Human Germline Genetic Engineering: The Ethical Imperative in Due Time

Emma Sheehan

Abstract: *As human beings race to replace science with better science, technologies such as IVF and PGD, which allow parents to selectively choose an embryo with the best chance of being healthy, are quickly being superseded by technology that can potentially cure embryos from inheritable disease altogether: human germline genetic engineering (HGGE). The benefits of curing disease are indubitable; however, the risks associated with doing so must be considered before proceeding with experimentation. Recent announcements regarding the clinical application of HGGE by He Jiankui in 2018 sparked a great controversy within the genetic engineering community, and the future of medicine will be shaped by HGGE research. Weighing issues ranging from physical and mental impacts on an individual, to impacts on future recipients' offspring, to concerns on a societal level, "Human Germline Genetic Engineering: The Ethical Imperative in Due Time" offers insight for medical researchers looking to begin experimentation for HGGE. Ultimately, this paper will demonstrate the need for a moratorium on the clinical application of human germline genetic engineering until there is a clear and thorough ethical and practical framework in place for future clinical applications of HGGE.*

Keywords: genome modification, medical intervention, medical ethics, clinical application, legislation

Introduction

When Aldous Huxley published his classic *Brave New World* in 1932, there was no way he could have known that the embryo factories he imagined would be nearing possibility within the next century. This classroom staple was written as a dystopian novel, one that forces us to grapple with the ethics of creating ideal humans and the boundaries of control and freedom in the natural world. Concerningly, Huxley's dystopia is approaching quickly. Although today's technology is not quite *Brave New World*-level, geneticists and bioinformaticians are

now able to read, analyze, and directly edit our genomes. CRISPR/Cas9 is one of the leading genome-editing technologies, but until around 2016 to 2017, CRISPR's use and overall genome modification research had been limited by scientists' unspoken rule: clinical application of gene editing techniques should be limited to somatic (body) and adult stem cells. The consensus within the scientific community was that they should not proceed with edits in germline (embryonic) stem cells, as those genomes would be passed down to the next generation (heritable changes) and could potentially result in grave consequences (Stein, 2013). With recent events and technological developments, the previous consensus within the scientific community has transformed into a larger controversy. As scientists ask whether human germline genetic engineering (HGGE) is safe to continue practicing, or whether genetic engineering of embryos has too many dangerous, unintended consequences (such as further mutation to the human genome or complete disarray of biomedical ethics), a consensus must be regained. Since the development and utilization of new technology will directly affect the next generation of children across disciplines, time is of the essence. Ultimately, this paper will demonstrate the need for a moratorium on the clinical use of HGGE until there is a clear and thorough ethical framework in place for HGGE research to follow. Importantly, a moratorium on clinical applications should not be considered a moratorium on all clinical research. Research is what will allow the possibility of future applications of the technology, but in order to arrive at that reality, the scientific and ethical community must reach a consensus about the regulations by which the technology will need to abide.

Scientific precedent on genetic modification research had been set by the 1975 Asilomar Conference, which established strict guidelines on recombinant DNA research. Those guidelines took three years to relax, and the relaxed versions are still present in the current National Institute of Health (NIH) guidelines (Hanna, 1991). Clustered regularly interspaced short palindromic repeats (CRISPR), one of the leading recombinant DNA technologies, was invented in 1987 and has since been ac-

cepted for clinical use on somatic, or body, cells. As technology has developed over the last fifty years, scientists have held the responsibility of self-regulation. Although the scientific community is confident with CRISPR for somatic cells, the use of CRISPR on germline cells is one of the many topics that have required further discussion. Precedent on CRISPR's applications in humans specifically was outlined in 2015 by researchers from UC Berkley, Harvard Medical School, and others, as well as some scientists who had been present at the Asilomar Conference. In summary, all clinical applications of HGGE are irresponsible and strongly discouraged across the globe, and the scientific community needs to highly consider the ethical implications of the usage of the technology (Greely, 2019). This recommendation should have been an obvious line for scientists to avoid crossing, and for many, it was. Unfortunately, some scientists pushed the boundaries and ignored the calls for a pause on HGGE.

