When is it Safe to Edit the Human Germline?

Janella Baxter

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Abstract

In the fall of 2018 Jiankui He shocked the international community with the following announcement: two female babies, "Lulu" and "Nana," whose germlines had been modified by the cutting edge, yet profoundly unsafe CRISPR-Cas9 technology had been born. This event galvanized policy makers and scientists to advocate for more explicit and firm regulation of human germline gene editing (GGE). Recent policy proposals attempt to integrate safety considerations and public input to identify specific types of diseases that may be safe targets for human GGE (Sarkar forthcoming; Guttinger 2019; Lander et al. 2019). This paper argues these policy proposals are inadequate in different ways. While Sarkar (forthcoming) intends to incorporate input from the disability community for the purpose of deciding the value of human GGE, I argue that his strategy for doing so is inadequate. I'll argue that an iterative, deliberative process is a more appropriate framework for allowing the disability community to inform policy on human GGE. Further policy proposals have been framed in terms of monogenetic or single-gene diseases (Guttinger 2019; Lander et al. 2019). I argue that this way of conceptualizing disease is not what matters for deciding which disorders are viable candidates for human GGE. Instead, what matters is that (1) the disease in question must have (among its set of causes) genes that have a high degree of causal control with respect to the disease and (2) alternative nucleic acid sequences variants that are likely to produce traits deemed desirable must be identified. Previous policy proposals leave (2) unspecified. What conditions must be met for satisfying condition (2) should not be left to individual scientists to decide for themselves. The present proposal offers some guidance on this issue.

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1. Introduction

In the fall of 2018, the biophysicist and entrepreneur, Jiankui He, shocked the international community with the announcement that two female babies whose germlines had been modified had been born. He attempted to use the cutting-edge gene editing tool, CRISPR-Cas9, to target "Lulu" and "Nana's" CCR5 protein coding gene for the purpose of introducing a mutation that is associated with increased resistance to HIV. The anthropologist, Eben Kirksey, paints a multilayered picture of the local and international cultural context in which He carried out his experiments (Kirksey 2020). Shiyi Chen, the president of Dr. He's home institution (Southern University of Science and Technology in Shenzhen China) encouraged ruthless and unscrupulous research agendas with fast results. Since the 1980s, the city of Shenzhen has been a special market capitalist zone known for its rapid economic growth and competitive innovation. In 2017, when James Watson gave a public lecture at the Shenzhen International Precision Medical Summit where Jiankui He asked him what should be done with gene editing, Watson replied, "[M]ake people better" (Kirksey 183). Although Dr. He's announcement was met with resounding condemnation and outrage by the international scientific community, it is common for CRISPR scientists to have financial investments in start-up companies whose aims are to incorporate the new technology into medical practices ranging from somatic stem therapy to in vitro fertilization and preimplantation genetic diagnosis. Included in Kirksey's analysis are interviews with medical researchers who share Dr. He's interest in using CRISPR-Cas9 to modify the germlines of human embryos for the purpose of eliminating undesirable genetic traits.

Aside from the financial and status motivations that drive scientific interest in using CRISPR-Cas9 for human germline gene editing (GGE), He's choice to target the CCR5 gene has hues of humanitarianism. Since the 1980s, China has been battling an HIV epidemic (Wu et al. 2019). The epidemic has been helped along by money making schemes in poor rural parts of China where unregulated and unhygienic blood donation sites infected large numbers of donors (Ning 2016). HIV-positive patients face severe social stigma and discrimination in China. HIV-positive children are marginalized in schools and HIV-positive individuals are at risk of losing their jobs (Yanhai et al.

2009). There is intense pressure to have children in Chinese society; however, Chinese law prohibits fertility clinics from administering services to people with sexually transmitted diseases (Qiao et al. 2014). Although existing IVF methods can be performed to enable an HIV-positive male to conceive children without spreading the infection, Dr. He's proposal to use human GGE to introduce the CCR5-Δ32 mutation may offer new hope to HIV-positive couples.

Setting aside the complex, multifarious motivations for performing the experiment, it remains the case that Dr. He's experiment was performed without proper safety precautions and ethical oversight. As I'll explain in the paper, the use of CRISPR-Cas9 technology for human GGE has two sources of risk – i.e., off-target effects and unintended consequences – neither of which were properly addressed by He's lab. Safety concerns have been a primary reason for why the international scientific community has decried He's experiments. Although human GGE has been technically possible since the development of earlier gene-editing technologies (i.e., zinc finger nucleases and TALENs), Dr. He's experiments have galvanized the scientific community to formulate more explicit and firm policy on the safe and ethical use of human GGE (Baltimore et al. 2015; Doudna et al. 2017; Lander et al. 2019). Authors advancing policy recommendations for human GGE attempt to (i) incorporate input from representatives of the public on the social value of this technique as a medical intervention, and (ii) restrict human GGE to specific types of disease (Guttinger 2019; Sarkar forthcoming; Lander et al. 2019).

The argument of this paper accepts (i) and (ii) as necessary conditions for adequate regulation of human GGE. What this paper shows is that the ways authors have attempted to satisfy these conditions are inadequate. When it comes to incorporating input from the public on the value of human GGE, how should this be done? Sarkar (forthcoming) attempts to identify candidate conditions (such as Huntington's disease and myotonic dystrophy) for which there are no ethical objections voiced by disability advocacy groups. While Sarkar's method is admirable in that it accords the disability community a privileged decision-making role in human GGE policy, this method doesn't address prevailing disagreement among members of disability communities on the ethics of human GGE. For while there may not be groups advocating for Huntington's disease and myotonic dystrophy as valuable forms of human diversity that should not be eliminated from human populations, the views of disability scholars and activists on human GGE are rather diverse. Some express the view that all uses of human gene editing are forms of ableism, while others are amenable to human GGE for some specific conditions and not others (Davis 1995; Genetics and Society 2017). How should disagreement among the public be managed? A more adequate regulatory framework would involve a deliberative process on par with what Lander et al. (2019) describe whereby representatives of the public are permitted to voice their concerns and (possibly) reach a consensus.

