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Chain Reactions:
Assessing the Potential for Heritable DNA Modification to Create Generational Benefits for Communities Affected by Sickle Cell Disease

By: Chinweoke Nweze

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Preceptor: Maria Bautista

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Abstract

This research paper focuses on heritable gene editing, which is a technology that modifies the germline in order to produce heritable changes to an individual and their subsequent offspring. This paper aims to assess its ability to provide an equitable and accessible form of disease prevention for those with sickle cell disease (SCD). Because of the advancements made in gene editing with SCD, and the disproportionate effect it has on marginalized communities, SCD will be evaluated as a case study for how heritable gene editing can address health disparities in a way that is equitable, sustainable, and accessible. In investigating this topic, I interviewed a variety of experts and stakeholders in the field such as those involved in gene editing regulation, gene editing scientists, SCD researchers, and an individual that has undergone gene editing treatments for SCD. My goal was to gain insight on the feasibility of the technology to perform these goals on a scientific scale, upon a regulatory landscape, and from SCD stakeholder perspectives. My findings through this process detail the necessity for precise and deliberate language when developing regulation around heritable gene editing, as well as methods for stakeholder engagement, mitigating risks, and improving accessibility.

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1.0 Introduction

Victoria Gray had lived with sickle cell disease, a genetic disorder resulting in deformed sickle-shaped blood cells, nearly her entire life. The disease left her, at times, incapacitated, needing to be rushed to the hospital when sudden intense bouts of pain occurred. In an interview with NPR, Gray recalls the many ways in which the disease debilitated her. The impact of the disorder left her frequently bedridden- unable to keep a job, finish school, or care for her children. Today, Gray experiences none of these symptoms. She describes how she is now able to work full time, and keep up with her children with a vigor she had never experienced before. In a summit of doctors, scientists, and bioethicists she declares: "The life that I once felt like I was only existing in, I am now thriving in" (NPR).

She attributes this sudden change in her health and lifestyle to the events of July 2, 2019, nearly three years prior when she first received the treatment in which doctors extracted some of her bone marrow cells, genetically modified them through CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) gene editing technology, before infusing these billions of modified cells back into her body. Sickle cell is a disease that affects approximately 100,000 Americans every day. The population disproportionately affected are, like Victoria Gray, African-American. Sickle Cell Anemia is just one of the hereditary disorders– alongside hemophilia, cystic fibrosis, Parkinsons and more– for which the scientific community hopes CRISPR gene editing technology can act as a possible treatment option.

CRISPR gene editing has revolutionized the scope of biology and medicine, and has numerous applications and methods that have greatly contributed to the treatment of sickle cell anemia and other diseases. While still a relatively new technology, its history has seen rapid advancements, and its future holds promising discoveries and innovations. However, responsible

and ethical application of gene editing remains essential as society navigates the complex implications of manipulating the genetic code, and CRISPR faces concerns such as unintended consequences, accessibility, and delivery methods. Perhaps its most controversial delivery method is the direct modification of a human embryo's germ cells. This is marked as a point of no return by critics due to the fact these modifications would also persist across the genetic code of future generations, leading to an array of ethical concerns surrounding the safety of the technology and autonomy of unborn beings. While those against germline editing do propose alternatives that would focus on using CRISPR methods that treat the individual, diseases such as sickle cell anemia are hereditary. Parents face significant probabilities of passing the genetic disorder on to their children. And those with the highest burden of disease are also often within the lowest socio-economic sectors, meaning affording gene therapy for multiple members of the family may not be feasible.

Because of the advancements made in gene editing with sickle cell anemia, and the disproportionate effect it has on those of African ancestry, this paper will focus on sickle cell disease (SCD) as a case study for how heritable gene editing can address health disparities. Given that the disease is at the forefront of current gene editing research, the importance of focusing on how the gene editing advancements used to treat SCD can address health- and thus socioeconomic- disparities is evident. In discourse surrounding heritable gene editing, the conversation often includes the technology's potential to promote health equity by providing long-term solutions. However, how this would happen in practice has not been detailed in the existing literature. In addition, a comprehensive analysis of the considerations that will be a necessity for equity and accessibility have not been previously outlined. This paper aims to fill these gaps by outlining these considerations and exploring the methods in which heritable

germline gene engineering (HGE) can reduce health disparities in sickle cell anemia and promote health equity in a way that is 1) Equitable 2) Accessible and 3) Sustainable for communities impacted by this disease.

This paper will begin by providing a background on the CRISPR gene editing technology and sickle cell anemia, as well as the intersection between the two in regards to current CRISPR gene editing treatments for SCD. Then I will undergo a literature review of the current discourse surrounding heritable germline editing, its current regulations, and the importance of gene editing treatment accessibility. Finally, in determining the potential for heritable germline editing as an equitable, accessible and sustainable method for treating sickle cell anemia, I will speak with a variety of actors involved in the scope of gene editing- from the scientists who aid in its advancements to the bioethicists involved in its regulation- to gain insight on the the use of germline editing for sickle cell anemia in both a scientific context and upon a regulatory landscape. I will also speak with SCD Researchers and stakeholders in order to understand how considerations specific to SCD will need to factor in when discussing HGE.

Then, based upon feedback from experts, I will then consider these inputs through a framework containing six elements: 1) Defining the Goal 2) Stakeholder Engagement 3) Risk and Uncertainties Analysis 4) Identifying Benefits 5) Accessibility 6) Contextualizing Regulatory Landscape. Drawing upon my findings, my policy recommendations first detail the necessity for precise and deliberate language when developing regulation around heritable gene editing, as well as engaging stakeholders such as the members of the sickle cell community– particularly through discourse containing timely and current information. I also detail the ways in which the informed consent process should be reformed in the case of heritable gene editing, especially when dealing with the vulnerable populations sickle cell disease encapsulates. I will

highlight the accessibility barriers on an international scale, as well as methods for how to address this. On a national scale, the United States, the findings will explore how who is funding the research can impact its future accessibility, and will discuss how an option for public funding can positively impact how accessible the technology would be. As this technology progresses, the potential to create long-term, multi-generational solutions for eradicating hereditary diseases and addressing socio-economic disparities emerges as a compelling rationale for exploring heritable germline editing, even as society navigates the ethical intricacies inherent in altering the very fabric of human inheritance.

2.0 Background

In this section, I will provide a background on SCD and the evolution of CRISPR gene editing, alongside definitions of the necessary terms. Because this topic has a lot of technical terminology that does not fall into the realm of common knowledge, in this section I will explain the terms that will reappear throughout this paper, as well the historical context that is necessary to understand the evolution of the conversation around CRISPR– from when it was first established, to its current available treatments for sickle cell disease, and finally the consideration of developing heritable gene editing for the purpose of preventing sickle cell disease. First, I will provide a background on SCD, detailing how the disease develops in individuals in the impacted demographics. Then I will delve into the history of CRISPR, the technology that would be used to perform gene editing, how it was developed, and where it has progressed to today. I will also explain the distinction between the different kinds of gene editing methods, the current gene editing treatments for sickle cell disease, and the barriers to accessibility for those with SCD with the current gene editing treatments.

2.1 What is Sickle Cell Disease and who does it affect?

Sickle cell disease, also commonly referred to as sickle cell anemia, is an inherited blood disorder that results in a lack of hemoglobin within the red blood cells. This results in the red blood cells taking on a crescent or "sickle" shape as opposed to their normal disc shape. Due to their altered shapes, these red blood cells cannot move easily through the bloodstream and often adhere to the blood vessels walls, blocking blood flow and oxygenation (Pokhrel et. al, 2023). This blocked blood flow is dangerous as it can cause strokes, eye problems, infections, and bouts of extreme pain known as pain crises. It affects approximately 20 million people worldwide, primarily people of African descent, with 1 in 12 carrying the sickle-cell gene (American Society of Hematology). Albeit with a lesser frequency, it also heavily affects those of Latin origin (Central and South America), as well some parts of Asia, such as India. Within the United States, approximately 100,000 people live with sickle cell anemia. It occurs in every 1 out of 365 African-American births and 1 out of 16,300 Hispanic Americans (Pokhrel et. al, 2023). As can be inferred from these numbers, there exists a large disparity within who is likely to have their lives impacted by sickle cell anemia. Between the years 2016 and 2018, out of the 74,817 hospitalized for the disease, 69,889 (93.4%) were Black, 3,603 (4.8%) were Hispanic, and 1,325 (1.8%) were White.

2.2 Overview of CRISPR Technology

In this section I will provide a brief background to how the CRISPR systems technology has evolved, and how the technology works in practice. This technology is what is currently utilized in the available gene editing treatments that will be described in the next section, and is

also the basis for understanding how heritable germline editing would work. Because of this, it is necessary to understand how the technology works and how it has evolved.

CRISPR gene editing is a rapidly progressing field in molecular biology. The discovery of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has origins dating back to 1987, when it was first discovered in the DNA sequences of Escherichia Coli (E. Coli) (Gostimskaya 2022). These repetitive DNA sequences present in the immune system of bacteria, were later found to be serving as a memory bank for the bacteria's past encounters with viruses. Since then, the technology has seen drastic advancements, particularly regarding the research of genome modification.

