.

Keywords

gene editing; enhancement; reproductive medicine; research ethics; genetics; translational research

1. Introduction

Discussion of the ethics of gene editing is haunted by the specter of biomedical enhancement. In one of the earliest papers on the subject, Leon Kass wrote that, regardless of clinical potential, gene editing raised profound ethical conundrums as “Genetic engineering...will be able to create new capacities, and hence establish new norms of health and fitness.”¹ A huge literature has developed on the use of gene editing for purposes of biomedical enhancement, with passionate defenses of its potential and equally passionate criticisms of its potential harms.² Even as research has progressed in different directions, much, if not most, work on gene editing in philosophical bioethics continues to focus on enhancement, including a number of articles in a recent special issue of this journal devoted to the topic.³ In another recent paper on the topic, the authors affirmed that “Of greatest concern is editing of genes to confer advantageous traits not related to avoiding disease or preserving health.”⁴ Most statements on the use of gene editing in human beings so far from

¹Kass LR. The New Biology: What Price Relieving Man’s Estate? *Science* 1971;174:779–88.

²For an overview, See Buchanan AE. *Beyond Humanity? The Ethics of Biomedical Enhancement*. New York: Oxford University Press; 2011:Chapter 1.

³*Cambridge Quarterly of Healthcare Ethics* 2019;28, especially the papers by Agar, Raki, and Emmerich and Gordijn.

professional organizations, ethics boards, and advisory panels—including the recent exhaustive report by the United States National Academies of Science, Engineering, and Medicine—have called for drawing the line at “therapeutic” uses and forbidding “enhancement” with gene editing, thus reaffirming the centrality of the distinction.⁵

The importance of enhancement for the ethics of gene editing is especially relevant for neuroethics. Though much of the discussion in neuroethics about enhancement is about methods such as pharmacological intervention,⁶ the potential for genetic enhancement of cognitive abilities is considered to pose a significant ethical issue for gene editing.⁷ The potential for enhancing cognitive abilities thus raises a particularly high bar for any clinical applications of gene editing that could affect, directly or inadvertently, neural development. There is possibly no place where the difference between therapeutic and enhancing uses of gene editing is more ethically important than where editing could affect neural development and psychological traits.

Since the advent of recombinant DNA technology, expectations (and trepidations) about the potential for altering genes and controlling our biology at the fundamental level have been sky high. These expectations, however, have gone largely unfulfilled. The ability to eliminate all inherited diseases, choose traits, and make ourselves stronger, faster, and smarter does not appear to be in our foreseeable future. But though the dream (or nightmare) of being able to control our biology is still a ways off, gene editing research has made enormous strides toward potential clinical uses in reproductive medicine. My aim in this paper is to argue that debates about enhancement are of limited value in dealing with questions about foreseeable clinical uses of germline gene editing. This is for two reasons. First, the use of gene editing for biomedical enhancement in any sort of interesting way is not just technically far off, it involves a *different kind of use* of gene editing than is currently being pursued in research. Any use of gene editing to enhance our physical or psychological characteristics would likely involve affecting the developmental pathways for these traits in completely different ways than researchers are currently exploring. Second, and more importantly, there are significant questions about future clinical use even for *very clearly therapeutic uses* of germline gene editing. I will focus on one in depth: determining rationale for germline gene editing in cases where there are competing therapeutic options.

None of this is to say that enhancement will never be possible, nor is it to say that it is something we should not discuss. Rather, the conclusion to draw from this argument is that, when it comes to determining permissible uses of gene editing in one important medical context—germline intervention in reproductive medicine—issues about enhancement and

⁴Daley GQ, Lovell-Badge R, Steffan J. After the Storm – A Responsible Path for Genome Editing. *New England Journal of Medicine* 2019;doi:10.1056/NEJMp1900504; available at <https://www.nejm.org/doi/full/10.1056/NEJMp1900504> (last accessed 12 Feb 2019).

⁵For these statements see National Academies of Science, Engineering, and Medicine. *Human Genome Editing: Science, Ethics, and Governance*. National Academies Press: Washington, DC; 2017; Baltimore D, Berg P, Botchan M, Carroll D, Charo RA, Church G, et al. A Prudent Path Forward for Genomic Engineering and Germline Gene Modification. *Science* 2015;348:36–8; and Friedmann T, Jonlin EC, King NM, Torbett BE, Wivel NA, Kaneda Y, Sadelain, M. ASCGT and JSGT Joint Position Statement on Human Genomic Editing. *Molecular Therapy* 2015;23:1282.

⁶See, for example, Farah MJ, Illes J, Cook-Degan R, Gardner H, Kandel E. Neurocognitive Enhancement: What Can We Do and What Should We Do?. *Nature Reviews Neuroscience* 2004;5:421–5.