When Chinese researchers announced the birth of their genetically modified twins, the "bright line" that scientists had established to halt germline genome editing became blurred. With recommendations from the scientific community in place but no legal limits on HGGE, He Jiankui was able to forge a path to engineer the first humans to be born with genetically modified DNA (Cyranoski, 2019). After He announced his experiment during the 2018 International Summit on Human Genome Editing, Harvard and Massachusetts Institute of Technology CRISPR researcher Feng Zhang "[called] for a moratorium on implanting edited embryos in humans" (Bergman, 2019). Following the summit, backlash from the scientific community largely advocated for the reinstatement of the "bright line" (Cohen, 2018). While the ethicality of genetic engineering has been a topic of controversy in the past, clinical ethicists were unaware of how soon they would be confronted with the reality of HGGE. Therefore, there is not yet any established ethical framework that medical professionals could follow to make decisions to treat genetic conditions with HGGE.

Background

Human germline genetic engineering is a complex topic, so some key terms must be defined. As this paper is dedicated to the ethical side of the debate, there will not be a deep dive into the inner workings of the technologies used, but it is essential to have a generic understanding of the scientific side. Firstly, germline engineering refers to edits made to human DNA while an embryo is in its early developmental stage. These edits are made to germline stem cells, which are cells that have not yet specialized (i.e., become a specific type of cell such as skin, bone, or other). When this germline engineering occurs, edits become permanent in the DNA of the embryo— therefore, when that embryo grows into an adult who has children of their own, the edits will be passed down to their children, and their children's children, and so forth. It is also important to understand that CRISPR/Cas9 is a technology that allows scientists to directly cut out and replace DNA, allowing for very specific alterations to be made to the genome. A genome is the entire genetic makeup of an individual, but even small changes to an individual's genome can have large consequences.

The role of ethics in HGGE is an important topic to comprehend as well. The main purpose of HGGE technology development is to be able to prevent genetic diseases from occurring in human offspring. This means that as a medical intervention, HGGE would fall under the domain of medical ethics. Medical researchers in the United States must submit their proposals to institutional review boards (IRBs), which all operate following ethical research guidelines. One of the primary references for these IRBs is the *Belmont Report*. This report was put together following the well-known Tuskegee study and was influenced heavily by the Nuremberg Code, which was established after World War II. The *Belmont Report* established five ethical parameters: (1) informed consent, (2) respect for persons, (3) beneficence, (4) privacy and confidentiality, and (5) justice (National Commission, 1978). Medical professionals are also bound to the Hippocratic oath, which enforces the need to balance treatment of illnesses and harm to persons. Ethical considerations, then,

are a determining factor of the continuation of HGGE research, as the use of HGGE technology becomes plausible.

Discussion

Proponents of HGGE believe that there are major benefits to editing the human germline, utilizing Julian Savulescu's principle of Procreative Beneficence to guide their decisions. Savulescu (2007) argues that parents have an obligation to prevent disease or disability in their children, as they "should not allow harm to occur when we can easily and foreseeably avoid it." In his rebuttal to objecting scientists, Savulescu defends his principle; he states that Procreative Beneficence inherently considers the objections raised. He maintains that genetic engineering is not "playing God," but in fact, it is quite the opposite: by selecting favorable traits, humans are merely "trying to improve the odds of doing well in an uncertain world of difficulty, threat and misfortune" (Savulescu, 2007). Furthermore, he goes on to argue that because preimplantation genetic diagnosis (PGD) for in-vitro fertilization treatment (IVF) already allows for the selection of favorable traits, there is already a foundation on which scientists can decide which embryos would reasonably qualify for HGGE treatment (Savulescu, 2007). Savulescu summarizes, in his final remarks, that he is not arguing that all parents must genetically select for favorable traits in their children, but it is instead the responsibility of science to provide the option for "parents [to] be free to select" the use of HGGE, or not, with informed consent (Savulescu, 2007). In Savulescu's explanation, he mentions that PGD can identify embryonic mutation and disease, and IVF selects the embryo least likely to have those diseases. In the case of HGGE, those scientists in favor of the use of the technology argue that instead of choosing the embryo with the best likelihood of having favorable traits, parents will be obliged to use HGGE to create the best possible life for their offspring by completely preventing unfavorable traits in their genome.