In 2012, Jennifer Doudna and Emmanuelle Charpentier, alongside their team, made a breakthrough discovery through their identification that the Cas-9 protein could be directed to sections of the DNA if provided with the right template, and essentially act as a molecular "scissors" on the target DNA section (Asmamaw & Zawdie, 2021). This discovery projected CRISPR-Cas9 editing to the forefront of genome research and is widely considered one of the most significant scientific discoveries of this century, one that won Doudna and Charpentier the Nobel Prize in Chemistry in 2020.

CRISPR-Cas9 is described as working in three steps: recognition, cleavage, and repair (Asmamaw & Zawdie, 2021). The first stage is recognition; this is when the guide RNA (gRNA) recognizes the target sequence in the gene of interest, after it is provided with a complementary base pair that serves as the template described earlier. The Cas9 protein acts as the "molecular scissors", creating a double stranded break. After the modification, the break in the strands is then repaired through cellular mechanisms that join them back together.

The CRISPR-Cas9 system remains the most commonly known and researched method. However, the double-stranded break created in the DNA, although repaired through cellular mechanisms, is still an area of concern due to this mechanism's greater potential for off-target effects. Since its discovery, there have been many advancements that improve this limitation. More recent developments such as prime or base editing, which will be discussed in greater detail by the experts in my findings, have the capability to alter the genome through precise modification methods that can greatly minimize the potential for off-target effects.

2.3 Somatic Gene Editing vs. Germline vs Heritable

Now I will outline the different types of gene editing that will be repeatedly referenced in this paper. Somatic gene editing is a method utilizing the CRISPR technology that involves the modification of the human genome to a somatic cell, which is a cell that is not a reproductive egg and sperm cells. Somatic gene therapy aims to eradicate the disease only in the individual receiving the treatment, meaning these modifications would not be passed on through reproduction to future generations. Depending on the type of disease, it can either swap a mutated gene with its functioning replacement, or it can attempt to mitigate the harmful effect of the mutated gene. For SCD, the primary methods that utilize the CRISPR technologies are somatic, and will be discussed in further detail soon.

Germline gene editing represents a new frontier in genetic technology, aimed at modifying the genetic material in reproductive cells—sperm and egg cells—that collectively form the germline. In contrast to somatic gene editing, germline editing has the profound capability to introduce heritable changes that are passed on to subsequent generations. Through

precise modifications to the DNA sequence, scientists hope to indefinitely correct genetic mutations responsible for hereditary disorders.

Heritable germline editing, are germline modifications to an embryo that are implanted into a uterus to be carried to term. While germline editing and heritable editing are often used interchangeably, this paper will make a distinction between the two in its discussion because the current regulation, which will be detailed later in this paper, creates a legal distinction between the two. A critical dimension in evaluating the ethical landscape of heritable germline gene editing involves assessing potential societal benefits, including the reduction of health disparities and overall impact on morbidity and mortality. As this technology progresses, the focus on specific genetic disorders, such as sickle cell disease in this context, becomes pivotal in understanding the implications of heritable germline editing.

2.4 Current Gene Editing Methods for Sickle Cell Anemia

As mentioned in the previous section, the available gene editing treatments for SCD are somatic gene editing treatments, and in this section I will go into detail about these available treatments that are either already established or in the research stage. Current treatments for SCD include ex-vivo and in-vivo. With the ex-vivo approach, the specific cell type, which in the case of sickle cell anemia are bone marrow cells, are extracted from the body and genetically modified outside of the body. Meanwhile, a patient's system is prepared for the delivery of the modified cells through standard therapies designed to guide edited cells to correct location within the body (Vertex). These modified cells are then infused back into the body for the therapeutic effect to take place. It requires many steps as it involves cell collection, isolation, expansion, editing, selection, and transplantation (Yamin et. al, 2019). However, because the method

directly delivers the modification to the specific cell type intended, it has safety benefits in regards to minimized delivery to off-target cells. Unfortunately, a drawback to the ex-vivo method is the cost. Because it is an extensive process, the estimated cost for a patient would be around $2 million USD.

The question of cost is helped with an emerging method called in-vivo, where gene editing tools (Cas-9) are transfused directly into the person in a way that allows for the DNA modification to take place within the cells without ever being removed from the body. There are two primary methods of delivery: a non-viral and viral vector. Which vector is used depends on which organ the therapy is delivered to. For example, the muscles, lungs, and central nervous system may be more suited for a viral vector, while the liver might be more suited to a non-viral one (CRISPR Therapeutics). The benefit of the in-vivo system is the reduced cost. Due to the elimination of a transplant procedure and the proceeding chemotherapy required for the ex-vivo method, it has the potential to bring the cost down from $100,000-$500,000 to $1,000-$2,000 per dose for low to middle income countries over the next decade (Gates Foundation). Because of its potential to provide a more accessible cure, over $200 million has been jointly invested in the research by the Gates Foundation and the National Institute of Health over the past four years. However, the drawback of in-vivo, and why more research is required before clinical use, is the risk of unintended delivery to an off-target cell that could result in unintended outcomes. While both methods have their tradeoffs, what they share in common is they are both somatic gene editing techniques. This means the effects are limited to the individual the treatment was given too, as opposed to heritable germline editing being able to impact multiple generations. As mentioned, ex-vivo treatments, which are the current and only gene editing treatments available for those with SCD, come with a price of millions of dollars due to the extensive process. As a

result, this treatment that can drastically improve the lives of those with SCD, is simply not accessible to the communities most impacted by it.

2.5 Accessibility of CRISPR for Sickle Cell Anemia: Who Would, and Who Should, It Be For?

In this section, I will discuss the financial impact of living with SCD as a result of life-long medical costs that largely impact the socio-economic mobility of these communities. Gene editing treatments have the potential to mitigate these lifelong costs, but these treatments themselves are also inaccessible.

Black Americans with sickle cell anemia, the demographic most affected with the disease within the United States, have a projected lifetime income that is $695,000 less than individuals without sickle cell disease. A “cure” could result in increased productivity and a new annual median earnings potential (from $25,442 to $38,618) for an individual, as well an increased lifetime earning potential increase from $661,507 to $1,930,920 (Graf et al. 2022). These differences in earnings and productivity are due to absence of health crises and hospitalizations related to sickle cell anemia resulting in increased life expectancy and the ability to pursue educational and career-related opportunities (Graf et al. 2022). The importance of studying how gene editing can be utilized as an accessible cure is not just limited to the health benefits of living without sickle cell anemia, but the improvement in socioeconomic mobility that could arise for entire communities that remain incapacitated by the disease in more ways than one.

Victoria Gray was one of these people that used to remain incapacitated by the burden of living with sickle cell anemia in her daily endeavors. As seen with her story, gene editing for SCD has the potential to change lives. Gray was one of the first to receive the CRISPR-based therapy, and since then around 75 other patients have received the same treatment with

promising results. In November of 2023, Vertex and CRISPR Therapeutics announced their authorization as the first CRISPR-Cas9 Gene-edited therapy after being approved by the United Kingdom's Medicine and Healthcare Products Regulatory Agency (MHRA). To date, they have filed with the United States FDA and are pending approval. As of December 2023, Casgevy has been the first gene therapy utilizing CRISPR-Cas9 gene editing technology to be approved by the FDA. The landscape for a potential cure for diseases like SCD is emerging rapidly. However, one of the most pertinent questions surrounding the topic is who will be able to access it when it gets here? While pricing has not been officially established as of date, the ex-vivo method the therapy utilizes is estimated to cost around $2 million US dollars (USD) per patient, similar to the pricing of other gene therapies (Wong 2023). This price poses a challenge regarding access, not just for the average American within these underrepresented groups that SCD heavily impacts, but for the areas with the highest SCD prevalence, such as countries within Sub-Saharan Africa.

In addition to the cost, another barrier is that most gene editing sickle cell treatments are ex-vivo (the bone marrow cells are collected outside of the body and are edited before being infused back). It is an intensive procedure that may be more accessible in the United States where there are over 200 specialized treatment centers for bone marrow transplant, but within sub-saharan Africa, there are only three of these centers, which are located in Nigeria, Tanzania, and South Africa (Molteni 2023). This makes current gene editing treatments widely unavailable for those that need it most. The absence of accessible gene therapies in these regions has a devastating impact, with 50-90% of Sickle-cell babies in Africa not living to see their fifth birthday (Uyoga et al., 2019). As will next be discussed in my literature review, these considerations are what propels arguments that the prevention route that HGE would take could

lead to more accessible and sustainable treatments that can help to alleviate the devastation of SCD in these communities.

3.0 Literature Review

In my review of the literature, I researched the current discussions being had in regards to heritable germline editing. HGE has been very controversial because of the ethical, religious, and cultural elements relevant in the concept of making modifications to the germline that would alter the DNA of that individual and their subsequent offspring– and these elements also configure into the current regulatory landscape. In this next section I will evaluate the arguments surrounding HGE from both sides, and will then review the current regulatory landscape pertaining to the research or development of the technology.

3.1 Discourse around Heritable Germline editing

Most reports agree that gene therapy should be restricted to dealing with diseases as opposed to any physical or cognitive enhancements. However, when it comes to gene editing for counteracting disease, the way in which we do so- disease *treatment* or disease *prevention*- have very different practices and implications. Disease treatment, treating someone that has already developed or been born with the disease, is largely done using somatic gene editing. With somatic gene editing, existing genes are modified, but these traits cannot be passed down to future generations. However, many argue that an even more effective method for eradicating disease would be disease prevention, which would involve HGE.