While Lander et al. (2019) outline a more promising model of human GGE regulation, they nevertheless make substantive policy guidelines based on epistemic considerations alone – independent of public input. Lander et al. (2019) along with Guttinger (2019) maintain that if human GGE is permissible at all, it should be limited to prevent single-gene (or monogenetic) diseases only. This policy prohibits the use of human GGE for complex diseases and for preventing infectious disease like what Dr. He intended. This leads me to the second major argument of this paper. I argue that the epistemic considerations relevant to making human GGE safe are inevitably entangled with normative judgments about what sorts of human traits are deemed valuable. What this suggests is that an adequate regulative framework is one that incorporates public input into stages of research aimed at addressing safety issues of human GGE. I argue that once the normative and epistemological conditions for the safe use of human GGE are carefully examined, the monogenetic/complex disease distinction is not what's relevant for regulating this technique. What matters for deciding the safe and ethical use of human GGE is that there is agreement on two crucial conditions:

1. The disease in question must have (among its set of causes) genes that have a high degree of causal control with respect to the disease
2. Alternative nucleic acid sequences variants that are likely to produce traits deemed desirable must be identified

Crucially, condition (2) requires input from both the scientific community and representatives from the public. These conditions are flexible to address any type of condition that might be deemed a viable candidate for human GGE – including genetic entry points for infectious diseases like HIV.

This paper proceeds in Section 2 by arguing that human GGE may be a necessary medical intervention for a narrow range of conditions. In Section 3 I show how editing a reactive genome inevitably raises safety considerations that cannot be addressed without making normative judgments about what types of human diversity are valuable. Here I

begin to outline a procedure by which such normative judgements should be made. Section 4 specifies the necessary scientific considerations that must be met for a condition to be a good candidate for human GGE. Finally, I argue the monogenetic/complex disease distinction that has framed recent policy proposals for human GGE is not what matters for the safe use of this technique.

2. Why Human Germline Gene Editing?

Human germline gene editing introduces permanent, heritable changes to the genome of individuals. As I discuss in Section (3), this technique risks causing traits in future generations that may be deemed less desirable than the traits it is used to prevent. The aim of this paper is to outline a set of conditions and procedures that need to be met for human GGE to be performed safely. Yet, this is at odds with a prominent alternative advanced by Lanphier et al. (2015). Lanphier et al. (2015) advocate for a temporary ban on the use of human GGE in clinical applications on the basis that alternative medical treatments are available for addressing the same conditions for which human GGE might be used. In what follows, I argue that this is not true. There are some, albeit a narrow range of, conditions for which human GGE is the most viable treatment option. Furthermore, access to alternative, less risky medical treatments is hardly fair and equitable. Social, political, and economic inequalities can mean that some medical treatments are simply not available to the patients who need it the most. In such cases, human GGE may be a more prudent option.

Somatic stem cell therapy is a promising medical intervention that can be used to treat many of the same diseases that human GGE can. The method by which DNA is modified is the same for somatic cell therapy as human GGE. The crucial difference is unlike the later technique, somatic cell therapy introduces changes to DNA that are not heritable by one's progeny. This approach proceeds by harvesting somatic stem cells directly from the patient, modifying the genome of the collected cells, then reintroduced to the patient's body where (ideally) they develop and perform normal (or at least better) functions (Xu et al. 2013). Development of CRISPR-Cas9 has substantially broadened the range of diseases that can be treated with somatic stem cell therapy. While in the early stages of the science somatic stem cell therapy was a very risky treatment option – in some cases, causing patient death – the technique has significantly improved recently, substantially reducing risk to patients. As a medical intervention, it has shown significant promise in treating neurological disorders, hematologic and cardiac diseases and more (Sheridan 2011). Somatic stem cell therapy comes with a host of payoffs that human GGE lacks: it poses no risk to a patient's progeny and it does not require intervening on the incredibly delicate process of embryo development. Why turn to germline modification if a less risky alternative exists?

Notwithstanding immense promise, somatic cell therapy nevertheless has limitations. Somatic stem cell therapy only has the capacity to "rewrite" DNA in some cells later in a patient's development. Some diseases may require the rearrangement of DNA in multiple cell lines; some cells may simply not be accessible for somatic stem therapy; and others may require genomic changes from the beginning of embryo development (National Academies of Science, Engineering, and Medicine 2017; Gyngell et al. 2017). Somatic stem cell therapy also requires targeting the genomes of thousands to millions of cells. When compared to the efficacy of human GGE, which requires targeting one or a few early stage cells, somatic stem cell therapy's efficacy is severely compromised.[1] A further limitation is that somatic cell therapy is simply ineffective at preventing the inheritance of severe genetic diseases. A patient who carries a dominant genetic determinant of a disease trait, like Huntington's disease, has a high likelihood of passing on this disorder to their progeny. This is likely to be a problem even in a world where somatic stem cell therapy is an available treatment option.

In vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) can help couples conceive children without many medical conditions deemed undesirable. IVF involves a process by which ova can be fertilized outside of the body to produce a viable embryo, which is implanted in a woman's uterus where it is allowed to develop. During this process, a clinician can select to implant embryos with genetic profiles that have a minimal chance of developing and passing on severe genetic disorders. This method has the benefit of significantly reducing the chances that some genetic disorders will be inherited by future generations. Some authors have advocated for a complete ban on human GGE in research and clinical contexts on the basis that IVF with PGD appears to have all of the benefits of human GGE without the same risks (Lanphier et al. 2015). Nevertheless, there are some circumstances IVF with PGD cannot address. In rare cases where both parents are homozygous for a recessive disease or where one parent is homozygous for a dominant condition, the couple is not able to produce any viable

[1] I am grateful to a blind reviewer for this observation.

embryos that are not carriers of the unwanted disorder from which IVF can select (Gyngell et al. 2017; National Academies of Sciences, Engineering, and Medicine 2017). In some cases, the number of embryos required to produce individuals with the genetic profiles that have a minimal chance of developing the disease can be quite large. Not only is this something that is not biologically or technologically feasible, but it also means that large numbers of embryos will be destroyed.

Even when alternative methods of disease prevention and treatment are available, this alone does not mean the patients who will benefit from such methods will have access to them. Somatic stem cell therapy and IVF with PGD can require multiple visits to medical facilities. In resource-poor countries, patients may need to travel far distances to receive care. This can be costly as patients may need to pay for travel and accommodations. Frequent trips from their home can also mean that they miss work or lose their employment altogether. For patients living in highly repressive regimes, access to somatic stem cell therapy or IVF can be denied to them entirely. HIV patients in China are an illustrative of these sorts of examples. Of course, the truly just solution to such circumstances may require significant transformation of unjust social, political, and economic structures. However, in the interim as we wait for such transformations to take place human GGE may be the most prudent option.

There are some – albeit a narrow range of – cases that can only be treated with the use of human GGE. Moreover, given the complex social and political nexus in which patients live, human GGE may be the most prudent medical intervention for some types of conditions. This means that Lanphier et al.'s (2015) proposal for a complete ban on research and clinical application is not justified – at least for the reasons they raise. A more sophisticated human GGE policy is needed to adequately manage the biological and ethical considerations.

3. Deciding What Traits to Value

Even though human germline gene editing with the CRISPR-Cas9 technology has some potential benefits that other types of interventions lack, this technique has the potential of causing traits that are deemed undesirable. While technological fixes may help eliminate some of the risks associated with using CRISPR-Cas9 to modify the human germline, it can't eliminate all risks. Does the risk inherent to human GGE with CRISPR-Cas9 warrant a complete prohibition of this technique? I argue that it doesn't so long as representatives from the public deem the traits that might result from human GGE to be more desirable than the traits that would result were human GGE not performed. This argument inevitably prompts questions about who should decide the desirability of human traits. In what follows I argue that members from the disability community ought to have a privileged decision-making role in settling such questions. The disability community is uniquely situated to know the value of diverse human traits. The view advanced in this paper is that an iterative process whereby the disability and scientific communities inform each other about the safety and value of human GGE.

Human GGE with CRISPR-Cas9 can cause undesirable traits in human populations in two ways: off-target effects and unintended consequences. An off-target effect occurs when a gene-editing tool targets and "rewrites" sequences other than what was intended by the user. Off-target effects at crucial loci – such as an oncogene, essential gene, or master developmental switch – can produce undesirable traits in future generations like cancer or developmental impairments (Ledford 2020). The risk of off-target effects is a matter of the gene-editing technology being prone to error. By contrast, unintended consequences can obtain even when the gene-editing technology is perfect. This problem arises from the inherently complex nature of human development (to be further clarified in the following section). An unintended consequence is when human GGE produces a change to the nucleic acid sequence of a nucleic acid sequence which alters the function of that sequence in such a way as to cause undesirable developmental or health consequences for the future individual (Sarkar forthcoming; Guttinger 2019). For example, modification of the CCR5 gene can increase one's resistance to HIV infection, but also increase the chances of having a severe reaction to other infectious diseases such as West Nile Virus (Glass et al. 2006).

Currently, the state of germline modification with CRISPR-Cas9 technology is nowhere near safe enough for clinical applications; nevertheless, many are hopeful that human GGE will eventually meet this requirement (Peng et al. 2015; Ormond et al. 2017). CRISPR-Cas9 technology commonly makes off-target effects – ranging from changes in single nucleic acid bases to large chromosomal rearrangements (Cullot et al. 2019). So long as off-target effects can result in physiological traits that are deemed less desirable than the traits it is intended to prevent, then there is little reason to consider human GGE as a viable medical treatment. Because of the unsafe nature of this technique, many scientists have called for a temporary ban on human GGE (Ibid, 2017; Baltimore et al. 2015; Ma et al. 2017). This ban prohibits the use of germline gene editing in human embryos that are permitted to develop to

term but permits continued non-clinical research of human GGE.[2] Non-clinical research has the potential of improving human GGE techniques to the point where it can be plausible medical intervention without conducting human experiments where less desirable traits result (Guttinger 2019). Non-clinical research is performed on embryonic stem cells and early-stage embryos that are not permitted to travel beyond the secure walls of laboratories. A hallmark of this sort of research is that modified embryos are not implanted in a uterus and allowed to develop. Instead, they are destroyed within a legally defined window of time.[3] This practice ensures that less desirable traits do not result from human GGE. Non-clinical research has the potential of significantly minimizing the off-target rate of existing gene-editing tools. Off-target effects of genome editing technologies are (in principle) observable within the window of time during which non-clinical research on human embryos is legally permissible (Ibid, 2019; Gyngell et al. 2017).[4] This can provide essential knowledge for how to minimize the off-target potential of gene-editing tools. Non-clinical research to improve human GGE techniques aligns well with proposals of a temporary ban.