⁷Most relevant here is the work of Nick Bostrom; see especially Bostrom N. Human Genetic Enhancement: A Transhumanist Perspective. *Journal of Value Inquiry* 2003;37:493–506.

eugenics are, for the foreseeable future, likely a red herring. Current research is taking us in a different direction, and discussions about the ethics of enhancement are of limited use in the place we appear to be headed. Arguing about enhancement is of little relevance to the issues we are likely to encounter there, and there are more pressing (and unresolved) questions that need attention if the clinical use of gene editing in reproductive medicine ever becomes a possibility.

In the sections 2 and 3, I will argue for these two reasons to move beyond worries about enhancement in the ethics of gene editing. In section 4, I will consider two alternatives to sorting uses of gene editing into “therapies” and “enhancements” for settling permissibility of, and guidelines for, future clinical use, before a brief conclusion in section 5.

2. On the Site of Gene Editing

The possibility of using gene editing on human beings to control our biology at the fundamental level has been a topic of intense discussion since the introduction of recombinant DNA techniques. Most of this discussion has been speculative, in the sense that it was based on speculation about what shape the application of gene editing technology to human beings would take. Over the past few years, this situation has changed. Several gene therapies⁸ for the treatment of diseases such as acute lymphoblastic leukemia and non-Hodgkin’s lymphoma have been introduced into clinical use in the United States,⁹ and there have been significant developments in research on germline gene editing (GGE).¹⁰ The debate about use of GGE in humans is no longer speculative; we can, now, begin to get a sense of what a clinical application of GGE in humans could look like.

One thing that is clear about the shape of GGE research is that it is different from the sort of editing that is likely to be needed in order to achieve the kinds of biomedical enhancement bioethicists fret about. Consider one of the most high profile research results to date,¹¹ in which a team at Oregon Health and Science University (OHSU) used the CRISPR gene editing system to target and cleave a mutated *MYBPC3* gene in human embryos.¹² The particular mutation they were after is the cause of hypertrophic cardiomyopathy, a disease that causes weakness (myopathy) in cardiac muscle. It is a monogenic, autosomal dominant disorder, meaning a child has to inherit only one mutated allele of the gene in order to develop the disease; individuals who are heterozygous for the mutated allele will still have

⁸Gene therapies are also known as ‘somatic gene editing,’ to distinguish them from germline gene editing. These therapies involve introduction of edited biological materials (somatic cells, hence the name) into individuals. This involves the introduction of edited genetic material into a person’s body, but the material would not be present in gametes and so not heritable.

⁹Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene Therapy Comes of Age. *Science* 2018;359:175.

¹⁰Greenfield A. Carry on Editing. *British Medical Journal* 2018;127:23–31.

¹¹Arguably, the most dramatic and high profile (but not the most solid or responsible) research result was the creation of a pregnancy from edited embryos, which resulted in the birth of twin girls, by He Jiankui, a researcher (formerly) of Southern University of Science and Technology in Shenzhen, China (He was subsequently fired). His announcement in November 2018 that he had used CRISPR to delete the *CCR5* gene in the girls, to prevent horizontal transmission of HIV during conception via IVF (for which there is already a very low baseline probability if, as in this case, the father is HIV positive but the mother is not) and confer limited immunity to HIV infection, grabbed headlines and garnered a great deal of notoriety. However, as of the writing of this paper, the case has not been confirmed and is still under investigation, and many scientists believe the research was shoddy (in addition to being irresponsible and ethically unacceptable). See Cyranoski D, Ledford H. Genome-Edited Baby Claim Provokes International Outrage. *Nature* 26 Nov 2018; available at <https://www.nature.com/articles/d41586-018-07545-0> (last accessed 12 Feb 2019).

¹²Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, et al. Correction of a Pathogenic Gene Mutation in Human Embryos. *Nature* 2017;548:413–9.

the disease.¹³ The team at OHSU used the CRISPR gene editing system to target the mutated *MYBPC3* gene by introducing the system into an oocyte simultaneously with fertilization by sperm via intracytoplasmic sperm injection (ICSI).¹⁴ Through homology directed repair, the fertilized zygotes then replaced the cleaved gene with a healthy version of *MYBPC3*, thus resulting in zygotes that were homozygous for two healthy “wild type” *MYBPC3* genes.¹⁵