For a multitude of reasons, HGE has remained controversial since it was first introduced as a possibility. As that future becomes ever more plausible, those against the technology bring up ethical concerns surrounding the use of embryos and the potential violation of autonomy that

occurs in changing the DNA of those not capable of consenting (Hammerstein et al. 2019). Additionally, while germline editing could have the potential to eradicate diseases across generations, gene editing is not yet a perfect science. The potential for off-target effects, when the Cas9 protein affects a genomic site that was not the intended target, could lead to adverse outcomes that would also be inherited across generations. It could be argued that, as a society, there is a greater obligation to not explicitly cause harm where it would have otherwise never occurred, even if that would mean forgoing the benefits of eradicating a disease.

There is also opposition based on the idea that HGE is a "slippery slope", meaning that accepting HGE for disease eradication could lead to its future use for non-necessary factors, such as enhancing physical or cognitive ability (Hammerstein et al. 2019). McKibben highlights the danger of this reality saying:

"These would be mere consumer decisions — but that also means that they would benefit the rich far more than the poor. They would take the gap in power, wealth, and education that currently divides both our society and the world at large, and write that division into our very biology." (McKibben 2003, p. 251)

Others argue that HGE in itself is simply unnatural, and criticize the practice as "playing God" (Locke 2020), implying that through the permanent altering of one's DNA, humans are entering a dangerous territory of modifying what has always been left up to nature thus far: our DNA. They contend that HGE undermines life as a gift and can lead to discrimination towards those with certain disabilities or conditions (Asch et al. 2012).

Alternatively, those in favor of exploring HGE argue that current, and more socially acceptable practices, such as preimplantation genetic diagnosis (PGD), still involve the process of "selecting" genetic traits. During PGD, embryos are implanted or discarded based on whether

they are found to harbor a specific genetic trait. Similarly, they say, HGE modifies embryos with a specific gene and proceeds with implantation based on whether this modification is successful (Gyngell & Savulescu, 2017).

While they acknowledge the relevance of concerns regarding the potential for a "slippery slope" regarding the use of germline editing potentially leading to greater disparities, they contend that this should not come at the cost of completely preventing development in this entire category of medicine, but rather should result in the development of appropriate safeguards to protect against the use of germline editing for the purpose of cognitive or physical enhancements.

Furthermore, they propose that HGE is actually more likely to lessen social inequality due to its potential to address health disparities more prevalent in certain communities (Gyngell & Savulescu, 2017), especially when considering potential for widespread and equitable distribution of HGE for therapeutic purposes, enhancing global immunity to certain diseases such as with smallpox and polio (Church 2017). These alternative perspectives challenge the prevailing cautionary stance on HGE, urging a nuanced exploration of its potential benefits in addressing complex medical and societal, and regulatory challenges.

3.2 Current Regulation of Germline editing

The concerns about HGE are reflected in the current regulation. A recent study done on the global policy landscape of HGE reviewed 106 countries and obtained policy documents from 96 of them. Similar to my own paper, this study makes a differentiation between germline editing research and heritable germline editing research, where they both involve genetically modifying sex cells (eggs, sperms, early-stage embryos), but heritable germline research would involve

actually implanting the modified embryo into uterus. With germline research that does not involve the implantation of a modified embryo, only 40 countries out of the 96 had a policy on this (Baylis et. al, 2020). More than half of them, 23 countries, prohibit this kind of research, while 11 countries allow it. On the topic of heritable genome editing, 78 out of 96 countries have policies specific to HGE. None of these countries currently permit HGE. On the contrary, 70 of these countries outright prohibit it. Five countries- Colombia, Panama, Belgium, Italy, and UAE- prohibit it with possible exceptions, such as for therapeutic purposes. The United States is one of these countries that currently prohibit HGE research. They do, however, permit research on germline editing but prohibit any federal funding. While the United States has had the most CRISPR publications regarding genetic editing thus far, China is coming up as a close second with its investments into research of gene editing applications. China, following a similar pattern to the United States and some other countries, allows for germline research, albeit without the caveat prohibiting federal funding. It also currently prohibits HGE research.

The study detailed above is the most recent one that gives a comprehensive look into the policies worldwide, and the analysis shows there is a lot more agreement regarding potential policies than perhaps previously anticipated. This brings into discussion the topic of global moratorium, which would be a global agreement to establish a momentary cease on heritable gene editing research.

Calls for a worldwide pause on HGE research started mounting back in 2019, when a researcher from China, Dr. He Jiankui, had announced his team had successfully implanted human embryos with a modified genome meant to produce an immunity to the human immunodeficiency virus (HIV) into a woman, resulting in the birth of twin girls, Lulu and Nana– the world's first genetically engineered children. This was widely denounced as unethical by

many, and in his appearance in front of the International Summit on Human Genome editing, the committee criticized the experiment on the grounds of failure to protect human subjects, insufficient medical justification, and a lack of transparency. Still, the committee did not demand a ban but rather stated that germline editing was not ready for clinical trials and needed a transitional pathway. In response to the news, in March of 2019, a group of international scientists and ethicists co-authored a commentary calling for a global moratorium of heritable gene editing (HGE). The idea was that each nation that joined the moratorium would commit to not engaging in HGE for 5 years, and during this five year pause there could be thorough discussion regarding the technology. After this five year period, a nation could choose to extend the moratorium or ban HGE. If they were to choose to engage in technology, they would first be required to disclose to the world regarding its specific intended use and possible consequences- and then they would be subject to oversight from an international committee.

In the United States, the National Institute of Health (NIH) backed the notion of a global moratorium by writing a letter of support to the Secretary of the Department of Health and Human Services. However, for many a simple agreement is not enough. They believe it must be established through legislation that imposes penalties for violations (Macintosh 2019). After all, by the time Dr. He Jiankui announced his research, China had already prohibited HGE. And while China acknowledges that Dr. He violated this ban, the ban alone was not enough to deter this research– as the regulation did not establish any penalties that would occur from violations. As a result, the China National Health Commission (NHC) has since established regulations that include the consequences of monetary fines, and loss of research funds and/or medical licenses in order to ensure compliance. In the United States, the Food and Drug Administration (FDA) established a jurisdiction over heritable gene editing trials, and a rider added to the Consolidated

Appropriations in 2016 stated the FDA could not consider applications for HGE clinical trials. Anyone found in violation and conducting unauthorized trials would be charged federally and subject to monetary fines and/or prison.

Proponents of a global moratorium believe a deeper understanding of the effects of heritable gene editing is necessary before it can be considered for research or clinical trials. Uniformity regarding policy is also seen as critically important, as different policies in this area would incentivize “medical tourism”, with researchers trying to circumvent the laws within their own country by traveling to another country with less or no restrictions to carry out research. It may also encourage countries to adopt relaxed restrictions in hopes of gaining revenue from said medical tourism. However, opponents to a global moratorium cite a flaw within this reasoning is that a global moratorium would discourage the research that would allow us to understand how to safely and effectively use heritable germane engineering. It would also discourage funding for basic research that could have legitimate and therapeutic use, such as the treatment of sickle cell anemia by modifying the gene located on a standard allele.

3.1 Heritable Germline Editing for Sickle Cell Anemia

In this section, I will discuss the arguments made in previous literature regarding the use of HGE for SCD in particular. Despite widespread agreement on the potential of in-vivo therapy given further research into off-target effects, as given by the last section, this line of thought has not been extended to germline editing research due to its controversial nature. However, in thorough examination of how gene editing treatments can be implemented in a manner that promotes accessible and sustainable health equity, I would like to give consideration to whether the solution to alleviating the impact of SCD in these communities that have battled it for

generations is preventing the disease's occurrence in future ones. The drawback of the previous in-vivo and ex-vivo treatments, both somatic gene therapies, were that the benefits only apply to the individual that receives them. However, if two people are both carriers of the sickle cell trait, there exists a 25 percent likelihood that any child of theirs will develop sickle cell disease, and a 50 percent chance their children will inherit the sickle cell trait. This means they may not develop SCD, but are capable of passing on the trait to their future offspring (CDC). For the average patient with SCD, especially in developing countries, the cost of financing individual treatment may be considered unattainable, let alone being able to afford treatment for multiple family members. Even within the United States, affording the therapy would impose financial burden on an individual, and because they may pass on the trait to their children, they face the possibility of that burden yet again in managing the illness within their children. Furthermore, it may become financially unsustainable for public health insurance to afford treatment for multiple family members, which could lead to the establishment of a triage system or a distribution mechanism to "allot" treatment to patients and families, which does not significantly aid in lessening the socio-economic gaps in these communities (Sharma et al., 2020).

The drawbacks of HGE are similar to the complications for the other CRISPR engineering methods: the possibility of off-target effects. However, unlike the other methods, any off-target effects, whether negative or in the form of physical/cognitive enhancements, will be inherited in future generations. Therefore, what makes HGE appealing for disease prevention is also what makes it so daunting. In treating a single person one is, in a sense, treating thousands-positively or negatively. There are researchers that propose methods for HGE within sickle cell anemia that would likely prevent off-target effects. For example, through directly correcting the mutated alleles, or through recreating naturally occurring mutations that would result in greater

fetal hemoglobin production, morbidity from sickle hemoglobin would be mitigated while likely not impacting the function of other cells in the body (Metais et al. 2019). Additionally, other research proposes methods of clinical research of HGE that can diminish potential for adverse effects, such as early intervention in embryos- before the formation of the sperm cell (Church 2017). If allowed further research, these works claim that HGE could become an option for SCD prevention that is more accessible and cost-effective for both individuals and global health systems. While they detail the financial burden currently present for those with SCD, they do not get into discussion any methods in which HGE can actually be made accessible in a way that promotes health equity. In my methods section, I will discuss the ways in which I aim to fill these gaps through my data collection.