Procreative Beneficence, in the case of HGGE, would mean that parents are obligated to choose the genes that will give

their child the best opportunities in life. Mark Sauer, one of the leading US scientists pursuing mitochondrial gene therapy, proclaimed his team's quest to use HGGE to prevent disease to be "noble" (Sauer, as cited in Stein, 2013). Specifically, Sauer drew evidence from the case of Lori Martin, a Houston mom who was told she should not have any more children after her firstborn son was diagnosed with Leigh syndrome (Sauer, as cited in Stein, 2013). This genetic condition is linked to mitochondrial DNA, which can only be passed down to offspring by their mother. In a few countries, mitochondrial replacement therapy (MRT) is offered, although MRT is highly unregulated and scientifically unproven (Cyranoski, 2019). Had they been legal technologies in the United States, MRT and germline CRISPR editing would both have given Martin a chance to have unafflicted children. Martin is not alone in this conundrum; many other families across the globe are in a similar position, unfortunately faced with the decision to abort or to stop having children due to the risks associated with certain genetic disorders that cannot be prevented with current legal technology. As Sauer's HGGE technology makes its way to the United States Food and Drug Administration (FDA) for a decision to be considered, we are approaching the legalization of heritable genetic modifications. I contend that this legalization should only happen once ample research has been done to ensure mother and embryo safety. Until then, science needs to take a step back and consider if all sides of this technology have been explored.

While the legality of developing HGGE technologies is under consideration, the ethicality of HGGE must play a distinct role in any legal decisions made. On an ethical basis, Dartmouth College ethics professor Ronald Green argues in favor of germline editing, highlighting Britain's Human Fertilization and Embryology Authority (HFEA) decision to let couples screen and select in favor of embryos. This HFEA decision, Green argues, was made even before He Jiankui's experiment crossed the "bright line," and it even probed the question of medical versus cosmetic genetics (Green, 2008). Green uses dyslexia as an example of a "gray area" disorder, stating that "geneticists

have already identified some of the mutations that contribute to this disorder. Why should a child struggle with reading difficulties when we could alter the genes responsible for the problem?" (Green, 2008). Once again, the principle of Procreative Beneficence comes into play, as clinicians and parents would be forced to weigh which option will truly give a child a better life. As the HFEA was able to come to a conclusive decision about embryo screening, Green argues that there are already ethical frameworks that can determine acceptable uses for germline engineering. Therefore, we should advance to the next step to allow HGGE to create better lives for our children (Green, 2008). Both Sauer and Green have reasonable perspectives; were we to allow the use of this new technology, it would be possible to prevent any individual from being born disadvantaged with struggles due to a genetic disorder. However, Green's claim that an ethical framework has already been laid down neglects the fact that HGGE would create heritable changes in the genome, and his view is not reflective of the view of many in the scientific community. Many voices have called for a moratorium on the clinical application of HGGE for the time being; among these voices, the NIH, an international group of geneticists and researchers from over seven countries; the European Society of Human Genetics (ESHG); along with the European Society of Human Reproduction and Embryology (ESHRE) have all expressed support for a temporary moratorium on HGGE (Collins, 2019; Lander et al., 2019; *Response to*, 2019). The clashing opinions between opposite sides of the scientific community keep the controversial flame burning, as Green receives pushback from even those close to him.