The experiment was a huge step forward. The first attempt to use CRISPR on human embryos in 2015 resulted in a large rate of off-target effects and mosaicism in the edited embryos.¹⁶ By contrast, the recent experiment by the OHSU team showed dramatic reduction in off-target effects, and a larger batch of zygotes that showed no detectable abnormalities. This is a dramatic step toward potential clinical use of GGE, and in a very short period of time. However, the team at OHSU used CRISPR to target only a single small mutation in one gene—in this case, a four base pair deletion in *MYBPC3*.¹⁷ The team was able to remove the mutation and induce the embryos to repair the deletion so the stretch of DNA on one chromosome matched the stretch on the other. Interestingly and very importantly, the team was unsuccessful in getting induced pluripotent stem cells (iPSCs) to take up synthetic DNA in place of the cleaved mutation; the rates of successful editing were extraordinarily low.¹⁸ Only when CRISPR was introduced simultaneously with fertilization via ICSI were the embryos able to repair themselves. So, this important experimental advance in human gene editing involved the use of CRISPR to target and cleave a *four base pair deletion in one copy of one gene*, and induce embryos to repair themselves so that the copy of the gene on one chromosome matched the “wild type” present in the population at large, and on the embryo’s other chromosome. To give a sense of the difference in magnitude in genetic causes of disease: there may be as many as forty one loci involved in risk for Parkinson’s Disease, and the causal pathways from these genes to development of the disease are largely unknown.¹⁹ Nevertheless, this is a very impressive result; by using CRISPR to repair a small defect in these embryos, the team showed that gene editing can be used to cure, and potentially remove from a family lineage forever, a fatal genetic mutation.
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¹³An individual who is heterozygous will have two different alleles of a gene; homozygous individuals will have two of the same allele.

¹⁴“CRISPR” stands for Clustered Regularly Interspaced Short Palindromic Repeats. It is a gene editing technique based on an archaic bacterial immune system.

¹⁵Homology directed repair is one of the mechanisms cells use to repair DNA lesions. The ‘wild type’ is the phenotype that results from having a ‘normal,’ nonmutated allele of a gene. In this case, the ‘wild type’ of *MYBPC3* is healthy cardiac muscle.

¹⁶Liang P, Xu Y, Zhang X, Ding C, Huang R, Zhang Z, et al. CRISPR/Cas9-Mediated Gene Editing in Human Triploid Zygotes. *Protein & Cell* 2015;6:363–72. Note: the embryos used in the 2015 experiment were triploid zygotes (eggs fertilized by two sperm cells, not capable of developing into a viable fetus) and so even if there had been higher rates of successful editing the embryos could not have been used to generate viable pregnancies.

¹⁷The mutation is a deletion of a GAGT base pair sequence in exon 16; the signifier for the mutated gene is *MYBPC3* GAGT. See note 12, Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, et al 2017, at 414.

¹⁸For explanation, see note 12, Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, et al 2017:414–5.

¹⁹Chang D, Nalls MA, Hallgrímsson IB, Hunkapiller J, van der Brug M, Cai, F et al. A Meta-Analysis of Genome-Wide Association Studies Identifies 17 New Parkinson’s Disease Risk Loci. *Nature Genetics* 2017;19:1511–6.

²⁰Whether the study achieved all it seemed to, however, is a source of controversy. See Begley S. Those CRISPR’d Human Embryos? We Got it Right, Scientists Insist, Rejecting Criticism. *STAT* 8 Aug 2018; available at <https://www.statnews.com/2018/08/08/crispr-human-embryos-scientists-reject-criticism/> (last accessed 12 Oct 2018).

It is, however, different in kind from the use of CRISPR or any other gene editing technique to “enhance” complex traits like intelligence. The issue is not that current gene editing tools aren’t sophisticated or powerful enough; the issue is that applications currently being pursued are very different from anything like enhancement. Complex traits like intelligence (assuming, for the sake of argument, they have a very strong genetic basis in the first place) are almost certainly the result of large numbers of genes working in concert over the course of development, potentially deep into an individual’s life. Research in genetics and developmental biology raises a number of problems with the very idea that complex traits can be affected by edits to single, or even small packages, of genes.²¹ There does not appear to be any, or at least many, ‘magic switch’ genes that are involved in the development of traits such as language use or other important cognitive skills.²² These traits are the result of large numbers of genes, and so any editing will have to involve making multiple changes. Current research into GGE in humans, on the other hand, involves targeting single genes that are heavily causally implicated in the etiology of a set of genetic diseases (monogenic, autosomal, inherited genetic disorders). Applications of GGE currently being explored simply do not involve the *kind* of editing that would be required for affecting complex physiological and psychological traits.

Second, complex traits are not just the result of large numbers of genes, but rather of *patterns of expression* over the course of development. Depending on the trait, expression is affected not only by conditions in utero, but exogenous factors of a dizzying variety. All of the interesting human traits that bioethicists fret about “enhancing” are the result of complex developmental and molecular pathways involving multiple genes, precisely orchestrated patterns of expression, and multiple epigenetic mechanisms. For this reason, many philosophers of biology argue that it is better to think of the relevant causal units here as “developmental pathways”—packages of genes, epigenetic mechanisms, and patterns of expression, that are canalized to varying degrees.²³ Gene editing techniques like CRISPR can be used to affect gene expression in simpler model organisms;²⁴ in humans, such moves have not even been tried, and given restrictions on embryo and stem cell research, may not be tried any time in the foreseeable future (or ever).