4.0 Methods

In the previous section, I discussed the claims that this paper aims to directly address– which is that heritable gene editing can create accessible and sustainable benefits for those with SCD. In my investigation of how this would occur in practice, in this section I will outline my methods of research through detailing the individuals I have chosen to obtain expert opinions from, their backgrounds, and how I plan to use their inputs in outlining the considerations necessary for accessibility. These inputs will also be referenced in my development of methods in which HGE can reduce health disparities in SCD and promote health equity in a safe and sustainable manner.

In evaluating how HGE can be used to address health disparities, I spoke with a variety of experts in the field to gain insight on the feasibility of the technology on a scientific scale, upon a regulatory landscape, and from a SCD stakeholder perspective. I hope to obtain a

comprehensive understanding of the potential for HGE to address health disparities in SCD in the future. From the gene editing scientists, I plan to gain insight on topics such as the potential for HGE research to address health inequity and the future of that research in regards to the possibility of minimizing off-target effects. From those involved in its regulation, such as regulatory committee officials and bioethicists, I want to understand what considerations go into the development of governance regarding the technology, and where they foresee the regulatory landscape going as discussion of the technology continues to gain traction. From SCD researchers, I want to understand the situation from the stakeholder's perspectives, and how the complexities of the disease will factor into the discussion of it being the focus of prevention through HGE. I also spoke to a public advocate for SCD, Tesha Samuels, who had received somatic gene editing treatment for the disease as part of a clinical trial back in 2017. For her, I asked a unique set of questions because she had a perspective that was different from the other interviewees. In total, I created four subsets of questions (Regulator, CRISPR Scientist, SCD Researcher, and Tesha Samuel's) that were asked to an interviewee depending on what their role was, or how I found them. For example, if I found them because they were a member of a regulatory oversight board or published a work on the regulation of HGE, my questions to them would gear towards regulation. If I found them through the staff list of a gene editing lab, their questions would be more focused on the science. Most of my interviewees, however, were obtained through recommendations after I had established an initial few interviews through the methods I detailed above. At the end of each interview, I would ask for recommendations on individuals to reach out to, and through this I was able to be connected with people of a similar knowledgeable background.

While there are four subsets of questions, there are a number of questions that are present in both because many of the individuals I interviewed can provide multiple perspectives. Most of the individuals that sat on regulatory commissions also had a scientific background or bioethics background, and were able to provide insight on more than one factor. Another example is that some of the gene editing scientists can also be very knowledgeable about SCD.

Below, I will provide a table that includes the individuals I interviewed, their background, interview date, and the subset of questions they were asked. The questions themselves can be found in the appendix. Six individuals preferred to remain anonymous, so I will refer to them using pseudonyms that correspond with the subset of questions they were asked, but again, there can be overlap regarding their expertise, so even if they are referred to as "Regulator X", they could still have scientific background they are bringing into the discussion. For anonymous individuals, the only category that will be left blank is their background. But one can look towards the questions they were asked in the appendix to get a sense of their expertise.

Table 1: Interview Profiles

Name	**Background**	**Interview Date**	**Primary Question Subset**
Ben Hurlbut, Ph.D	• Associate Professor of Life Sciences at ASU, specializing in the governance, politics, and ethics of biotechnology. • Holds a PhD in Science and Technology Studies, with a focus on the history of science, from Harvard. • Co-leads Global Observatory on Genome Editing	January 25th, 2024	Regulatory
Andy Greenfield, Ph.D	• Degree in Natural Sciences from Cambridge and obtained PhD in Molecular Genetics while in London. • Spent 25 years leading a lab investigating molecular genetics, primarily focusing on science. • Joined the Nuffield Council on Bioethics and chaired a working group on genome editing, including heritable genome editing. • Involved in the National Academies' International	January 17th, 2024	Regulatory

	Commission on Heritable Genome Editing.		
Kelly Ormond, Ph.D	• MS in Genetic Counseling from Northwestern University • Post-graduate certificate in Clinical Medical Ethics from University of Chicago (2001) • Directed genetic counseling education programs at Northwestern and Stanford for over 20 years. • Transitioned into empirical bioethics research while at Stanford, particularly interested in societal reception of new genetic technologies.	January 26th, 2024	Regulatory
Helen O'Neill, Ph.D, M.S.	• Professor in Reproductive and Molecular Genetics and Director for the MS in Reproductive Science and Women's Health at the Institute for Women's Health, University College London (UCL). • MS in Prenatal Genetics and Fetal Medicine from UCL. • Completed PhD and postdoctoral research on the genetics of ovarian development at the Department of Stem Cell Biology and Developmental Genetics, National Institute for Medical Research. • Research primarily focuses on preimplantation embryo development and the application of genome editing techniques to understand and treat infertility-related disorders. • Serves as the CEO and Founder of Hertility Health, a precision medicine-focused initiative addressing reproductive health concerns.	March 4th, 2024	Regulatory
Regulator A	–	January 25th, 2024	Regulatory
Regulator B	–	February 23rd, 2024	Regulatory
Regulator C	–	January 30th, 2024	Regulatory
Kiran Musunuru, M.D., Ph.D., M.P.H., M.L	• Cardiologist, geneticist, and gene editor, integrating all three disciplines into his career. • Currently serves as Professor of Cardiovascular Medicine and Genetics at the Perelman School of Medicine, University of Pennsylvania. • Research focuses on the genetics of heart disease, aiming to identify protective genetic factors and develop novel therapies. • Co-founder and Senior Scientific Advisor of Verve Therapeutics, contributing to advancements in gene editing technology for therapeutic applications.	February 26th, 2024	Regulatory/Science
Ryan Clarke, Ph.D	• CEO of Syntax Bio, a Chicago-based company founded on his PhD dissertation work.	January 30th, 2024	Science

	• Conducted PhD research at UIC focusing on the early embryo, where CRISPR technology was adopted for manipulating stem cells and directing their differentiation. • Leveraged CRISPR technology beyond its conventional use as molecular scissors to develop potential cell therapies, particularly focusing on hematopoietic stem cells. • Founded Syntax Bio with the goal of addressing manufacturing challenges and reducing costs associated with cell therapies, particularly those derived from stem cells, by leveraging innovative methods and technologies.		
CRISPR Scientist A	–	January 19th, 2024	Science
Sanghamitra Das, Ph.D	• University of Chicago Postdoctoral fellow in the Department of Anthropology, sponsored by the Committee on South Asian Studies. • Completed a PhD at Arizona State University with a focus on sickle cell research. • Specialized in science and technology studies, medical anthropology, and Indigenous Studies in India • Research focuses on bridging social, humanistic, and scientific perspectives, driven by a desire to contribute to societal change, particularly for oppressed communities in India.	January 26th, 2024	SCD Researcher
SCD Expert A	–	February 2nd, 2024	SCD Researcher
SCD Expert B	–	February 2nd, 2024	SCD Researcher
Tesha Samuels	• Founder of sickle cell advocacy group, Journey to ExSCellence • Organization seeks raise awareness about SCD and provide survivors with aimed at improving their quality of life, such as medical, social, financial, and professional development services • Received gene editing treatments after participating in an NIH clinical trial back in 2017	February 16th, 2024	Individual Subset

I will then consider inputs of the experts through a framework of 1) Defining the Goal 2) Stakeholder Engagement 3) Identifying Potential Benefits 4) Risk and Uncertainties Analysis 5) Accessibility Considerations 6) Contextualizing Regulatory Landscape:

Table 2: Analytical Framework

1. Goal Definition	*Clearly defining the goal of gene editing with reducing health disparities. The purpose of this section is to detail how framing should happen in regards to drafting HGE legislation, and highlight the ways in which improper framing can have dire consequences.*
2. Stakeholder Engagement	*Detailing the importance of stakeholders engagement with heritable gene editing in particular, and the methods in which it should occur, especially with SCD community. The goal of this section is to establish what necessary components to stakeholder engagement, such as informed consent, outreach, education, and collaboration should entail*
3. Risks and Uncertainties Evaluation	*Consideration of ethical, social, health-related risks, such as unintended consequences, potential long-term health effects. Although there are still unknowns regarding this considering it is an evolving field, the section aims to detail the way in which risk or accounted for can be mitigated during research.*
4. Identifying Potential Benefits	*Exploring potential benefits through the lens of reducing the prevalence of the disease, improving treatment outcomes, and decreasing overall burden on affected populations. The goal of this section is to establish what would make HGE worth considering.*
5. Accessibility	*Identifying barriers to accessibility and the discussion of methods for how the technology could be distributed equitably. The purpose of this section is to gain a comprehensive understanding of any barriers to accessibility*

	that could exist so that considerations of how to overcome them can occur.
6. Contextualizing Regulatory Landscape	*In this section, context as to why the current regulation is what it is will be established, the goal of this section is to understand the cultural, political, and religious considerations that will affect how the regulation is implemented.*

These four categories allow me to engage with the primary considerations regarding the topic of heritable gene editing for sickle cell anemia through the nuanced perspectives that the individual experts and stakeholders offer in my next section.