Ronald Green's own medical students responded to a survey which indicated that "80% of [his students believe] that society should not move in the direction of human genetic engineering," a stunningly high proportion that reflects the views of much of the public (Pray, 2008). To have such a high percentage of his students feel wary of the developing technologies, we must give weight to the fact that there are genuine concerns regarding the use of HGGE. Many members of the sci-

entific community echo that feeling of concern, citing various reasons for withholding the clinical use of HGGE, including, but not limited to intentional misuse of the technology, current unspecific ethical guidelines, the plausibility of "professional self-regulation," and positive and negative precautionary principles (Kleiderman et al., 2019; Gyngell et al., 2019). These are valid concerns, but they should be solvable with careful consideration and ample time for preparation. To come to a conclusion, there must be a moratorium put in place to allow ethical and legal considerations to be addressed, as well as controlled research before HGGE is clinically applied.

Opponents of the clinical use of HGGE largely agree that the technology has great potential; however, professionals argue about the ambiguity within HGGE usage guidelines, with those in opposition declaring that the ambiguity must be resolved for the technology to become legalized. Kleiderman et al. (2019) state that the criteria for determining whether a genetic illness is deserving of genetic engineering are "vague and poorly defined, rendering its application challenging and decision making subjective and arbitrary." The ability to determine which embryos are eligible for HGGE will need to be clearly defined before clinical use can be reinstated to avoid crossing into eugenic territory. Kleiderman et al. (2019) cite the Quebecois Commission on Ethics in Science and Technology's statement that HGGE "if proven to be safe and effective, should be limited to 'very serious, high penetrance diseases, where there are no other reproductive or therapeutic options available'" as an example of such nonspecific guidelines (Kleiderman et al., 2019). The authors contend that "serious" is not specific enough to prevent unethical treatment or to invoke ethical treatment of genetic disease, as there is no consensus within the medical genetics field as to what constitutes "serious versus non-serious genetic diseases." In fact, there is overlap in geneticists' beliefs about the classification of diseases (Kleiderman et al., 2019). For a moratorium to be lifted, the ambiguous definitions and guidelines must be addressed. One article that calls for a moratorium proposes that during a moratorium period, an international

panel should be established, with "two distinct subpanels - one consisting mostly of biomedical specialists for the technical, scientific and medical considerations, and the other comprised mostly of those focusing on societal, ethical and moral issues" (Lander et al., 2019). The authors reiterate the importance of transparency; for governments, hospitals, clinics, researchers, and clinical providers alike, transparency and ethicality will allow the future of HGGE to progress responsibly (Lander et al., 2019). Similarly, Kleiderman et al. (2019) suggest two approaches to addressing this concern: "(1) the creation of lists of serious genetic diseases and (2) the development of criteria that guide case-by-case determinations of what is considered 'serious.'" Due to the complex nature of genetic diseases, the authors believe that the latter approach will prove to be more valuable in the establishment of ethical guidelines for HGGE, which will in turn "foster an equitable and inclusive approach to [HGGE] while ruling out its most contentious applications" (Kleiderman et al., 2019). Indeed, having the ability to address genetic concerns on a case-by-case basis according to ethical criteria that prevent the misuse of HGGE would seem to be the most viable plan for implementing HGGE.

Even if genetic diseases can be classified more specifically and criteria for evaluating diseases developed, the concern that HGGE leads to changes in inheritable traits is an ethical issue that is not yet "fully iron[ed] out" (Yeager, 2021). Austen Yeager, a pediatric resident at Oregon Health and Science University, argues that "careful consideration and clinical trial design" can remedy the issue of multigenerational follow-up of HGGE experimentation but concedes that such clinical trials will be difficult to design until clinical research ethicists have dedicated time and effort to smoothing over the concern of the generations subsequent to the F1 generation (Yeager, 2021). Her viewpoint reflects that of Lander et al., with a call to hold off on clinical application of HGGE until thorough research of the consequences and outcomes of HGGE are addressed via controlled studies during a moratorium on clinical application (2019). Instead of rushing into the use of HGGE because the theory is understood

and the technology is available, geneticists should heed to a temporary moratorium as the long-term consequences are researched thoroughly.