I do not mean to suggest here anything about, to use the old-fashioned terms, the relative value of ‘nature’ versus ‘nurture’; nor do I mean to make claims about the scientific or technical possibilities of enhancement. GGE research (along with research on early human development, generally) will surely yield better understanding of the pathways from genes to traits, as manipulating genes to see how this changes the developmental pathways for different pathogenic traits is an excellent way to learn more about genetic causation.²⁵ This

²¹A similar point is made by note 4, Daley GQ, Lovell-Badge R, Steffan J 2019.

²²For discussion of beliefs about ‘magic switch’ genes for cognitive traits, see Reich D, *Who We Are and How We Got Here: Ancient DNA and the New Science of the Human Past*. NY: Pantheon; 2018.

²³Jablonka E, Lamb MJ. *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symbolic Variation in the History of Life*, Revised Ed. Cambridge, MA: MIT Press; 2014. “Canalization” refers to the variability in development of a trait based on exogenous factors. A phenotype is said to be heavily canalized if it will develop from the relevant genotype in a wide variety of environments and when exposed to different factors influencing development.

²⁴Mei Y, Wang Y, Chen H, Sun ZS, Ju XD. Recent Progress in CRISPR/Cas9 Technology. *Journal of Genetics and Genomics* 2016;43:63–75.

²⁵The value of basic research involving GGE for understanding human development is argued for forcefully by Greenfield; see note 10, Greenfield 2018, at 24–6.

is something that gene editing in model organisms has shown in developmental biology research.²⁶ It is very possible that one day scientists can build on all this research to see how developmental pathways for complex traits can be manipulated in vivo, and biomedical enhancement may become a technical possibility. We cannot wish away the general hard questions about enhancement and eugenics, and I do not mean to argue that they should be ignored.

What I *do* mean to argue here is that the two differences discussed above show that the current state of research on GGE involves *a difference in kind*, not just in degree of technical sophistication, from the use of GGE for biomedical enhancement. Use of GGE in enhancement involves targeting multiple genes, and influencing expression over the course of development, and potentially even deep into an individual's life span. By contrast, current research on GGE is focused on techniques for making edits to pathogenic mutations in single genes that are heavily causally implicated in development of specific diseases. The experiment discussed in this section involves investigating whether CRISPR—a highly useful research tool in the life sciences—can be adapted for clinical uses in human beings. It is wrong to assume that translation of the technique for one kind of clinical application is either the same as, or at least strongly connected to, other (currently speculative) potential uses.²⁷ Use of gene editing for biomedical enhancement will involve making multiple edits, using the technology to influence gene expression, and will in many cases have to involve swapping of pieces of DNA with synthetic DNA (something that, as the OHSU experiment showed, is still not technically feasible in human embryos). This is a different application of gene editing technology altogether from repair of pathogenic mutations.

Another way to think of this is in terms of implementation. In a commentary on an article about moral enhancement in a special issue of this journal on gene editing, Nicholas Agar noted that there are two levels of question about enhancement. One is about whether it should be done at all: whether biomedical enhancement is ever permissible, and if so what uses of it would be justifiable. A second level concerns what he calls “implementation problems,” which includes questions about what technologies should be used to achieve enhancement goals, how they should be distributed, and whether they are likely to have the intended effects (and not, for instance, a slew of unintended consequences).²⁸ Suppose we did consider biomedical enhancement permissible, and considered GGE a feasible and morally permissible way to achieve this. If so, the kind of editing that is the focus of current research would fail as a means of implementing our enhancement goals. We likely could not effect changes to traits such as intelligence by making small edits to single genes. This is a different kind of editing than what is necessary to implement the sorts of biomedical enhancement bioethicists typically discuss.

²⁶On the basic science benefits of gene editing research, see Bedau MA. The Intrinsic Scientific Value of Reprogramming Life. *Hastings Center Report* 2011;41:29–31.

²⁷This is discussed further in Cwik B. Ethical Challenges for Germline Gene Editing Research Using Human Embryos. In preparation.

²⁸Agar N. Commentary: The Implementation Ethics of Moral Enhancement. *Cambridge Quarterly of Healthcare Ethics* 2019;28:56–7.

There is an important caveat to all of this. Though it may not be possible to affect complex cognitive traits, it may be possible to create propensities for developing enhanced versions of more fine-grained traits through small edits. A good example of this is the previously mentioned (see note 11) controversial use of CRISPR to edit the *CCR5* gene in two twin girls carried out in 2018 by He Jiankui. *CCR5* is believed to be involved in memory; lab mice with the *CCR5* deletion He induced in the twin girls perform better in experiments to test memory than other mice, and *CCR5* is implicated in quicker recovery from stroke in humans.²⁹ There is no conclusive evidence, but there is enough to suggest—emphasis on *suggest*—that editing of this one gene could impact neural development and memory.