5.0 Findings

5.1 Goal Definition

In this section I will discuss the process of defining the goal of HGE for SCD. Key conversation points were when should it be considered, the necessity for regulators to be deliberate with the language used regarding the goal for HGE, and who this should be for.

Before even the discussions of how society should pursue this technology begin, there should first come the establishment of the goals regarding its use. The first question that arises during this consideration is why use the technology to begin with, especially given the fact that other options are available. Dr. Ben Hurlbut believes that the conversations regarding the pursuit of heritable gene editing in any capacity should begin with the question of what it is for:

*"**Is there a human situation** to which when you confront that situation, your response would be we need heritable genome editing for this [...] it's very difficult to come up with a problem for which heritable genome editing is a solution. Where there's no other way to approach it"*

Regarding SCD treatments, one of the most widely utilized treatments on the market is hydroxyurea, a medicine that increases the amount of hemoglobin present in the blood cells, enlarging them so they are rounder and more flexible, and ultimately less sickle-shaped. There are also the somatic gene editing treatments that are emerging, such as the recently legalized Casgevy treatment. Regarding the issue of having children, there are numerous ways to have children that would hopefully not have to suffer through the same disease. One measure that would still possibly have the genetic material of both parents is preimplantation genetic diagnosis (PGD). This is the process of screening embryos for certain disorders before implantation into the uterus. In most cases, this may be enough to have a child without the genetic trait the parents wish to avoid, but as Dr. Kiran Musunuru explains, this is not a possibility for every couple:

"[PGD] is not an option for two parents who both have the same recessive disease. The other scenario, which is much much rarer [is] someone has a dominant disease, where just one bad copy is enough to cause a disease but they're really unlucky and they have two bad copies [...] same thing [with] every embryo, it doesn't matter who they end up [...] They are going to pass along one bad copy of the gene to all of their embryos. And that is going to be enough to cause disease. So those are the scenarios where if you want a naturally born child with full genetic relatedness to you, you're not gonna be able to have a healthy child unless you do something like editing right? It's just not an option"

Dr. Andy Greenfield also spoke of this scenario stating, *"in these rare instances, genome editing would be the only solution"*. Dr. Greenfield goes on to speculate that this is perhaps how most jurisdictions would answer this question: "*[...]is there an unmet need, where PGD would not be adequate because of questions of probability, and could gene editing assist perhaps in combination with PGD"*?

Some of the experts also expressed a deeper reason for investigating the technology. Regulator A stated that it is a *"moral imperative"* to explore its possibility. While not necessarily saying it should be pursued, they believed at the very least it should be investigated, stating: *"if*

we have the tools that allow us [...] efficiently and [have] the result that we want to have [and] make changes to the human genome that will prevent horrible heritable disease will prevent human suffering […] It's a moral imperative."

However, given the scenario that society reasonably establishes a justification for pursuing heritable gene editing logistically– instances of unmet need from existing options– there is still the question of what diseases would necessitate the need for HGE. Should it be in cases of unmet need for any heritable disease or disorder, and why should sickle cell anemia be considered in particular?

To the first part of the question, the determination of a disease that constitutes the need for HGE is a precarious evaluation. It carries the implication of an inherent defectiveness that needs to be "corrected", and Dr. Sanghamitra Das warns of the possible danger that underscores this rhetoric:

"[..] the thing about [heritable] gene therapy is that it says we will eliminate all patients in the future. But what would that elimination look like? [...] ***What does it tell you about when you say that you have a defect that needs to be eliminated? There is a very complex value judgment.*** *It's not just scientific, it is also very socio because they are telling that some people's genes are inherently defective."*

These decisions are culturally contextual, meaning what is considered acceptable for genetic editing will not adhere to a standard set of guidelines. Instead, it will be subject to the cultural and political climate of countries adopting this technology. Dr. Das, speaking from her experience in India, notes how the conversation has shifted from treating specific diseases like SCD to treating *"tribal communities [in India]"* because of the belief that these groups inherently have "many disorders" that gene editing could target. While certain diseases may be more prevalent in minority populations, such as SCD, the harmful aspect of this rhetoric lies in its shift from treating diseases in certain populations to "fixing" populations.

This shift in framing has significant implications, as it portrays groups of people with specific shared traits as targets who need refining and correction through genetic modification rather than focusing on addressing the diseases themselves. This rhetoric has been historically and contemporarily harmful because of its close ties to eugenic theories such as those espoused by Nazi Germany, highlighting the need for extremely careful consideration and ethical reflection in the discourse surrounding heritable gene editing.

Dr. Hurlbut echoes these concerns. In our discussion, he considers the case of societies in which certain diseases or disorders can carry immense social stigma. Even if other options exists to treat the disease, parents may be understandably motivated to pursue HGE for the purpose of removing the stigma that their children would face if born with the disease:

"if you start thinking about the kind the ways [...] societies treat people on the basis of traits, and the way people might start thinking about how they want their kids to not have to deal with that [...] you can pretty quickly see the really understandable reasons that people might reach for this technology in the name of making their children, their future children's lives better. And the way that at the same time would basically double down on what would effectively reinforce the forms of discrimination that those parents are trying to respond to, and would essentially preserve things that are quite horrible in, in the societies where the technology has been deployed [...] ***A genetic fix to a social problem basically encodes that social problem into people's genes forever****"*

This adds additional importance to considering the social and cultural context of the societies this technology would be implemented. Additionally, in defining the goal for this technology, the language is imperative, and should be framed with intention. As Dr. Das asserts, regulation will have to establish *"clear boundaries about what this technology is for [and] which value systems it will serve"***.**

In addition to the conversation of the value systems the technology will serve, there is also the question of *who* it will serve. This brings me to the second point regarding why SCD

should be considered as a candidate for HGE if the technology is established. As has been discussed, this paper will investigate the claims that HGE can address health disparities more prevalent in certain communities (Gyngell & Savulescu, 2017). Because SCD is a global disease that affects underprivileged communities in every region, HGE's claim to remove the disease from an individual's genome could theoretically be a long-term solution and reduce the prevalence of disease in these communities.

However, as many of the people in this study have expressed, the reality of this could look completely different. The most recent gene editing technologies to become available, while somatic instead of heritable, come with an exorbitant price tag of $2-3 millions dollars. Regulator B, in particular, justifiably criticizes the notion that "an unaffordable technology is going to help the poorest regions of the world"

In particular, the issue for Regulator B arises when this technology is propositioned by companies as aiding *"historically marginalized communities"*, which affords them a lot of *"moral capital"* without needing to establish the political or economical structures that would allow this aid to occur: *"That's a disconnect. It's a problem"*.

They go on to talk about the importance of framing the question, and the necessity for a diversity of voices in this process in order to widen the scope in which the question of equity is considered. They explained this through a comparison of the COVID public health responses for the United States versus South Africa. While the focus for the United States was the expedited development and distribution of the vaccine, one of South Africa's public health responses was establishing universal childcare:

"The first public health response in South Africa was the extension of universal childcare grants to all women in the country. Now, I'm not saying that that's better or worse. And I'm not saying that these two are mutually exclusive. I'm not saying let's stop vaccine development [...] but I am saying that there is an imagination that thinking about universal childcare as a public

*health solution that is **beyond the imagination** of the American policy establishment"*

While both public health responses were essential and beneficial during the pandemic, Regulator B's point is that the scope of what is considered public health, can be limited when only looking from one context. In this example, universal health care is not something that would be considered a public health response in the United States, and that limitation in imagination is a product of a historical, cultural, and political context it has been situated in. In that same line of thought, in order to have a comprehensive discussion regarding what equity would look like, there needs to be a broadened imagination that can only come from broadening our perception of who gets a seat the table during these discussions:

*"You're not really going to advance an equity agenda beyond the point [...]because the questions have already been framed in this kind of very narrowly imaginative way[...] **to think that you're going to solve the healthcare problems of much of the world with that narrow imagination**, you know, I think that's doomed to failure from the get go"*

Dr. Ben Hurlbut also brings up this critic**:** *"regulation of this technology has been very, very narrowly conceived. And it's been conceived in a way that has basically excluded any pathway through which that diversity of values could even become visible"***.** Who these voices should be, who gets a seat at the table, should first and foremost be the people that would be affected most by the implementation of this technology. As the next section will explore, how should policymakers engage the communities at the center of this discussion. To this, Professor Sanghamitra Das, poses the question:

*"how will the stakeholders, the main stakeholders who are individuals with sickle cell disease [...] **what will their position be on the table** when important negotiations are being made?"*

5.2 Stakeholder Engagement

In this section I go over the necessary components for stakeholder engagement. While first acknowledging that the stakeholders involved are primarily marginalized communities, the key considerations addressed in this section are understanding and addressing the historical implications of this through reforming the consent mechanism, outreach through established sickle cell advocacy organizations, direction interaction with the sickle cell community from researchers and regulators, and the multiple scales in which community engagement should occur.

