The Bioethics of CRISPR-cas9 and Potential Solutions

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

When Jennifer Doudna, Emmanuelle Charpentier, and their team first published their landmark findings on their work with CRISPR-cas9 in *Science* in June 2012, the world of science stood in shock. The pair and their team had harnessed the power of prokaryotic DNA sequences and proteins to essentially create a pair of "genetic scissors," capable of cutting out specific DNA sequences, predetermined by the user. After this initial discovery, more researchers began to expand upon Doudna and Charpentier's work, finding out more ways to apply this newfound technology. Fast forwarding almost a decade later to the present-day, CRISPR seem widespread usage in the agricultural industry, creating genetically modified crops that are resistant to the elements, as well as enhancing their nutritional value. Additionally, CRISPR has been applied to other industries, such as in biofuels where it is used to modify yeast. Furthermore, use of CRISPR in human therapeutics, specifically with genetic disorders, has reached experimental stages in recent years. For example, in 2019, treatment of sickle cell disease in a 34-year-old woman began, setting the stage for possibly one of the most anticipated experiments of the century. Furthermore, mice studies are being conducted into potentially curing HIV, which is the virus that causes AIDS. All these prospects in human therapy and in other industries point to a bright future for CRISPR.

But what about uses of CRISPR for non-therapeutic purposes? It has been theorized that CRISPR, in addition to the multitude of therapeutic benefits that it offers, can also be used to genetically modify parts of the genome that affect the phenotype of an individual. That is, with CRISPR, it is possible to edit the traits that define an individual. This ranges from characteristics as simple as hair color, all the way to something more complex as intelligence. The use of genetic engineering for recreational purposes has been a significant topic of controversy since the idea of

using it in such a way was conceived. This debate was especially popularized by the movie *Gattaca*, which was a 1997 movie centered around eugenics and genetic discrimination.

The debate becomes even further complicated when germline editing is introduced into the problem frame. Germline editing involves editing the genetic data of germ cells, which are the primitive cells that dissociate into somatic cells, which are what most of the body is composed of. Genetic data between sexually reproducing organisms is carried through germ cells. Thus, any editing done to the germ cells will affect the rest of the germline (i.e. any offspring conceived by the organism). Currently, genetic editing of human embryos is banned in the United States, which was instated in 2019. However, the debate still rages on in this controversial practice.

The premise of this paper is to explore the bioethical concerns surrounding the usage of CRISPR-cas9 in human gene editing for both therapeutic and recreational purposes. Some of the primary bioethical concerns that have arisen are the lack of individuality caused by engineering, abuses by global governments for military purposes, and an increase in social disparity. This paper will attempt to view the use of regulating genetic engineering through the lens of utilitarianism, which is an ethical framework that centers around maximizing the happiness for given individuals for a certain action. By viewing the use of gene editing through a utilitarian perspective, it is possible to fully analyze the ethics of the practice and come to part of a conclusion on the issue.

Research Methods

Research for this paper will be conducted in rigorous fashion. Information for the technical background was acquired through studies conducted in high-level peer-reviewed journals. Information for the ethical analysis of this technology will be drawn from the perspectives of researchers in bioethics journals. Additionally, the current policies of various governing bodies will be compared to reach an overall extensive understanding of public perspectives. Together this

will allow for a conclusion to be reached regarding how to regulate this novel and fast-approaching technology.

Technical Background

Cures for genetic diseases have eluded scientists for many centuries, even to this day. While it is possible to treat symptoms of these diseases and ameliorate their effects, completely curing the disease itself had proven to be a seemingly impossible task. However, the discovery of CRISPR-cas9 by Charpentier and Doudna in 2012 as a gene editing tool changed the outlook for treating these genetic diseases (Doudna & Charpentier, 2014). An explosion of research into treating a wide variety of genetic diseases arose as a result of their landmark paper, paving the way for therapeutics previously thought to be only unreachable.

CRISPR, short for clustered regularly short palindromic repeats, are significant components of adaptive immune systems for bacteria and other prokaryotic (i.e. single-celled and lacking a nucleus) organisms. Cas-9 (CRISPR-associated protein 9) is an enzyme that cleaves specific strands of DNA which are defined by the CRISPR molecule(Gupta et al., 2019). Together, the two form a complex, yet easy-to-use technology which allows for any sort of gene editing that is defined by the sequences in the CRISPR molecule.