Cases such as this show that successful regulation of the kinds of clinical applications being pursued require drawing very fine grained lines of permissibility. We need to consider not just specific clinical applications and their goals, but also specific *targets*. This may look like an impossible task, but it is not, and in fact, as I will argue in section 4, is much more conceptually tractable than trying to sort applications into “therapies” and “enhancements” and drawing a bold line between these two categories. This sort of case also illustrates the unique neuroethics issues raised by GGE, as it shows the extra stakes involved with any editing that could effect neural development. Quite apart from whether editing *CCR5* can boost memory, there is enough evidence to suggest that it could have some effect on neural development. Targeting the gene for one particular purpose—in this case, inducing immunity to HIV infection—could have a significant set of unintended effects on the girls’ cognitive traits and psychological makeup.³⁰ There are then an important set of questions in neuroethics about what sorts of impacts on neural development and cognitive traits would be permissible, what sorts would raise the risks of GGE beyond acceptable levels, and what these impacts would mean for the resulting persons, that have significant bearing on the ethics of GGE.

Cases like the *CCR5* editing case look like they pose a significant problem for the line of argument pursued above. The *CCR5* editing case seems to show that any kind of GGE, even its use to correct pathogenic mutations in single genes, inevitably opens the door to more controversial uses of gene editing, and shows why germline intervention *of any kind* crosses an ethical red line—an ethical and psychological barrier that, once crossed, introduces new possibilities and changes the probabilities of all sorts of uses of gene editing in the future.³¹

This is an old argument, and has been deployed in different forms against different assisted reproductive technologies (ARTs) and research using embryos and embryonic stem cells.³² The argument depends on a significant hidden premise: that *we could not draw more fine-grained lines* between different germline interventions, permitting some but not others. This premise in turn depends on a suspect conceptual move: lumping all germline interventions

²⁹Joy MT, Ben Assayog E, Shabashov-Stone D, Liraz-Zaltsman S, Mazitelli J, Arenas M, et al. *CCR5* is a Therapeutic Target for Recovery After Stroke and Traumatic Brain Injury. *Cell* 2019;176:P1143–57.E13.

³⁰As one scientist involved in the research put it, “The simplest explanation is that those mutations will probably have an impact on cognitive function in the twins.” Quoted in Regalado, A. China’s CRISPR Twins Might Have Had Their Brains Inadvertently Enhanced. *MIT Technology Review* 22 Feb 2019; available at <https://www.technologyreview.com/s/612997/the-crispr-twins-had-their-brains-altered/> (last accessed 22 Feb 2019).

³¹On the germline as an ethical ‘red line,’ see note 5, Baltimore D, Berg P, Botchan M, Carroll D, Charo RA, Church G, et al. 2015.

³²Perhaps the most infamous example is President’s Council on Bioethics. *Human Cloning and Human Dignity: The Report of the President’s Council on Bioethics*. NY: PublicAffairs; 2002.

together into a single category, regardless of their respective technical details and clinical goals. The discussion in this section shows why this is mistaken. We were easily able to make a threefold distinction between edits to single genes to *correct* a pathogenic mutation, edits to single genes to *induce* a propensity for a better-than-baseline cognitive trait, and edits to multiple genes to impact complex traits. There is no reason why regulation of GGE could not permit the first but forbid the second and third (in section 4, I will propose exactly this).

Another response is that we cannot take our cues about what ethical issues are important from the current state of a technology; given how rapidly research on gene editing is progressing, this above picture of the current state of the art could well be outdated in the future. (Depending on when you are reading this article, maybe it already is!) This is partly true; just because some foreseeable use of a technology is not proximate in time does not mean it is not important, or is not important enough to subject to ethical scrutiny. However, though ethical issues about technological changes that are nearer to us in time may not have more importance than those that are farther off, they may have more *urgency*. In considering the ethics of a new technology, priority may need to be assigned to uses of technology that are closer in time than those that are farther off, even if the farther off uses are equally or more significant. Consider: the development of a fully intelligent artificial agent may be a far more significant advance in AI technology than better facial recognition technology or more efficient autonomous driving programs, but the urgency of ethical issues about the latter (use of this facial recognition technology by governments in law enforcement, for instance, or wholesale shifts in transportation to autonomous vehicles) may require us to assign them greater priority in considering the overall moral geography.