The first avenue of exploration regarding stakeholder engagement is who should be engaged? There are many voices to incorporate in this conversation, such as the impacted communities and the parents who will ultimately be utilizing this technology. There are also considerations of the stakeholder at the center of this discussion, one whose views cannot yet be heard– the embryos- with one edited embryo essentially representing the new DNA of an infinite number of generations. As Dr. Andy Greenfield points out, incorporating the multiplicity of perspectives into a policy is a regulatory challenge:

"We live in diverse societies, and as a consequence[...]we have an ethically diverse set of responses, how do you incorporate ethical diversity into a single policy? That's not easy. And you know, there's a major challenge for any regulator in any policy, to try and integrate diversity into the policy"

Dr. Ben Hurlbut, however, posits that the issue does not lie in how to incorporate these variety of values, but rather the fact that these multiple perspectives have been *"pushed to the margins and silenced"* in favor of a *"specific set of values"* dominating the discussions regarding what is at stake.

The relevance of this is all the more pertinent when the demographics at the center of this are ultimately black and brown bodies. Historically, these communities have been exploited by medical communities, and so the idea that this new, potentially risky technology centers these communities as its first recipients is a point of contention that will need to be adequately addressed in regulation.

Tesha Samuels, a gene editing therapy recipient and public advocate for SCD, highlights this being a primary concern for her family when she first told them she would be participating in the clinical trials: *"My family was like,* ***oh, so you're going to be a guinea pig?*** *And that is pretty much how African Americans are, we are so skeptical of the medical community, we aren't sure how to take it"*.

The term "guinea pig" was one that came up on more than one occasion during my research, and valid concerns regarding this are reiterated by Dr. Helen O' Neill, who emphasizes the necessity for explicit measures that counteracts a repeat of this reality:

"the historical context that black history has lived through with being a guinea pig. With being maltreated, with being abused, with being horrifically treated throughout clinical trials in history [...] ***we need to tread carefully and bear in mind the historical sensitivities and atrocities that have taken place*** *and pay homage"*

A key aspect of counteracting this lies in the capacity for individuals to be self-advocates, and according to Dr. Das, this is not possible in India because there is minimal discourse on medical discrimination:

"People don't even know that they're going through injustice, that they're being deprived or something and they are being discriminated [against] because they have no knowledge about the way these [happen]. ***If you have people who have been excluded from institutions for so long, you cannot expect them to know how these institutions have not been serving them.****"*

Lack of complete information creates a barrier for patients to be self advocates- and this lack of complete information can manifest in many ways, such as through minimal effort on the

part of researchers to dismantle barriers to communication. Onus is on the researchers to ensure research participants are fully informed. And in a situation of this gravity, what has been traditionally considered informed consent needs to be reimagined. As Dr. Das explains, gene therapy clinical trials for sickle cell therapy rely "*primarily on black bodies, indigenous or diverse bodies"*. Seeing as these populations are more vulnerable to exploitation, Dr. Das asks**:** ***"Where is the consent mechanism?"***

Although I have outlined the danger of exploitation of black and brown bodies for research, it should also be established that if research on disorders affecting mostly marginalized communities is going to be conducted, it *should* involve the communities that are disproportionately affected. I am not saying that these communities should not be present in research such as this because it would inherently be exploitative. However, I *am* asserting that honest conversations through a reformed consent process are necessary in order to avoid research entering that trajectory. The first way informed consent needs to be reimagined is making the focus of that process genuinely for the patient as opposed to being for the researcher. Dr. Kelly Ormond, speaks to this saying:

"I think that oftentimes what ends up happening in medical research studies is that, you know, the researchers have to develop a consent form, and they are worried about lawsuits and they write down every bad thing that could ever happen. And it's a huge long list [that] ***doesn't really tailor things to what that research participant needs or what their differences or values are****, and how they're approaching things. [...] What I would hope is that for something that's as big a deal as gene editing, that it really is a process where people get to know the potential research participants, talk with them about what they're hoping is going to come out of this, what they're worried about, what we know about it"*

Dr. Das reaffirms this, calling the current system of rating a pain scale to be a *"violent, epistemic process"* that the communities she has worked with have pushed back against: *"How much pain am I supposed to read from one to ten. How can I measure my pain? Yes, sickle cell*

pain is also a social suffering. It's not just medical stuff". SCD affects so many different areas of an individual's life that a pain scale cannot possibly measure. While there is the physical pain, there is also pain associated with the inability to work, go to school, or be present in the lives of loved ones– and of course the financial strain from a lifetime of costly treatments. There are so many different avenues in which pain manifests that translate into the outcomes individuals with sickle cell wish to see from a treatment.

One point Dr. Das emphasizes is that this cannot be framed as a complete solution or cure in the way that gene editing has traditionally been framed. Because sickle cell can be an all-encompassing disease, there is no cure-all solution, and to market something as such would be misleading:

"Gene therapy cannot claim that it is the one all be a cure for sickle cell disease, because ***it's a socio-biological problem. It's a socio-political problem. It's a problem of human suffering****. So as long as gene therapy doesn't assume to be the solution, and just be there as one of the therapies available to people to participate, its implementation will be more ethical"*

One critique from Dr. Ben Hurlbut, in reference to the National Academies International Commission on HGE**,** is the way in which parents have been left out of this discussion. Although it is parents who are making the decisions to engage with this technology, he has noticed the parental perspective has been shut out from these conversations:

"I pointed out to the chair of that committee at one point, like, ***you don't have anybody with any expertise about being a parent.****[...] this is about having children, where are the people who have the experiential knowledge of parenting, let alone have understood the significance of kinship, the ways in which procreation figures in different cultures and societies [...] There's a vast number of things that one would want to know about with regard to parent child relationships, let alone a whole set of other relationships, visa vie genome editing, and yet that just didn't even occur."*

The parental perspective is an essential one to both hear from and educate. The parents are the ones acting as a proxy for their future children. Whether they should, however, is contemplated by Dr. Ormond. Although parents are typically the ones that consent on behalf of their children, given that children are considered not yet able to consent on their own, it becomes complicated when discussing an embryo that is quite literally unable to consent on its own. Even if one could argue that parents can consent on behalf of an embryo that will eventually become their children, Ormond contends that it's *"trickier when you talk about unborn future generations,[...] it's not clear that parents can indefinitely consent for an infinite number of generations going into the future"*.

These are ethical judgments that may not be resolved within the scope of this paper, but considerations such as this are what needs to occur in public discourse. As Dr. Hurlbut emphasizes, public engagement needs embody the meaning of *engagement*:

"Public engagement is not just about [making] people aware so that they can say, Wow, that's cool, then go back to whatever they were doing. It's about public deliberation. It's about saying ***what is a good future?*** *What is the future we want for us, for our children? [...] What are the kinds of responsibility we have to take for that? Those are democratic questions".*

However, Dr. Hurlbut believes this is not only not being done, but that there is an deliberate resistance to having these conversations on the part of regulators and researchers:

"There's been very little effort to bring these things out into public space and to say, Hey, this is a pretty big deal. This is about the human future. This is about deploying a technology that could change what it means to be human. This is not for the biotech companies or the scientific societies or whatever to decide this. This is a better [discussion] for all of us. There has been very little effort to do that. And in fact, ***there's been active resistance to doing it****."*

Regulator C talks about how there are multiple levels in which community engagement can occur, such transparency pertaining to the research process and *"democratic accountability*

of the scientific enterprise". They assert that it will need to be *"community engagement at different levels or at different stages in that decision chain"*. As they continue, they explain the necessity of this for trust going forward: *"...if you want people to trust medical research and treatment organizations, they've got to see their values and their concerns reflected within its priorities and with decision making"*.

Tesha Samuels reflects this sentiment as well, explaining that there are communities and populations that are not as knowledgeable about their options, such as gene therapy, and emphasizing the role of regulators and researchers in *"making us as the community feel like we are a priority; that they want to know what we think about how we're receiving information and use that as the basis of how they move forward."*

However, what are the methods in which researchers should be engaging with these communities? Tesha Samuels believes it should be through collaborations with recognized community-based sickle cell advocacy organizations, such as Journey to ExSCellence. Additionally, the way in which communication is conducted needs to be *"palatable for all educational levels"* through resources such as *"pamphlets, QR codes [and] patient advocates within the hospital that can take information from a scientific level and break that down*". She also highlights the importance of regulators and researchers actually being present at sickle cell community events: *"we want to see the faces behind the scenes"*. This would allow for more direct communication and would additionally foster a sense of familiarity and trust.