Unfortunately, the kind of research required to minimize the risks associated with unintended consequences may not be compatible with a temporary ban (Guttinger 2019). The problem of unintended consequences is not a technical problem unique to CRISPR-Cas9 – it is a biological (and I'll argue below) a social and political problem. Even were CRISPR-Cas9 or other gene editing tools perfect and never made off-target effects, the problem of unintended consequences would still hold. Safety risks associated with unintended consequences arise from intervening on complex, reactive biological systems. Most genes perform multiple functions (pleiotropy), which in turn may change throughout developmental stages, environmental conditions, and tissue types. Most phenotypic traits are caused by the activities of many, interacting and reticulate networks of genes (epistasis) (Sarkar 1998). Furthermore, the functions of gene products are not solely determined by the corresponding nucleic acid sequence in DNA. Proteins often receive posttranslational modification that can have significant developmental and evolutionary consequences (Millstein 2007). Gene activity is controlled by epigenetic factors that sequester away some regions of DNA from being expressed, while exposing others (Griffiths et al. 2013; Keller 2014; O'Malley et al. 2014). All of this complexity enables genomes to respond to changes in environmental conditions that influence development and health (Heintzman et al. 2009; Heintzman et al. 2007). The set of DNA segments, patterns of epigenetic histone and nucleotide modifications, gene regulatory networks, etc. that are in play in a blastocyst are very different from the set of relevant factors in play in fully differentiated cells.[5] What this means is that the consequences of germline gene editing are likely to be observable only as human development unfolds over time. It is likely that any unintended consequences that result from intervention on the human germline will not be observable within the time frame that is legally permitted for research. Research into the unintended consequences of human GGE editing very well may demand the implantation and development of fertilized embryos (Guttinger 2019). What may begin as a non-clinical research program may transform into a clinical research trial. As a clinical research trial, genetically modified humans, their mothers, and possibly future offspring will require observation throughout pregnancy and development into adulthood.

Whether clinical trials are worth the risks associated with unintended consequences requires that we make normative judgements about the value of human traits. Whether human GGE trials are worth the risk depends on how desirable are the traits that result from human GGE in comparison to the desirability of traits that would otherwise result were

[2] Jiankui He's use of CRISPR-Cas9 to target the CCR5 genes in "Lulu" and "Nana" was performed at a time before the scientific community had proper understanding and control of the technology's off-target effects. This was a violation of the temporary ban.

[3] Whether it is morally permissible to destroy human embryos for research purposes is a topic that will not be explored in this paper. With that said, a number of countries abide by the 14-day rule, which states that human embryos may not be kept alive beyond the 14th day after fertilization. Recently there have been calls to extend the number of days research on embryos is permitted (Appleby et al. 2018).

[4] Further developments in genome sequencing methods are also necessary for this sort of information to be possible.

[5] I am grateful to a blind referee for suggesting an ethical and conceptual contrast between human GGE and somatic stem cell gene therapy. The problem of unintended consequences is a more serious concern in the case of human GGE than in somatic cell gene therapy. This is due to the former introducing genomic modifications that will be inherited by all the cells of an individual, which in turn will influence development over the course of an individual's lifetime. The problem of unintended consequences in the case of somatic stem cell therapy will be more contained to specific cell lineages and developmental stages and, thus, will be less serious than in the case of human GGE.

human GGE not performed.[6] Such judgments should not be made by the scientific community alone. Scientists are not selected to represent the interests and values of the broader public, nor are they trained to do so (Sarewitz 2015). Scientists can be driven by academic accolades and even commercial interests that may deviate from the interests and wellbeing of the broader society.[7] Moreover, editing the germline can have far-reaching, societal consequences beyond the recipients of human GGE (Baylis 2019). For example, modification of the GJB2 gene to prevent deafness can reduce the size of deaf communities. A reduction in the size of an already marginalized group may further marginalize and impoverish the lives and culture of deaf individuals (Blankmeyer Burke 2017). It may also provide less incentive for hearing-able communities to value the perspectives of deaf communities and invest in more equitable social structures (Wolbring 2003). Considerations such as these have prompted authors and major scientific institutions to acknowledge that human GGE policy requires input from representatives of the public (National Academies of Science, Engineering, and Medicine 2017; Olson 2015; Lander et al. 2019).[8]

Among the representatives from the public that should have a privileged decision-making role in determining the value of human traits are members of the disability community.[9] Members of the disability community can achieve a unique epistemic perspective when it comes to the value of human diversity.[10] They have first-hand knowledge of what it is like to live with traits that are deemed by society as a bad difference. Yet, as many disability scholars and activists argue, many traits associated with disability are neither good nor bad differences (Barnes 2014; Wong 2017; Cokley 2017). Instead, they are mere differences – differences associated with unique experiences and properties on par with sex, gender, and racial differences. Disabled communities suffer from systems of thought and social arrangements that disproportionately accord honor, power, and privilege to able-bodied individuals and that simultaneously degrade and subordinate disabled individuals (Jaggar 2008; Wilson 2017; Porter 2018).[11] Human GGE editing has the potential to amplify and exacerbate ableist systems of thought and social arrangements. Thus, it is no surprise that disability scholars and activists have expressed a strong interest in participating in public discussions about the value of human GGE (Wong 2017). In a world shaped by ableism, the intuitions of the privileged (majority) have (and are likely in the future to) systematically and unjustly disregarded the value of traits associated with disability. When it comes to determining the value of human traits, the intuitions of the privileged alone are likely to be poor guides to how we ought to value human diversity. The disability community are more likely to make accurate predictions about how societal values concerning human diversity will affect already marginalized groups. At minimum, the judgments of the disability community should help guide decisions about which traits warrant human GGE.