3. Beyond ‘Therapy’ and ‘Enhancement’

Even though the kind of editing discussed above would likely fail as a path toward biomedical enhancement (with the caveat of cases such as “dual use” editing of genes like *CCR5*), there are still very serious ethical issues about how it could, or should, be used. A legacy of the intense focus on enhancement in the ethics of gene editing is that the line between therapeutic and enhancing uses of gene editing is treated as very relevant. The difference between a therapeutic application and one that aims at enhancement is supposed to be a very consequential one.³³ There are, however, serious ethical issues with even very clearly therapeutic uses of GGE, and classifying applications of GGE as therapeutic and delineating them from enhancements does little to alleviate them.

There is a huge literature on the therapy/enhancement distinction in medicine. The problems with drawing the distinction clearly are well known, and the ground is well trodden.³⁴ I am not going to rehearse the main arguments or the well-known difficulties with the distinction here. For purposes of the following argument, we can assume that these problems have all

³³See note 5.

³⁴For examples, see Juengst ET. Can Enhancement be Distinguished from Prevention in Genetic Medicine? *Journal of Medicine and Philosophy* 1997;22:125–42; Miller FG, Brody H, Chung, KC. Cosmetic Surgery and the Internal Morality of Medicine. *Cambridge Quarterly of Healthcare Ethics* 2000;9:353–64; and Mehlman MJ, Berg, JW, Juengst ET, Kodish E. Ethical and Legal Issues in Enhancement Research on Human Subjects. *Cambridge Quarterly of Healthcare Ethics* 2011;20:30–45.

been solved. Even if we had a clear therapy/enhancement distinction, this would do little to shed light on some very difficult problems regarding therapeutic uses of GGE. Consider the following situation. Suppose we are at the point where we can use GGE to, as in the OHSU team's experiment, correct small pathogenic mutations. A treatment for, say, beta thalassemia is developed that involves making precise corrections at the point of fertilization of an oocyte via ICSI.³⁵ But, at the same time, a gene therapy for beta thalassemia has also been developed, a medical goal which is actively being pursued today.³⁶ Let us also suppose the treatment is effective and safe early in life, so that the individuals involved can, with either treatment, live the bulk of their lives (*ceteris paribus*) free from beta thalassemia. For individuals who carry the gene, with a family history of beta thalassemia, there are thus two different treatment options (assume, for the sake of argument, we have ruled out the relatively "low tech" options of adoption and use of preimplantation genetic diagnosis). One is to bring a pregnancy to term, see if the child has the condition or is free of disease, and if the child has beta thalassemia, to treat it through gene therapy. Another is GGE—to make edits to the gene at the point of conception, and use only those zygotes free of the mutation to create a pregnancy, thus ensuring the child is free of disease.

There are two questions here. One is a clinical question: how do we determine which is the better therapeutic option?³⁷ This is not an ethical question in and of itself, but it does involve at least some weighing of harms and benefits. The second though *is* an ethical question: if both of these treatments are available, does this affect the permissibility of using GGE? Given the higher general risks (at least early in its potential clinical use) of GGE as opposed to somatic gene editing, and given background concerns about opening the door to other, less clearly therapeutic uses of gene editing, we may think that absent any compelling reason to prefer it to alternative therapies, editing at the germline should not be permissible.

In this hypothetical case there is, however, one significant clinical benefit that germline gene editing has over gene therapy: fixing the mutated *HBB* gene that causes beta thalassemia could potentially wipe it out of the subject's family lineage, as editing at the germline means the fixed gene will be present in all the individual's cells, including gametes, and so will be heritable. A gene therapy used in infancy will only treat the disease in this particular individual. The heritability of changes to the genome of an individual at the germline is the source of a great deal of ethical consternation.³⁸ But paradoxically the heritability of changes at the germline is also a significant clinical benefit over other treatments for the same disease. It not only removes the disease from the next generation, but decreases risks to future generations through future reproductive choices, and removes a significant dark cloud hanging over the reproductive choices for successive generations—or in other words, the children and grandchildren of those opting for GGE never have to go through the same difficult and expensive decisionmaking process.³⁹

³⁵Beta thalassemia is a family of inherited disorders in which individuals underproduce hemoglobin, resulting in a variety of conditions such as severe anemia. It is caused by a mutation of the *HBB* gene; this mutation was the target of the first experiment using CRISPR on human embryos. See note 9, Liang P, Xu Y, Zhang X, Ding C, Huang R, Zhang Z, et al. 2015.

³⁶Biffi A. Gene Therapy as a Curative Option for β -Thalassemia. *New England Journal of Medicine* 2018;378:1551–2.

³⁷This question is considered with respect to GGE and preimplantation genetic diagnosis in Cavaliere G. Genome Editing and Assisted Reproduction: Curing Embryos, Society or Prospective Parents?. *Medicine, Health Care and Philosophy* 2018;21:215–25.

³⁸See references in note 5.