Dr. Kelly Ormond shares a similar thought regarding how we need to engage with the Sickle Cell Foundation and begin educational efforts from "within", such as through support group moderators. She emphasizes the need to involve the efforts of those that are already

established as trustworthy individuals in these spaces, which can result in comfortable spaces for people to talk about their options and ask questions. On the topic of language, Dr. Das cites language barriers as roadblocks regarding education and consent, calling for the need to *"simplify languages to the local context"*:

"There is a necessity I feel if in regulation [to] ***center community knowledge and not say that they're illiterate or they don't know enough technical details*** *[...] actually pay attention and give serious thought to what they're saying. Why are they saying that this is not going to work? [...] it is most likely that they will have an opinion about these transformative radical technologies. Maybe not in the language that we're used to, but they definitely will because it's* ***their bodies that will ultimately be on the line****"*

Because it is black and brown that will "ultimately be on the line", SCD Expert A exerts that the topic of community engagement is not a question, but a requirement: *"[...] community engagement is essential… you must have [the] community at the table.* ***Don't do anything without us".***

The final topic I will explore in this section is the perceptions of stakeholders with SCD, both on the topic of HGE as well as their knowledge of gene therapies in general. SCD Expert B, who works closely with the sickle cell community, gives clarity on how the views on HGE for individuals he has worked with are "clearly mixed" regarding the "appropriateness" of the technology:

"Those that were supportive of it were from the perspective of eliminating sickle cell disease from that family. Future children would not have it, and they were supportive of it. And so there were some members, particularly individuals living with disease, and some of the caregivers that just want to stop sickle cell disease within that family. But there were a lot of concerns expressed about the perceived risk, and not knowing the future. And so that there was concern that the potential adverse impact it could have on future generations in a family and not knowing that. And so that was articulated as an important issue. And so ***you're not just making a decision for yourself****, but you're making a decision for your future family"*

SCD Expert B speaks on how the community is very *"engaged"* and *"aware"* regarding these discussions of new therapies, and have been *"seeking knowledge to understand the risk and benefits to help them make decisions"*. They bring up a point, however, that the level of information people have varies, and there is an importance in education regarding gene editing technologies in general, because the distinction between the different "kinds" of gene editing (somatic versus heritable) is not clear to someone without a background in this space:

"[...]society wise, when we think of gene editing, there are so many different things that are raised. Part of that is heritability. And so I think some individuals are like, Oh, well, I had my genes manipulated, and genes, you know, infer a level of heritability, therefore, my future generations will be fine"

Education is required from the ground-level up. Outlining definitions, goals, as well as being transparents about the risks and the unknowns. As the next section will detail, there are risks and still many uncertainties regarding heritable gene editing. Tesha Samuels details the work that will have to go into the communication of these factors:

"It's an uphill challenge, and that's why I said this community really wants to see and talk to and learn from those who are behind the science to kind of come from a humanist perspective [...] it really is going to take work on the behalf of warriors, community based organizations, practice practitioners, scientists to really formulate and strategically put a plan in action of how to present this treatment in a way that is palatable that they can actually understand what is happening with the genes. And what the potential lifelong implications are, ***be honest about the unknowns and come confidently with what you do know****."*

5.3 Risks and Uncertainties

In this section, I will outline the risks and uncertainties still present within discussion of HGE. Key points of consideration include how the conversation of risk is altered when discussing *heritable* gene editing, the necessity for updating discourse surrounding these risks, and methods from both a regulatory and research standpoint for reducing risk.

While somatic gene editing is considered a form of gene therapy, Dr. Ben Hurlbut contends that this label should not be extended to heritable gene editing:

"It's a false analogy to call this therapy because you're not treating anybody? ***You're creating somebody. There is nobody until you do the CRISPR*** *[…] Can we just approach risk the same way we approach risk conventionally in biomedical research? I think the answer is no, because it's a kind of fundamentally different thing."*

He goes on to express how the most significant risk associated with the technology is that if something goes wrong, researchers are essentially *creating* someone with genetic abnormalities they would have otherwise not had. Dr. Ormond supports this notion that the unprecedented novelty present in HGE would require a *"language of risks"* that *"implies more precision"*. Dr. Kiran Musunuru also mentions this necessity regarding a distinction in language. Particularly regarding the word "cure", he states that we should not use the rhetoric of this being a cure when *"they don't have the disease to begin with"*. Rather, he refers to it as prevention, but also acknowledges the ethical concerns regarding whether the decision to prevent is one society can make for the future: *"You're making a pretty big decision for unborn generations"*.

As discussed in my literature review, much of the discourse surrounding HGE encompasses concerns such as the presence of off-target effects, as well as its implications for the future. Dr. Helen O' Neill wishes to reign these conceptions in on both fronts. In order to

have productive discourse, she says, we need to position current capabilities at the center of discussion: *"we talk about possibilities far too far away, and limitations that are actually outdated"*. In particular, Dr. O'Neill criticizes the obsolescent discourse around risks, stating that it is very outdated. She explains that the CRISPR technology has been an extremely fast-paced technological landscape, and the literature is being left behind, even from reputable sources such as the World Health organization:

*"As a researcher working in genome editing, I have **never seen a faster evolution of discovery than with CRISPR** [...] the abundance of new research, new capabilities, new cast enzymes, new guide design mechanisms [...] the technical feasibility that we have today is miles ahead of last week. Miles ahead, like within a year we're just seeing wild differences in our capabilities. [...] three to four years ago, it was classic CRISPR Cas-9. Now we have base editing, prime editing, even down to like EPJ epigenome editing [...] the way we've harnessed and engineered genome editing capabilities is unbelievable. And yet, people don't keep up. They still talk about, well, CRISPR causes unwanted edits– which one? CRISPR Cas-9? CRISPR Cas-12, CRISPR-cas12a [...] it's inaccurate, and this doesn't [just] happen on smaller levels. The World Health Organization's report was so wildly outdated"*

Dr. O'Neill explains that unwanted edits or off-target effects are largely associated with CRISPR Cas-9: *"you literally had to break the DNA. And so you would imagine that the DNA does quickly repair and that causes unwanted edits"*. However, other methods, such as prime or base editing address these caveats in the previous technology quite efficiently: *"with prime editing, you literally unwinding the DNA, replacing a base and then it winds back together. You don't get the same collateral damage. It's hugely efficient, unbelievably reliable, but **the rhetoric is so slow to move on because people copy each other's words**."*

Regulator A, and multiple other researchers, also brought up these alternative methods that can minimize the risk of off-target effects, and explains further the science behind their efficiency:

"Rather than both strands of the DNA being broken. Just one strand is broken, but the difference is that if you make a break in both strands, they can do wacky things. This is actually how lots of cancers start, because double stranded breaks can occur naturally if your cell is exposed to a carcinogen or some kind of a salt, high energy, radiation, maybe from the sunlight [...] It causes DNA breakage like this. And this can be carcinogenic. So actually, your cells have machinery to actually stick the ends back together very quickly. Otherwise, they can stick onto other chromosomes, the end of the other chromosomes over here, or another double stranded break over there. And so ***it can lead to a complete catastrophe, for the cell and the organism because cancer can be lethal. And so, double stranded breaks are generally things that you want to try and avoid****, but CRISPR Cas-9, the original version, makes double stranded breaks, and that's how it is. So it starts by making double standard break and then the repair machinery of the cell [...] comes in and fixes it in a certain way and you hope that it takes it in the way that you want so that you've sorted out the you know, the hemoglobin gene variant or if we're talking about [...] But the trouble is, things can go wrong and these things can do all sorts of other things [...] Now, if you just make a single nick, actually the DNA hasn't come apart because there's still the other strand there. That's good"*

While Dr. Andy Greenfield expresses his belief that there is still no foolproof solution, options such as base or prime editing are certainly safer when considering correcting single-point mutations, which is the case for sickle cell anemia, because *"neither of them involve having to introduce a double entry in the DNA and it causes that double stranded break, which is really the most risky process"* .

However, even if there are methods for minimizing risk, even with how gene editing technology is utilized presently, adverse reactions can be continuously monitored in the patient. Additionally, because there is a "before" and "after" treatment, there is a baseline in which you could compare a newly treated individual to how they were functioning in the absence of any treatment. With heritable editing, there is no "before" to be measured in the sense that the individual would essentially be born with the preventative treatment. One question going forward will have to be how researchers will be able to make a causal argument regarding whether an issue observed is a result of the gene editing or would have otherwise occurred naturally? For SCD Expert A, this is a main concern regarding the conversation of risk:

"I think that risk is just sort of amplified in heritable gene editing because, essentially, what you're saying, is the period of 'wait and see' is much longer and so you will need a person to be born and turn to the world, live their life and, you know, sort of see if there's any issues and then [if] you have another issue on top of that, ***how are you sort of going to make like a causal argument*** *that it was the gene editing? That the gene editing from their parent has caused whatever maybe genetic mutation that they're seeing now"*

On the topic of being unable to observe fully risk until a child is born, Gene Editing Scientist A says, *"one thing that's charming about DNA is that everyone has a different set. [...] you can do studies, [observe] trends generally, but it's hard to predict how it's gonna affect a grown up by the end of the day, what someone is going to grow up to be"*. How we can begin addressing these risks, ultimately falls back to research. Specifically, how research is conducted. Dr. Kelly Ormond details how determining and mitigating risk in gene editing interventions will be a product of how we *"structure our clinical trials"*, in particular, the involvement of stakeholders:

"[...] who is being included in the trials, how they're assessing it, and how much do we know about the genetic and genomic backgrounds of people from diverse populations, essentially. So if they're looking at off-target changes, how are they going to be able to say there have been changes or not, ***if we don't have a clear sense of what the normal variation is just between people from different populations?****"*

Regarding how research is conducted, Dr. Andy Greenfield sheds light that "the first basic rule of thumb" of safety assessments would be ensuring that the gene editing intervention is only introducing the mutation it claims it will, and nothing else to the genome. From Dr. Kiran Musunuru's perspective of currently going through the FDA regulatory process for his gene editing treatment focused on heart disease, he explains that ,regarding gene editing in particular, the FDA has decided to set the bar *"very high from the very beginning"*. In comparison, other countries, such as Australia where he has also worked on somatic gene editing, treat the regulatory process for gene editing more in line with traditional drugs:

"It's a totally new type of treatment, right? You're talking about rewriting DNA. It's like a one time thing. You give it once and then it makes the change. And then the intent is that it's good for the lifetime. And so no one really knows the best way to handle this right? So everyone's kind of making up their own rules, and the FDA decided to be very, very conservative. Other countries have not been as conservative and they've treated it more like traditional drugs. In the end, the bar will still be high [...] no matter what country you're in. It's just the question of the process of getting there."