Extending a privileged decision-making role to the disability community is one thing, another thing is how policy makers should go about facilitating this. This can be achieved in various ways. For example, Sahotra Sarkar argues that human GGE should be restricted to conditions for which there are no advocacy groups defending a mere difference view – Huntington's disease and myotonic dystrophy are such examples (Sarkar forthcoming, chapter 6). Unfortunately, this method is not adequate. Even though there may be no advocacy groups defending Huntington's

[6] A common concern expressed about human germline gene editing is its impact on human evolution (Doudna et al. 2017). The social, political, and epistemic considerations that are relevant for the evolutionary impact human germline gene editing might have on human populations deserves its own treatment. In this paper, the focus concerns the social, political, and epistemic considerations that are relevant for clinical trials with human germline gene editing. This is a noteworthy distinction as gene editing technologies alone are not sufficient for influencing human populations on an evolutionary scale. Further technological advancements (such as a method for editing the germlines of early-stage embryos in vivo) are likely to be needed for this sort of effect.

[7] Indeed, there is a burgeoning and unregulated market for implementing CRISPR technologies in fertility clinics in which a number of scientists are financially invested (Kirksey 2020).

[8] Broad societal consensus was originally one of two requirements for the responsible use of human germline gene editing included in the statement issued by the first International Summit on Human Gene Editing in 2015; however, this requirement has since been removed from more recent statements issued by the International Summit. (For criticism of this revision see Baylis 2019).

[9] This proposal is compatible with other communities from the public having a say in deciding the value of human germline gene editing.

[10] The view I am proposing is similar to the idea of a critical standpoint found in feminist epistemology (Wylie 2012) and Rolin's (2015) concept of a scientific/intellectual movement.

[11] This characterization of ableism applies Alison Jaggar's characterization of sexism to the issue of disability (Jaggar 2008, pp. vii).

disease or myotonic dystrophy as valuable forms of human diversity, the disability community's position on the ethics of human GGE is far from univocal. Members of the community express a range of ethical concerns that are amenable to different policy solutions. Some hold the view that any genetic modification of humans – whether it be in somatic or germline cells – rests on ableist attitudes (Davis 1995; Genetics and Society 2017). Others express the concern that racial and economic inequalities will bar already marginalized communities from having access to the benefits (if there are any) of human GGE (Cameron 2017). Some maintain that human genetic modification may be acceptable for some diseases and disorders provided the technique can be performed safely (Genetics and Society 2017). Disagreement among members of the disability community suggests that a deliberative process by which the community may reach a consensus is needed. The view defended in this paper is that an iterative process is required whereby the disability and scientific communities inform each other about the empirical nature of human GGE – e.g., the state of technology, risks and benefits, the details of living with traits associated with disability, etc. – and the value of diverse human traits.[12] It may be that new scientific advancements or the emergence of real-world problems change the opinions of the disability community. Moreover, I'll argue below that scientists cannot address the epistemic requirements in deciding which conditions are viable candidates for human GGE without making value judgments about the desirability of human traits. These judgements should be guided by what the disability community decides. Taking the views of the disability community seriously on the issue of human GGE requires giving them a forum to actively deliberate on the merits of this medical intervention and inform public policy on its use.[13]

Provided the disability community is amenable to human GGE for some conditions, their decision needs to be informed by scientific understanding of how effective this intervention is likely to be. While clinical trials are essential for determining the safety of any medical intervention, I argue that scientists can (and should) meet several epistemic conditions before performing clinical trials.

4. What can we Know without (Human Germline) Intervention?

Before human germline gene editing reaches clinical trial stage, researchers need to have an adequate understanding of the unintended consequences that a particular gene edit is likely to have. I argue that this requires knowing two things: (1) that a gene edit (or set of edits) are causally significant relative to the disease and (2) the odds and nature of any unintended consequences that might occur from germline editing. Satisfaction of these conditions requires integration of evidence from diverse areas of scientific inquiry.

Much can be learned about disease and potential curative measures from an integration of model organisms, human population genetics, evolutionary biology, and epidemiological studies. Model organism research involves the study of genetic, molecular, and cellular mechanisms that operate throughout an organism's development. Mechanisms that are highly conserved across humans and model organisms may justify applying the models and theories developed from model organism study to human development and disease (Ankeny et al. 2011). Population genetics and genome wide association studies (GWAS) are necessary for determining the inheritance patterns of genetic diseases as well as significant correlations between variables (Reimers et al. 2019). Evolutionary biology can provide invaluable insights into why some genetic determinant is present in a population and what might happen in its absence (Sun et al. 2010). Epidemiological studies are necessary for describing the distribution of a disease across diverse populations and environments, and symptoms thought to be associated with a disease (Maier et al. 2019). This sort of evidence can identify healthy variants of a gene known to cause disease as well as the range of genetic and environmental background conditions that are causally relevant to proper development and health. Undoubtedly, the theoretical knowledge developed from research programs subsumed under each of these areas of study will provide only a partial understanding of human health and disease. Furthermore, the integration of models and theories developed from these areas of research will be no small feat. Nevertheless, theoretical integration of the

[12] The process outlined by Lander et al. (2019) is a more adequate model for enabling representatives of the public to inform the value judgments of human GGE; however, as I'll argue in Section 5 their proposal falls short in other ways.