As Soren Holm points out, in his contribution to a special issue of this journal on gene editing, the use of GGE to affect the creation and constitution of future persons raises a number of questions.⁴⁰ First, risks to the child from the gene therapy are, to a large degree at least, known and quantifiable. Risks to the child (and future generations), in this hypothetical example of the first use of GGE, will not be. Second, some of these risks are caused by the very thing that makes GGE a potential benefit over gene therapy—the heritability of the change to the child’s genome. The risks of making heritable changes have to be weighed against the potential benefits of making nonheritable changes through a gene therapy. And third, opting for gene therapy involves imposing risk on an existing person, whereas GGE will involve risks for a *potential* person.⁴¹ The already existing child has a baseline set of risks and expectations resulting from their disease, against which we can weigh the harms and benefits of gene therapy. The potential child has no such baseline—they will be born with whatever risks are induced through the gene editing process built into their physical makeup. It is not clear what the relevant comparison class is for settling risks versus benefits for the potential, edited child. The natural comparison class would seem to be those born with beta thalassemia who have to undergo gene therapy.

But a case could be made here that the right class is the population at large. Any child at all will be born with such built in risks. Do risks introduced via the editing process depart significantly from those for a representative child (with a family history, say, of heart disease, or parents who smoke, and/or a myriad of other risk factors)? If the answer is no (emphasis on *if*), then GGE seems to offer a much better option over gene therapy: the risk to the potential child is much higher with the latter than the former. This is, paradoxically, the case even if the risks of GGE are *higher* than those from the gene therapy. The latter set of risks involve the imposition of harms on a child, whereas the former do not—the child is simply born with a biological property (being an edited subject) that introduces a set of risks that are not significantly different than the biological properties that introduce risks to any of us (having a family history of diabetes, or alcoholism, and so on). Or to put it differently, even if GGE is riskier than gene therapy in this case, bringing an edited subject into the world involves no more harm to them than bringing a child into the world at all, whereas bringing a child into the world with beta thalassemia and then putting them through a process of gene therapy involves two factors (having beta thalassemia, going through gene therapy) that involve significant departures from the average level of risk. If this line of argument goes through, then, as Holm notes, “...almost no uses of genetic modification in reproduction can be deemed as unsafe.”⁴² The relevant comparison class here, then, matters a great deal.

³⁹This raises some interesting adjacent, but ultimately off-topic, issues in population ethics about these sorts of reproductive decisions, which I will not address here.

⁴⁰Holm S. Let Us Assume That Gene Editing is Safe – The Role of Safety Arguments in the Gene Editing Debate. *Cambridge Quarterly of Healthcare Ethics* 2019;28:100–11. The arguments given by Holm differ from those here, and Holm brings in some metaphysical discussion about personhood and time (the infamous “nonidentity problem”). Despite this, the respective arguments end up at the same conclusion.

⁴¹Depending on how one comes down on a host of questions about when personhood begins, and whether the application of GGE in the OHSU experiment involved *existing* persons, or—because the editing was done simultaneously with fertilization via ICSI—future, potential persons. Given the mechanics of the process discussed in section 2, I have assumed the latter, but this is something that is debatable. See note 37, Cavaliere 2018, at 220, for discussion of GGE and identity.

⁴²Note 40, Holm 2019, at 106.

These are tricky ethical calculations. But crucially—*they have little to nothing to do with enhancement*. The use of GGE in this hypothetical scenario is an unquestionably therapeutic use, and any ethical considerations about the distinction between therapeutic and enhancing uses of GGE is of little relevance for this clinical application. The complications in this case stem from the particulars of GGE (that it involves making heritable changes to embryos that could become future people). These are questions, then, specifically about clinical uses of GGE, that require us to move beyond worries about ‘therapy’ versus ‘enhancement.’ These are also questions that weigh heavily on current ethical issues about GGE research. If it is true that, in our future scenario, the existence of the gene therapy cancels out any justification for GGE, then we may think that it is better to invest resources into research for gene therapies for these diseases instead of the (ethically more controversial) option of editing at the germline.⁴³

4. Ethics for GGE Where the Action Is

Instead of sorting different uses of GGE into broad categories like ‘therapies’ and ‘enhancements,’ and treating any use of GGE as crossing an ethical red line that automatically introduces the possibility of the latter, it is better to focus attention where the action is: the specific techniques and targets themselves.⁴⁴ The experiment described above in section 2 involved *correcting* a genetic abnormality that causes disease. The editing in this case resulted in an embryo that had two healthy alleles of a common gene. It involved, in other words, restoring the mutated allele to a healthy “wild type” version present in the human population. This is different from *inducing* a change in what would be an otherwise healthy embryo (which is what He Jiankui did, in the case discussed in section 2), or in *introducing* a gene via transfer of synthetic DNA that an embryo would not otherwise carry. Correcting a genetic abnormality is something that is perfectly permissible in adults (through somatic gene editing). The ethical issues that arise from it have to do with editing at the germline, not with the editing itself. This is not the case with inducing changes to otherwise healthy individuals or in introducing novel genes, which may well be impermissible no matter what.⁴⁵