As stated previously, CRISPR-cas9 as a therapeutic technology holds an inexhaustible amount of potential in medicine. For example, a study in 2016 showed that CRISPR-cas9 has the potential to ameliorate the effects of hemophilia, a genetic disease which reduces the ability for blood to clot in mice models (Fogleman, Santana, Bishop, Miller, & Capco, 2016). A more recent study in 2019 saw the restoration of high-sensitivity vision to previously blind mice through mediated genomic editing by CRISPR-cas9 (Berry et al., 2019). In actual humans, the gene-editing tool has not seen as much use, but the cases in which did see use have received high-profile

attention. The most recent and prominent study to date is that on Victoria Gray, who received gene editing treatment through CRISPR-cas9 for her sickle cell anemia, a disease in which some red blood cells have an altered (sickle) shape, resulting in early cell death and causing significant pain. Her treatment began in 2019 and currently does not show any signs of waning ("Experimental CRISPR Treatment For Sickle Cell Disease Appears Effective : Shots - Health News : NPR," n.d.).

Summary of Current Perspectives

A considerable number of bioethicists have argued towards a pause on the use of making germline modifications in patients. In response to the infamous and controversial case of He Jiankui's attempt to prevent a group of baby twins from contracting HIV during birth, the bioethicist Henry Greely echoes the scientific community's consensus that human germline editing should be reserved for cases in which there is no other alternative. In the case of Dr. Jiankui's pair of twins, it is possible to prevent HIV infection and suppress viral disease without the need for the genetic mutation that was introduced into the yet unborn children (Scully, 2021). This perspective is also shared with Dr. Robert Truog, director of the Center for Bioethics at Harvard Medical School, who also sees the debate as a consensus on the oversight of science as an institution.

In the case of Krystal Tsosie, who is a geneticist and bioethicist, she argues that genetic diseases are currently being looked at purely through a lens of DNA modifications and not holistically including factors such as gene-environment interactions and another socioeconomic factors. She cites alcoholism in Native Americans as an example of this, wherein the genetic factors that play into predisposition of this disease are a result of a long history of social and cultural factors that have been imposed upon this group ("An Indigenous Bioethicist on CRISPR and Decolonizing DNA," n.d.).

Additionally, leaders with religious backgrounds have varying perspectives on this novel technology. In the case of Dr. Francis Collins, a previous director of the National Institutes of Health and a devout Christian, he believes that great care and humility must be taken prior to taking the step to start manipulating the human species. In contrast, Ronald Cole-Turner, a theologian and ethicist, believes that these concerns are unfounded and that idea that the human genome is sacred with respect to God's other creations is not legitimate ("Gene-Editing, Religion and One Scientist's Quest to Reconcile the Two," 2016).

Current Policies

Many different countries around the world have taken preemptive steps to address the possibility of using CRISPR-cas9 to edit the human germline. In the case of the United States, a ban was restored on any clinical trial "in which a human embryo is intentionally created or modified to include a heritable genetic modification." However, the issue did not seem to be addressed comprehensively by both parties as it seemed to only appear during debates about appropriations (Liu, 2020). Prior to the restoration of this ban, the Food and Drug Administration had placed a soft moratorium on human germline editing by rejecting any clinical trial proposals for germline alterations.

South Korea currently echoes a similar policy on germline editing to the United States, although it is more defined than its western counterpart through its Bioethics and Safety Act, last amended in 2014. Although gene therapy itself is not directly regulated by the Bioethics Act, how its regulation could be handled can vary depending on the interpretation of the text. However, this does lead to confusion for various researchers about how their work should be classified. Definitively, though, there is a complete ban on "gene therapy…to an embryo, ovum, sperm, or fetus." (Kim, 2017).

At the Oviedo Convention of 1997, the Council of Europe imposed a ban on any genetic modification whose aim was "to introduce any modification in the genome of any descendants," referring to germline editing. However, other genetic modifications are allowed in the case of "preventative, diagnostic or therapeutic purposes." A majority of the Council's member states have signed and ratified the Convention, although most notably, the United Kingdom, Russia, and Germany have not. However, the United Kingdom and Germany share similar legislation as that of the Council of Europe with regards to a blanket ban on germline editing, while Russia supports the World Health Organization's opinion that germline editing should not be conducted, though they do not have any legislation that directly regulates the practice of gene editing.

Discussion

The use of CRISPR-cas9 in both therapeutic and non-therapeutic settings has clearly sparked a major discussion across multiple institutions, whether it be in legislative governments around the world or overarching scientific bodies. Furthermore, the technology itself is bound to have an effect on various cultures and ideologies. In order to understand its potential impact on these entities and how to approach crafting any sort of potential solutions to address the ethical issues that have arose from CRISPR-cas9, we look towards the basic, yet simple theory of utilitarianism. Specifically, we will be looking at this topic through the lens of classical utilitarianism, which is the first holistic perspective of utilitarianism perpetrated by Jeremy Bentham and John Stuart Mill. Later formulations of this theory, such as act and rule utilitarianism, will not be used in this analysis, although it still can hold reasonable application for this topic as well.