[13] Incorporating the perspectives of disabled individuals – especially individuals with cognitive impairments – requires its own theoretical framework as such individuals may not be able to communicate their perspective in a standard format (see Warren 2016). For this reason, it may be that caregivers and allies also be included as representatives of disabled communities.

knowledge gleaned from distinct research programs has the potential to help researchers make informed predictions about how a gene edit will operate against the background conditions of a particular individual.[14]

Yet, this alone is not sufficient for determining whether human GGE editing will be effective. Additional conceptual and practical questions must be settled. Not all diseases are amenable to human GGE as a medical intervention. Many diseases are not genetically heritable and, furthermore, not all genetically heritable diseases are good candidates for human GGE. A genetically heritable disease may be a candidate for human GGE provided scientists have an adequate theoretical knowledge of (at least some) crucial aspects of the disease's causally significant genetic determinants. Condition (1) outlines part of what is meant by "causally significant:"

1. The disease in question must have (among its set of causes) genes that have a high degree of causal control with respect to the disease

Genes correlate with almost every disease, but this does not make every genetic correlate a viable target for human GGE. For human GGE to be an effective medical intervention it is crucial that the genes modified make a significant difference to the disease. A gene is a significant difference-making cause when intervening on it provides a high degree of control over the occurrence/nonoccurrence of the disease across a wide range of background conditions and environments (Ross 2018; Ross forthcoming). It is imperative that scientists have good evidence to believe that a disease meets condition (1). This raises something of a paradox. How can scientists know that an intervention on a gene will provide a high degree of control over the occurrence/nonoccurrence of a trait without actually intervening on human germlines? Scientists can avoid this paradox by drawing from human population genomics data, genome-wide association studies (GWAS), epidemiology, and model systems research. Sometimes, comparing the genetic, epidemiological, and biochemical profiles of human populations can uncover populations with and without a set of genetic determinants. If a medical condition strongly correlates with one population and not the other, scientists may be justified in inferring that some genetic determinants have a high degree of control over the state of the trait.

At play in this analysis are genetic concepts of penetrance and expressivity (Sarkar 1998). Penetrance has to do with the proportion of individuals in a population who (1) possess the relevant gene(s) and (2) exhibit the corresponding phenotypic (or outward) trait. So, if a gene is highly penetrant, a large proportion of individuals who possess the gene – say, nearly 100% – will also express the trait. Expressivity has to do with the intensity with which a phenotypic trait associated with a gene (or genotype) is expressed. A trait that has low expressivity may not be present in individuals carrying the relevant genetic determinants. Satisfaction of condition (1) requires that the genetic determinants of a disease be sufficiently penetrant and expressive. (I take up this issue again in the following section.)

It is not enough that medical researchers have identified causally significant genetic determinants of a disease. Genetic editing involves the changing the nucleic acid sequence from one that has a deleterious function to one with a different function. This can be done by removing a functional element altogether or inserting a different functional element in the place of a deleterious one. Either way, some nucleic acid sequence will be in place of the deleterious gene as a result of gene editing. Whether or not the resulting sequence is intended to be a functional element, scientists need to know whether the new sequence is likely to have unintended consequences and what the nature of those consequences are likely to be. For clinical trials on human GGE to be performed safely, condition (2) must also be met:

2. Alternative nucleic acid sequences variants that are likely to produce traits deemed desirable must be identified

Any given nucleic acid sequence can have a very large number of alternative variants.[15] Of the large number of alternative sequences that encode information for a protein coding or a cis-regulatory sequence, only a small number of variants are present in the human population. So long as scientists select only from the set of variants already

[14] In fact, study of the CCR5-Δ32 mutation marked the beginning of this sort of integrative research program (see Jackson 2015).

[15] The number of alternative variants will depend on whether one is removing a functional element entirely or simply replacing a deleterious functional element with a different one. Nevertheless, a sequence that is n-nucleotide bases long, will have $\sim 4^n$ number of possible alternative sequences from which scientists may choose. That is, for each nucleotide base in a sequence, there are four possibilities (adenine, thymine, guanine, cytosine). For an average protein coding gene, the number of alternative possible sequences is $\sim 4^{900}$.

present in human populations, they can make justified predictions about the likely outcome of a gene edit.[16] Condition (2) is explicitly normative. It requires more than just that scientists be able to make justified predictions about the likely outcome of a gene edit. It also requires that the likely outcome of a gene edit be deemed desirable by members of the disability community.

Yet for the disability community to be able to make a judgement about the value of particular gene edits, the scientific community needs to have an adequate understanding of how a nucleic acid sequence is likely to influence health and development across a range of genetic and environmental backgrounds. Genetic and environmental variation can mean that the health and developmental consequences of a nucleic acid sequence are variable. In some genetic and environmental contexts, a nucleic acid sequence can have no unintended consequences, while in others the same sequence can cause shortened lifespan, susceptibility to infection, increased risk of cancer, early onset dementia, etc. Scientific and disability communities need to know the chances and nature of any unintended consequences associated with particular gene edits to decide the value of such an intervention. This requires knowledge of how alternative nucleic acid sequences associate with health and development in a diverse range of human populations.

Inevitably scientific knowledge from each domain I've discussed – population genomics, epidemiology, model systems, evolutionary biology etc. – will offer only a partial understanding of the overall pathway or mechanism by which genetic determinants contribute to health and development. Moreover, knowledge in each domain will advance unevenly – for example, scientific understanding of a disease's inheritance patterns may be more developed than, say, understanding of the molecular processes by which a gene operates in human health and development. My view is not that scientists must have complete and accurate knowledge from all the relevant domains of inquiry. Rather, my view is that scientists must integrate knowledge generated from diverse domains of inquiry to formulate an adequate theory of the causally significant genetic determinants of a disease.[17] This process is bound to involve negotiation among scientists on a myriad of issues – like what counts as quality evidence, how well an epidemiological study represents the broader human population, how to manage apparently conflicting evidence, and more. What this means is that even at the stage of theory building, a process is needed by which communities of scientific experts deliberate about the existing state of scientific knowledge and reach a consensus on whether there is sufficient knowledge to satisfy conditions (1) and (2).