Various other researchers have come to similar conclusions, voicing their concerns regarding possible risks affecting future generations. In a special edition article of *Bioethics*, researchers Gyngell et al. (2019) state that "[i]t might be thought that the risks entailed by [HGGE] are incalculably greater than the potential benefits because these risks, if realized, affect an indefinite number of future generations." The researchers use the precautionary principle to guide ethical decision-making regarding human germline engineering, explaining that there are two types of precautionary principles:

> **Negative precautionary principle**. When an activity may cause harm, we should not abstain from taking precautionary action because we lack certainty that the activity in question would cause harm.
>
> **Positive precautionary principle**. We should take (some form of) precautionary action against activities that may cause (some kinds of) harm. (Gyngell et al., 2019)

After analyzing their data, Gyngell et al. concluded that the negative precautionary principle does not provide helpful guidance for the current controversy within HGGE; instead, they conclude that "plausible versions of [the positive precautionary principle] would endorse [HGGE] in at least some contexts – in particular, contexts where [HGGE] could be used to correct otherwise catastrophic genetic mutations and/or to promote the long-term robustness of human populations" (2019). While the data showed the potential positive outcomes of HGGE, their study also stated that HGGE should not be put into clinical use until precautionary ethical guidelines are further established, reinforcing the need for a pause on the clinical application of HGGE until the regulation of the technology has advanced (Gyngell et al., 2019).

There is a clear call for a suspension of the clinical usage of HGGE coming from those bodies concerned about not only the readiness of HGGE technologies but the readiness of society to

apply HGGE ethically. In response to the Lander et al. call for a moratorium, which had over eighteen signatories from seven countries, the ESHG made their opinion public and very clear: the ESHG "supports the call for a global moratorium on all clinical uses of human germline editing - in sperm, eggs or embryos - that will lead to a pregnancy and/or to the creation of genetically modified children," and they urge those bodies involved in potential HGGE to invoke complete transparency (*Response to*, 2019). Furthermore, the American Society of Human Genetics (ASHG) warns against present-day HGGE usage, separating the potential ethical consequences into two broad categories: "(1) those arising from its potential failure and (2) those arising from its success" (Ormond et al., 2017). Consequences of failed HGGE experimentation exist because "the magnitude of the potential risks of off-target or unintended consequences are yet to be determined" (Ormond et al., 2017). When CRISPR/Cas9 technology edits one gene, it affects an individual's entire genetic makeup. While we can now identify the whole human genome, many traits are polygenic or have proteins that can become edited off-target, which is a consequence that HGGE research has yet to explore in depth. The latter category, repercussions of HGGE experimentation, include such societal concerns raised by obstetric-gynecologist Paul Burcher (Burcher, 2013). Burcher voiced his concerns in the *Contemporary OB/GYN* journal, stating: "the intentional manipulation of these personal characteristics […] is the story that I find more ethically disturbing than the quest to treat [disease]." Burcher's (2013) concern centers on societal considerations rather than individualistic ones; the "intentional manipulation of personal characteristics" would allow for misuse of the technology which could lead to "designer babies." In other words, HGGE is capable of enabling quiet eugenics. The ASHG acknowledged Burcher's concerns in their research, stating that some of the biggest ethical concerns with HGGE revolve around the deliberate selection of genes, as it could send "a message about the 'fitness' of such traits or conditions, thereby reflecting on the worth and value of people who have that trait in our society" (Ormond et al., 2017).

The ASHG's position reflected these concerns as they advised to hold off on "germline gene editing that culminates in human pregnancy" until these ethical issues have been resolved by society— yet another cry for a, at least temporary, moratorium on HGGE application (Ormond et al., 2017).