Briefly, the concept of classical utilitarianism revolves around the basic idea that the morally correct option is that which produces the greatest good, or rather the greatest amount of

pleasure. This simplistic, yet far-reaching perspective of ethics is key to understanding how CRISPR-cas9 can potentially impact our society.

From a purely medical perspective, CRISPR-cas9 at face value appears to bring nothing but pleasure. The benefits of CRISPR-cas9 in a clinical setting are seemingly limitless, given enough time for safe and ethical research to be conducted. The ability to correct genetic anomalies and mutations holds a wide variety of applications for therapeutics, particularly towards "incurable" genetic diseases. One of these diseases is sickle-cell disease, which was previously mentioned with regards to Victoria Gray, the patient who had received gene therapy for it ("Experimental CRISPR Treatment For Sickle Cell Disease Appears Effective : Shots - Health News : NPR," n.d.), but this list also includes debilitative sicknesses such as Huntington's disease and Parkinson's disease. Both diseases are progressive neurodegenerative diseases of the brain which have underlying genetic causes. Because of the nature of these diseases, it could be surmised that germline editing would be appropriate for these cases. Not only does this cure the patient of any possible genetic defect, but it also allows for future generations of offspring to not have to worry about the effects of this disease, leading to an overall increase in pleasure, thus making the decision morally correct under the scope of utilitarianism.

However, does CRISPR-cas9 have the potential to harm under the clinical perspective? Although ideally the clinical use of CRISPR-cas9 would not progress until gene therapy protocols have been established and that the technology would be determined to be safe to use, there would likely be unfortunate cases of unwanted genetic modifications occurring because of malfunctions in the treatment. This can lead to a cascade of unwanted and potentially life-threatening effects on the patient that could cause severe impairments across the body. Additionally, if the procedure were being conducted on the germline, any of these unwanted genetic defects (along with the

original defects which might not have been cured) could be passed onto later generations without additional treatment (Ormond et al., 2017). This additional treatment would also be severely cost-ineffective for both the patient and the physicians. Despite this, however, the multitude of benefits that CRISPR-cas9 provides almost wholly outweigh the risks, since the use of this technology would likely not be approved without deeming its nearly certain safety. From the classical utilitarian perspective, the pleasure significantly overcomes the potential pain of this technology.

This positivity for CRISPR-cas9 may not ring as true from the cultural and societal perspectives. One of the most known philosophical arguments against the use of CRISPR-cas9, regardless of germline editing or not, is the lack of self-identity for the individual because of having their genome modified. One of the defining traits of an individual from a philosophical standpoint is the sum of their unique experiences, whether it be through hardships or blessings. The argument suggests that if CRISPR-cas9 were used to eliminate all hardships resulting from their own unique genome, then they have lost their own personal identity. This applies not only to disease, but also to other aesthetic phenotypes as well, such as facial structure, hair, and height. The lack of hardships, instead of increasing the pleasure derived, can indirectly increase the pain by not being able to have unique experiences from different individuals, thereby being a moral evil in the context of utilitarianism.

Additionally, the cost of gene therapy treatments using CRISPR-cas9 can inflict a heavy financial burden on those who need it the most. According to Doudna, the price of one treatment with CRISPR-cas9 is around $2 million (Thomas, 2021). The cost of this treatment for a large majority of people makes this treatment simply inaccessible and those who do want to commit this potentially life-saving treatment will be taking on an extreme financial burden that will more than likely affect their quality of life, thus trading one hardship for another.

Culturally speaking, CRISPR-cas9 has the potential to embrace genetic dispositions that were introduced through outside factors. This is clear in Krystal Tsosie's analysis of the effects of colonialism on Native American genetic evolution. Rather than solving the issue with respect to the underlying social and cultural factors that led to predisposed alcoholism, the use CRISPR-cas9 instead threatens to reinforce this stereotype and encourages a surface level treatment of an underlying problem.("An Indigenous Bioethicist on CRISPR and Decolonizing DNA," n.d.) Underneath the scope of utilitarianism, the use of gene editing for this disease overall increases pain as it does not resolve generations of genomic adversity and moreover fails to address any of the outside factors that contributed to this disease. Furthermore, the use of CRISPR-cas9 poses a large problem towards religious institutions too, as evidenced by the concern presented by Dr. Collins. This concern is likely not exclusive to Christianity either; many other theistic religions view the body as sacred and not meant to be tampered with, as doing so would violate the laws of nature set forth by their practice. Transgressing these statutes would undoubtedly cause a more mental and spiritual pain for any individual who participates in these religions as it affects their relationship with their respective deity and their communities.