Consensus among scientific experts is crucial for determining the adequacy of a theory for individual practioners. An adequate theory of a disease involves the integration of knowledge from a wide range of scientific inquiries. This means that it's unlikely that a single expert is sufficiently knowledgeable to judge the adequacy of such a theory. Experts from many areas of inquiry are needed to evaluate and determine the potential for knowledge from say, stem cell research to integrate with knowledge from epidemiology and human genomics. Consensus among communities of experts is not just a epistemic requirement. It's an ethical one as well. Consensus among experts is crucial for setting guidelines for how individual researchers should proceed. In the absence of such guidelines, individual researchers are left to make these judgments for themselves when they are neither qualified to judge the adequacy of such diverse evidence nor make normative judgments about the value of germline modification.

In formulating the epistemic conditions that must be met for human GGE to be safe, I've said nothing about whether this intervention is safe for monogenetic or complex diseases. This may strike readers as odd given that the common way of formulating research policy and ethical views for clinical research on human GGE relies on this distinction (Guttinger 2019; Lander et al. 2019; Sarkar forthcoming). In what follows, I argue that a more nuanced view is needed.

5. Conceptualizing Disease – When is it Safe to Edit the Human Germline?

[16] This framework only works for genetic variants present in human populations. Whether it is safe to introduce variants from non-human species is a question that raises its own unique set of epistemic challenges and, thus, requires a separate treatment.

[17] Theoretical knowledge of how a gene edit is likely to influence health and development may (in some cases) be more justified than theoretical knowledge concerning how a novel pharmaceutical will influence humans. This is due to conditions (1) and (2) requiring scientists limit their theories and predictions to genetic determinants actually present in human populations. Consequently, researchers may have access to more evidence as to the outcomes of germline edits than researchers may have for a genuinely novel pharmaceutical drug.

Genetic diseases display different types of causal complexity. Some diseases (i.e., monogenetic diseases) have a simpler causal structure than others. From a causal perspective it may be tempting to conclude that if clinical research on human GGE is safe at all, it is safer to intervene on simple diseases than more complex ones. Here I argue that full appreciation of conditions (1) and (2) should lead us to reframe the way we think about the types of diseases for which it is safe to use human GGE.

For many authors, monogenetic diseases are the only viable type of candidate for human GGE (Guttinger 2019; Lander et al. 2019). Monogenetic diseases, such as Huntington's Disease, are disorders that are hypothesized to have a single causally significant genetic determinant. The *huntingtin* mutation is highly penetrant – most individuals carrying the mutation develop the disease. The presence or absence of most variants provides a high probability – as near a probability of 1 as possible – of producing the occurrence/nonoccurrence of a disease. Inferences to the hypothesis that a disease is monogenetic are often based on genetic homogeneity among all instances of the disease in a population. That is, all individuals with the disease also possess the same (or similar) genetic determinant. For example, all individuals with Huntington's disease possess some variant of the *huntingtin* mutation, and individuals without Huntington's disease lack this mutation. In monogenetic cases, studying genetic variation, health, and biochemical processes in human populations can provide scientists with cases where a genetic determinant of a disease is present in some populations and absent in others. This can help scientists formulate justified theories about what sort of control a single genetic determinant is likely to have over the occurrence/nonoccurrence of a disease.

Monogenetic diseases are rare. More common diseases display a more complex causal structure. Complex diseases are often multicausal – they have multiple – sometimes hundreds! – genetic causal variables. Often, scientists hypothesize that each individual genetic determinant of a complex disease only provides a very small degree of causal control over the occurrence/nonoccurrence of a disease. Complex diseases are also incompletely penetrant. Each distinct instance of the same disease (like some types of cancer, diabetes, coronary artery disease, etc.) are caused by different combinations of causes. As a toy example, for a complex diseases, 25% of patients with coronary artery disease may share one set of genetic determinants, while another 45% of patients share another set of genetic determinants, and the remaining 30% have yet a different set of genetic determinants. The multicausal and incomplete penetrant nature of complex diseases makes their study more challenging. Furthermore, the greater causal complexity dramatically increases the number of biological processes in which each genetic determinant plays a role. Intervening on any genetic determinant of a complex disease is likely to produce changes not just in the targeted disease phenotype, but other phenotypes as well. This often means that treatments for complex diseases, if they work at all, are likely to have unintended consequences.

An adequate research policy for human GGE requires more nuance. Monogenetic diseases can fail to satisfy condition (2); whereas complex diseases can in principle satisfy both. For a monogenetic disease, researchers may have clearly identified the genetic determinant that is causally significant with respect to the occurrence/nonoccurrence of a disease but have failed to identify an alternative sequence that is associated with desirable traits. Some loci have more than one – sometimes many – alternative gene sequences in the human population. Some sequences may have different effects in different genetic and environmental contexts. Determining whether a monogenetic disease satisfies (2) requires us to ask whether the effect of each alternative sequence less desirable than the trait targeted by human GGE. This requires a decision based on the empirical facts the scientific community has gleaned about each sequence variant with the broader social and political significance of the traits in question. It may turn out that the scientific and disability communities decide there is no acceptable alternative sequence to satisfy (2).[18] While some monogenetic diseases may not be good candidates for human GGE, some complex diseases may turn out to satisfy conditions (1) and (2). In the case of complex diseases, there is no single genetic determinant that provides a high degree of control over the occurrence/nonoccurrence of a disease. Nevertheless, there may be some cases where a manageable subset of genetic determinants does provide a high degree of control over a disease phenotype when intervened upon jointly (Ross forthcoming). Just like all three keys – "control," "alt," and "delete" – must be hit at the same time to interrupt a function in IBM PC computers, there may be some (albeit rare) complex diseases with a small number of genes that must be manipulated jointly to control

[18] Sarkar (forthcoming) is sympathetic to the disability community having a say in human GGE policy and Lander et al. (2019) also advocate for public input on the matter. However, both sets of authors advocate for the restriction of human GGE to monogenetic diseases alone independent of what the disability community (or broader public) might have to say.