This looks very much like a good place to draw an initial line. There are still many significant philosophical questions here: What is the difference between an otherwise healthy embryo and one that has an ‘unhealthy’ abnormality? What would be the difference between correcting an abnormality that causes a disease, and one that creates a propensity for a chronic disease? What is a ‘wild type’ gene, and how does it differ from a novel or synthetic gene? What is the difference between correcting a genetic abnormality and inducing a change? Nevertheless, these are at least somewhat tractable because of their specificity. We can consider what genotypes are pathogenic or which changes result in an

⁴³As argued by Lanphier E, Urnov F, Haecker SE, Werner M, Smolenski J. Don’t Edit the Human Germ Line. *Nature* 2015;519:410–1.

⁴⁴I borrow the phrase here (and in the title of section 2), and the overall metaphor, from Cohen GA. Where the Action Is: On the Site of Distributive Justice. *Philosophy & Public Affairs* 1997;26:3–30.

⁴⁵James Hughes makes a similar point, in his contribution to a special issue of this journal on gene editing. Hughes JJ. A Defense of Limited Regulation of Human Genetic Therapies. *Cambridge Quarterly of Healthcare Ethics* 2019;28:112–20.

abnormal genotype by comparison with the population as a whole, instead of debating about what counts as ‘normal’ and ‘pathological.’⁴⁶

Another possibility is to draw the line at edits to one gene. Editing single genes, as the initial research has shown, has many potential clinical uses. But there is only so much that you can do to affect phenotypes with edits to single genes. Drawing the line at single gene edits makes it virtually impossible to do many of the things with GGE that many bioethicists (and people, generally) find objectionable (again, with some caveats). It is also the case that single gene edits have a drastically lower threshold of risk than multiple gene edits. There are large, and still not completely defined, risks to editing single genes. But once you start editing multiple genes, you not only have to worry about adding risks from multiple different edits, you also have to worry about intragenic effects, and so the risk not only is additive, it is compounded. Given the current state of gene editing technology, it is hard to see multiple gene edits in human embryos being a safe and effective clinical possibility in the foreseeable future, so the *de facto* line of permissible use of gene editing will be drawn at single gene edits anyway.

Both of these are perfectly serviceable as conditions on permissibility for future clinical uses of GGE. Should GGE become a real possibility, guidelines for use will be necessary. These will be important for a number of reasons: they will make it clear to the public and to patients what the technology can be used for, they will set clear boundaries to hold providers accountable and determine what is and is not an abuse or an ‘off label’ use, and they will help to mitigate risks from more adventurous uses of gene editing until the technology has become more familiar, and a large body of data on its overall safety and efficacy in reproductive medicine is available. But they are, also, a significant improvement over simply lumping all germline interventions into a single category. There are real differences between different uses of GGE. Some of these uses will appropriately trigger worries about enhancement. Others do not, and breaking out these uses into different categories allows for a greatly improved understanding of the ethical terrain and better regulation and governance overall.

5. Conclusion

I have argued in this paper that debates about biomedical enhancement are of limited value when it comes to some potential clinical uses of GGE in the foreseeable future. This is because current research is of a different kind than research into uses of GGE for biomedical enhancement, and because there are significant ethical questions for even clearly therapeutic uses of GGE. I have also made some proposals for initial lines of permissibility for these foreseeable clinical uses. Regardless of worries about enhancement, the safest bet is that, for better or for worse, research on GGE in humans will continue, and the world will get closer and closer to the point where its potential clinical use is a real possibility. Bioethicists should not give up on broader questions about whether GGE is permissible, or even desirable, and certainly should not stop caring about biomedical enhancement or the distinction between

⁴⁶Nicholas Agar notes as well the connection between these questions about gene editing and issues in the philosophy of medicine about health, disease, and illness, in his contribution to a special issue of this journal on gene editing. Agar N. Why We Should Defend Gene Editing as Eugenics. *Cambridge Quarterly of Healthcare Ethics* 2019;28:9–19.

therapy and enhancement in medicine. But there is also great need for work on other issues. As I have pointed out at several places in this paper, there is a particularly relevant role for neuroethics in this discussion, as many important issues in the ethics of gene editing intersect with issues in neuroethics about altering cognitive traits through medical interventions.

A perhaps rosier look at it is this: many technologies were let loose on the world without sufficient scrutiny, and without reflection on what the right way to use them would be. Right now there is a great opportunity for all those who study medicine to avoid this situation for what could be one of the most significant medical innovations in human history. We should continue to talk about biomedical enhancement, and what it means for our notions of dignity, autonomy, and human nature. But, given the possibility that we may end up in a situation in which gene editing is done regardless, we also need to talk about how, in such a world, it could be done right.

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