Possible Solutions

Unsurprisingly, the ethics on using CRISPR-cas9 is extremely muddy and varies significantly between everyone. However, there have been broad attempts at trying to address this issue. In the policies that were presented prior in this paper, almost all the legislative entities that were mentioned imposed a strict ban on human germline editing. This is likely to prevent clinicians from introducing any potentially unwanted and dangerous genetic defects into a patient in the process of trying to correct any that were already present, while also passing it onto further generations. While this ban does address the potential "pain" that CRISPR-cas9 can cause onto

individuals, it completely disregards the therapeutic and financial benefits that germline editing can provide. In doing a single germline edit of the mutated genome, the patient not only has their own disease corrected, but also eliminates the possibility of any offspring from having it and relieves them from the burden of having to pay the hefty price.

With respect to societal concerns, the idea that CRISPR-cas9 can lead to a lack of individuality is unfounded and a prime example of a slippery slope fallacy. One of the reasons that lack of individuality should not be a major concern is because there are a significant number of other contributing factors to an individual's unique personality other than their personal well-being. Each individual's background is distinct from one another, whether it be culturally, economically, or spiritually. Eliminating their hardships resulting from their genetic predisposition would be extremely unlikely to affect their individual personality and would moreover allow them to live closer to their fullest potential.

However, the case of dealing with equality in access to this treatment is significantly more difficult. As previously mentioned, the current cost of treatment sits at around $2,000,000 (Thomas, 2021), an amount that is held by staggeringly few amounts of people. Although it is to be expected that the cost will diminish over time, there is a likely chance that it will still remain an extremely costly treatment. If the treatment were to be allowed to be used more liberally as of now, there is a considerable chance that a significant widening of the class disparity will occur. That being said, withholding this treatment because lower classes cannot afford it also has its own moral wrongs, as it directly prevents those in the upper class who actually need the treatment from receiving life-saving care. But, since genetic diseases affect only a small portion of the population, and with the upper class that can afford this treatment being even smaller, is it worth sacrificing this minute portion of the population to prevent this disparity from growing ever larger? An argument could

be made for either side; the upper class can more than likely afford treatments that can ameliorate the effects of said genetic diseases and likely be able to live comfortably through their disease, but is willingly keeping treatment from them morally correct? Even through the use of a simple framework like classical utilitarianism, this dilemma is difficult to solve.

The same dilemma in equity arises in deciding if allowing use of CRISPR-cas9 in non-healthcare related instances is appropriate. However, this case is less morally demanding due to the lives of the few wealthy that can afford it not being at stake. Since the use of this technology for this scenario is solely for vanity, there are primarily only negative effects that can arise from this. Unlike the case of using CRISPR to treat the privileged, the lives of the privileged are not at risk. Thus, the only end result of this is the increased disparity mentioned prior.

The current solutions being implemented by legislative bodies (Kim, 2017; Liu, 2020), although done in good faith to prevent possible defects, are currently extremely stringent. However, this may be for the best as the technology continues to grow and evolve. But, a blanket ban on the technology as a whole is unnecessary under the scope of utilitarianism, as the number of benefits it can possibly provide to those with debilitating diseases (and their future generations) very clearly outweigh any sort of pain that it may cause. It should instead be approached with care and with individual considerations in mind, which is what the technology was intended to do. Personalized medicine should be the focus of the technology; any use of it outside of that scope, however, should be severely restricted. That being said, although the technology has yet to move to a stage where it is being widely used in clinical settings, whether because of safety issues or for financial reasons, once it has reached a stage where it can be commonly used in the clinical setting, there is very little reason to limit its potential.

Conclusion

The ethics of CRISPR-cas9 is still a heated debate to this day that will likely continue for decades to come as the technology evolves in the upcoming years. Although a majority of the concerns that contribute to this discussion certainly have their foundation, there is no doubt that the benefits of CRISPR-cas9 outweigh the pains it may cause, although this may vary from individual to individual. However, the usage of CRISPR-cas9 should not be completely limited as a result of the potential drawbacks it may cause to certain individuals, as it would be doing a disservice to the current and future generations who may require it to even live a functional life. Instead, it should be used with a keen eye on an individual basis to further the field of personalized medicine. It would be in society's best interest to allow CRISPR-cas9 to be used to its fullest potential in the clinical setting without any regulation.

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