the occurrence/nonoccurrence of a disease.[19] What this shows is that condition (1) does not require monogeneticity. A further consideration about human GGE of complex diseases has to do with how much control counts as a "high degree" of control. While in the monogenetic case, intervention on the causally significant gene provides nearly complete control over the occurrence/nonoccurrence of a disease. It is likely that intervention on the set of causally significant genes in complex cases will provide a degree of control that is less than complete. For example, intervention on the set of causally significant genes may only decrease the chances of a future individual developing a disorder by, say, 60%. Such a scenario may yet be permissible. Depending on the severity of a disorder and the availability of alternative treatments, many non-genetic medical interventions are morally acceptable to administer even when they may fall short of reducing an individual's chances of contracting the disorder to 0. From the perspective of clinical trials, human GGE may not be different. This discussion reveals that condition (1) does not require complete control over the occurrence/nonoccurrence of a disease to be met. What about the issue of incomplete penetrance? This is not necessarily an insoluble challenge. So long as a significant proportion of all instances of a disease in a population share a common set of genes, this will allow researchers to make inferences about how the presence/absence of the common set of genes associates with health outcomes. There may be a case where 30% of a population has the equivalent of the PC "ctrl-alt-delete" function, while another 25% have the Apple equivalent ("option-command-esc"). What this shows is that condition (1) doesn't require that all instances of a disease in a population share the same set of causally significant genes, only that some significant proportion do. Finally, can complex diseases satisfy condition (2)? Yes, in principle. Satisfying condition (2) requires scientific and disability communities judge the possible outcomes associated with each genomic intervention to be more desirable than the targeted trait.

The framework offered here is flexible and can accommodate the use of human GGE for a wide variety of medical conditions in various social and political contexts. Conditions (1) and (2) also apply to cases like the CCR5 gene for increasing HIV resistance. Lander et al. (2019) have explicitly advocated against the use of human GGE to prevent HIV. Not only does this assertion ignore the system of oppression that HIV patients experience in China, but it denies the public any opportunity to decide the value of human GGE in this case. Nevertheless, Jiankui He's experiments failed to meet the conditions defended in this framework. While the presence/absence of the CCR5 gene does have a high degree of control over one's risk of contracting HIV (condition (1)), there is disagreement as to whether the CCR5-Δ32 variant is likely to have unintended consequences. For example, the CCR5-Δ32 sequence may put "Lulu" and "Nana" at greater risk of having a severe reaction to West Nile virus (Glass et al. 2006). Is susceptibility to a severe reaction to West Nile infection a less desirable trait than being at greater risk of contracting HIV in a society that severely stigmatizes and marginalizes HIV positive individuals? As of now, there is no scientific consensus on what the likely health and developmental outcomes of the CCR5-Δ32 variant are across a broad range of genetic and environmental conditions. Furthermore, no members of the public were given a chance to form a normative judgment about the value of this particular gene edit. He's experiments were unethical on these grounds as well.

The point of this discussion is to destabilize the monogenetic/complex disease distinction that has shaped recent policy proposals and reorient the discussion towards what matters. What this discussion shows is that framing human GGE policy in terms of the monogenetic/complex disease distinction is not adequate. We can have sufficient knowledge about whether a disease is either monogenetic or complex, but still not satisfy the conditions necessary for safe and ethical use of this technique. Indeed, there is little evidence that He was much concerned with condition (2). Kirksey (2020) illustrates that the primary concern on He's mind in the planning and execution of his experiments was off-target effects. If true, this suggests that human GGE policy needs to explicitly require that condition (2) be met by scientific communities and representatives of the public. In the absence of such a policy, it is left up to individual scientists to evaluate the epistemic, social and political concerns of human GGE; a burden that may be too demanding for individual scientists to manage responsibly.

[19] Even though complex diseases may be candidates for human germline gene editing, there are pragmatic reasons to limit the number of genome edits to as few as possible. It is challenging enough to successfully introduce a single edit to germline cells so that the change is inherited by all cells of the organism. Performing multiple edits at this stage risks mosaic effects – an effect where only some cell lineages carry a desired edit and others don't – as well as premature cell death and chromosomal rearrangement (Chari et al. 2017).

6. Conclusion

The scientific considerations that need to be addressed when determining whether a disease is a good candidate for human GGE can't be met without making value judgments about the desirability of human traits. This has significant implications for how human GGE policy should be formulated. I've argued that scientists alone shouldn't be allowed to make these value judgments. Instead, members from the public – notably, members from the disability community – should inform decisions about which traits are worth targeting with human GGE. Yet, establishing that representatives of the public should have some say on this issue is only one (albeit important) step. The further challenge is deciding how to bring the public into this discussion. I argue that an iterative, deliberative process is what's most appropriate in this case given prevailing disagreement on the value of human GGE among key communities. Public input shouldn't be just limited to whether or not human GGE should be permitted and for what conditions. For in addressing the necessary epistemic considerations relevant for improving the safety of human GGE, value judgments about the desirability of human traits must be made along the way. So, I've built a role for the public to inform such value judgments into the regulatory framework for human GGE. I've argued that what's relevant for determining which disorders can be candidates for human GGE, the following conditions must be met:

1. The disease in question must have (among its set of causes) genes that have a high degree of causal control with respect to the disease
2. Alternative nucleic acid sequences variants that are likely to produce traits deemed desirable must be identified

Conditions (1) and (2) are formulated to accommodate both the genetic and social, political, and ethical complexity that characterizes the fraught issue of human germline gene editing. Condition (2) is especially crucial for how we formulate human GGE policy. The case of Jiankui He illustrates that there is no guarantee individual scientists will properly manage the problem of unintended consequences when planning and executing their experiments. When is it safe to edit the human germline? This is not something any individual should be able to decide. It's a matter for collective consensus on both epistemic and societal matters.

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