While the 2019 ESHG call for a moratorium occurred in response to He Jiankui's unethical experiment, the ASHG position statement was released in 2017, and Burcher voiced his concerns in 2013. Although the issues with the clinical application of HGGE had been voiced prior to He's 2018 experiment, he applied the technology regardless. His experiment just exacerbated the aforementioned concerns. Sheila Jasanoff, director of the Science, Technology, and Society program at Harvard Kennedy School, was quoted in the *Harvard Gazette* stating that He was not trying to cure sick babies; instead, He experimented on the embryos because the "father [of the embryos] had [AIDS] and agreed to the intervention because he wanted to keep his children from contracting AIDS" (Jasanoff, 2018, as cited in Bergman, 2019). The Lander et al. article further explains that the gene He used to decrease the risk of AIDS had unintended effects, such as increased risk for West Nile virus and influenza (2019). He's experiment demonstrated to the scientific community how easy it is to perform HGGE without ethical regard. Since He's embryos were modified to prevent an illness later in life, but not to cure a life-threatening disease the embryo was suffering from, it created a slippery slope for stigmatized traits to become edited. Burcher's concern that "designer babies" would become a reality drew near with He's experiment, and it is the responsibility of ethicists to establish guidelines to protect further experimentation from sliding down that slippery slope from treatment to enhancement to eugenics.

Final Remarks

Ethics, in simple terms, is the standards of right and wrong. To come to an ethical decision regarding HGGE, ethicists will need to lay down a set of guidelines that allow the moral "right," in this case, the treatment of illnesses, to outweigh the moral

"wrong," or harm to persons. In the case of HGGE, there are controversial issues within at least three of the five "basic ethical principles" of the 1978 *Belmont Report* research guidelines (National Commission, 1978).

Informed Consent

Legally, minors cannot give consent, but their parents are allowed to give consent on their behalf. Therefore, the F1 generation (the original genetically modified offspring) has given consent via their parent. The F1 generation's consent by proxy of their parent is possible, but genetic modification of the germline genome creates inheritable traits, which will be passed down from the F1 to F2 and further generations. It is imperative ethicists come to a conclusion regarding consent given by the F2 and future generations.

Respect for Persons

According to the National Commission's *Belmont Report* (1978), respect for persons requires that "[research] subjects enter into the research voluntarily and with adequate information." In the case of HGGE, the technology is complicated, our genomes are complicated, and conclusive data about the risks can only be narrowed down to a ballpark. If and when HGGE clinical trials are ready to move into the human experimental stage, it will be necessary for medical researchers and doctors to find the best way to explain genetic probabilities and complications to patients of different backgrounds. Furthermore, women's health in HGGE should be considered carefully in the ethical deliberations. The *AMA Journal of Ethics* identifies that pregnant women's autonomy may have further "ethical and clinical implications" than the average autonomous person, and because HGGE is centered around pregnancy, this aspect is important to consider when creating ethical research guidelines for HGGE (Farrell et al., 2019).

Beneficence

The Hippocratic oath's famous phrasing "do no harm" is extended to research through the principle of beneficence. Medi-

cal researchers should not be allowed to perform HGGE until the ethical concerns of HGGE, including both the ethical consequences of success and failure, have been identified and reconciled. It is especially important to note that ethical guidelines should not only focus on the physical health of a subject and its offspring but on the consequences of HGGE to the mental state of an offspring recipient of HGGE. Further, the American Medical Association notes that "key discussions about women's health and well-being as patients and subjects are lacking" (Farrell et al., 2019). Therefore, ethics and research committees must design guidelines for keeping the mother of an embryo safe, not just the embryo itself, before concluding that no harm will be done to recipients of HGGE.

After careful consideration of research guidelines, the current state of HGGE technology, and the global inconsistencies and uncertainties surrounding the ethics of genetic engineering, the clear call from scientists across the world for a moratorium is being heard. It is vital that we suspend the clinical use of HGGE to allow medical ethicists to begin working on a set of clear, specific guidelines for HGGE, as medical ethics should undergird HGGE legislation (Dunn & Hope, 2018). The established guidelines should take into consideration all the aforementioned factors and should be acceptable for international standardization. Only once there are guidelines in place and the relevant institutions have shown their commitment to transparency and ethicality can a moratorium be lifted to allow the clinical use of HGGE.

Note: This essay was originally composed in Dr. David Reamer's AWR 201 class and revised for publication under the guidance of Dr. Jeremy Lakoff.

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