He goes on to explain that with heritable editing in particular, the standards would be "doubled" from a regulatory standpoint because there are multiple parties involved in the treatments: *"it's not just the kid in the womb [...] make sure it's safe for the fetus, but just as important, arguably more importantly, gotta make sure that it's safe for mom"*. How this is done in scientific research, with producing any medicine, is through animal models. Only when you have *repeatedly* observed both safe and effective results in many animal models, will the FDA begin to consider clinical trials with humans. In describing this very extensive process that he is undergoing for his clinical trial process, Dr. Musunuru says:

"Now we're starting to do clinical trials, we're starting to get [that] data. It seems to be relatively safe, with the first one to 100 to 200 patients, and so that will open the door for more trials. As the FDA gets more and more comfortable with this as more and more trials are done as more and more patients are treated and it looks like nothing too bad is happening. Then it will really start to open up and it won't be such a high bar [...] We had to go through years and years and years and work just for one treatment."

However, even with extensive trials, there is always the possibility that unanticipated events would occur, as Dr. Musunuru explains. The only way to monitor this would be through following the patients for many years in order to catch anything that would be amiss *"sooner rather than later"*. The struggle, he says, goes back to the discussion of informed consent: *"it can be very hard to define the risks, right? Because some risks you can't even anticipate, you*

know, they're undefined [...] And so how do you communicate that to patients? How do you communicate that to parents ".

Dr. Kelly Ormond acknowledges that there will be varying amounts of risks that individuals will be willing to take, and it will take a balanced communication style on the part of researchers to ensure individuals are "understanding what they are getting into", but not in a way that is going to attempt to talk them out of something they wish to do *"[...] some people really would be more willing to take risks and that's okay, but what we don't want to have, [is] people go down this path [where] they don't really understand what this might actually be like"*. She adds that this will be difficult due to the unknowns, but that it is even more reason for a reformed informed consent process as detailed in the previous section: *"most of us don't really understand what it's going to be like because it's new and we haven't done it before. And there are a lot of unknowns. So in those situations, it's not just 'please read me the form and tick the boxes'."*

For Dr. Das, she recognizes that these adverse events are *"sadly a part of a clinical trial"*. However, her concern lies with how such events will be recognized and reckoned with in the greater scheme of the trial. She emphasizes a necessity for accountability when a life is lost, rather than researchers attributing adverse outcomes to individuals not following protocol or their biology being at odds with the treatment:

"What counts as acceptable level of risk? For example, you know, 100 trials, 70% of them are successful, 30% of them are not. Be accountable to that 30% too, they fall off the grid. They got into the trial thinking that my life will be a little better but they weren't. Their life didn't become better. [...] How do we not let people slip between the cracks and how did we let their stories not matter? That is something more of a risk to me. We should not let people just slip through the cracks, and pay attention to each and every story. Because without their participation the trial would not have been successful. ***Their physical death matters****"*

For Gene Editing Scientist A, and many in this study, the priority is the research being as "precise" as possible before it is ever considered for release to the general public. While ensuring

this level of accuracy will not be an easy process by any means, it goes without saying that it is a necessity, because as Scientist A puts it, there is *"no way back"* once the door is opened.

Tesha Samuels brings up how it is not just a question of literal risk, but the spiritual and ethical concerns at the center of the HGE conversation. She admits to being very conflicted:

"Just to be able to live at this level. For me, it blows my mind each and every day. And it's something that I'm grateful for. My concern is that, how do we do it and approach it in a way that is ethical. When you go into a point where you're changing it prior to the child's birth, I see it as, wow, this child is getting a chance to have a normal life but then are we playing God, you know, with changing the trajectory of a lineage…generations down the line? That is the conflict within me [...] not just on a human level, but a spiritual level for me and my beliefs. But it's almost like how could you deny someone this experience of having life and enter a higher level where they're able to from birth, you know, be able to have access to all of the things and experiences I wish I had at the time [...] still it's twofold for me. And I don't have a definitive answer."

She brings up the concern of "playing God", which is a phrase and concern that was also present during the literature review I conducted regarding the discourse around HGE. For Samuels, she comes from the perspective of experiencing a life with SCD before and after her gene editing treatment. While gene editing has led to many benefits– tangible and intangible– in her life, she is understandably undecided on the morality of the technology. In the next section, the benefits that Samuels alludes to in this quote will be discussed in more detail. As she also mentions in her quote, the reasoning behind HGE is to prevent someone from ever having to live with disease. In order to pontificate on whether HGE should be utilized in preventing someone from ever living with a disease, it must first be understood what it is like to live with said disease to begin with.

5.4 Identifying Potential Benefits

Tesha Samuels paints life before and after receiving gene editing therapy in stark contrast. For Samuels, the disease was the only thing she had known for almost her entire life:

"At seven is when I had my very first crisis that landed me in the hospital. It is called an aplastic anemia crisis. And so this is when your hemoglobin is not producing red blood cells, the way it should be [...] Consistently as I age and progress, pain became an everyday thing. So from the age of 13, I cannot remember or could not remember a time where I was not in pain, like every day"

She details occurrences throughout her childhood that would happen as a result of the disease, such as mild strokes that rendered her with no feeling on her left side for a span of 6 to 8 months. Because she was young, she was able to make a full recovery from this. However, just a few years later, at 16, she would suffer a pain crisis that almost took her life:

"I had to have two, three chest tubes [...] and was sedated and placed into a drug induced coma in order to keep my brain and my body from feeling that type of pain. They thought it best for me to be in that state so that the body can heal from the inside out. But as a result of that, I had to regain and learn how to do everything, from taking care of my own personal hygiene, getting dressed, things of that nature"

The crisis left her wheelchair-bound for the remainder of her highschool years, spending her senior year in a rehabilitation hospital, having to make decisions regarding pain pumps as opposed to prom. In her adult years, she is able to become more independent, although she required monthly blood transfusions since the age of 18. By her 30s, she was on medication that meant she had to get transfusions weekly. She recalls a hematology appointment when she was 34 years old, where her doctor informed her that there had been damage to her kidneys as a result, and there was nothing more they could do for her– she would need kidney dialysis. Sickle cell disease had dictated so many aspects of her life: *"I was tired of the merry go round. I was tired of living in pain every day. I wanted children and had been unsuccessful with my husband because of the sickle cell and so…I was desperate."*. In her worst moments, Samuels admits that

the burden of the disease was enough of a drain to her mental health to the point that she considered taking her own life:

"And I just remember a moment where I was driving and it was a ditch. I was in so much pain, I was leaving work. And I almost felt like if I just drive over this ditch and just end this, I would be out of pain. It'd just gotten to a point [where] I was fed up [...] thank God that I did not and my faith really kept me grounded to say there's a purpose for me"

After this appointment, she reached out to the National Institute of health (NIH) which is where she found out about the gene editing clinical trials. Upon learning about the study, she felt as though it was meant for her. Admittedly, she knew it would come with risks and that nothing was a guarantee, but at the stage she was at she expresses that she was ready for any outcome: *"Didn't know if it [would] even work, but for me at that point healing will either come through treatment like this or it will come by death and that was okay".*

The treatment, however, was successful, and Samuels life has experienced a significant shift in her quality of life:

"So many improvements. The first would be then not having pain. As I explained there ***hadn't been a day that I didn't wake up in pain and go to bed in pain****. And so as the gene therapy started to take effect [...] you realize, wait a minute, I woke up and I don't have pain. So that was the remarkable difference. Another thing is the energy. A lot of times the pain would just deplete me of energy [...] I would be out of breath needing to take multiple breaks.* ***I had downsized my dreams so many years*** *of, you know, what can I do that wouldn't interfere with the pain episodes or could I finish a semester[of] school without being sick in the hospital for two months and missing out on all this schoolwork. Would I be able to contribute to society by actually being able to go work a full time job, still be a good wife, still be a good daughter, disciple, all of those things that mattered to me. So the energy has been different. I'm back in school. I'm able to kind of really use my time for me, things that I love to do. So that is some [improvement] that only scratches the surface."*

While this is Tesha Samuel's story, her life prior to gene editing is also a reflection of the reality for many individuals that are born with SCD. The impact on their everyday lives can be encompassing- physically, mentally, and financially. Even with available treatments, they are still experiencing immense pain. And not only do they have to suffer physically, there is also the

psychological burden of their pain being dismissed, and not believed within medical institutions. Samuels cites this as the reason for her beginning her advocacy work at just 13 years old, after overhearing doctors outside her room accusing her of exaggerating her pain: *"[they said] she's on so much medicine we could kill a horse, she cannot possibly be in that much pain. She's lying"*. The therapy Samuels received was somatic editing, meaning that it only affects her genome. However, the theoretically proposed benefit of HGE is that the quality of life (QOL) of Tesha Samuel's experienced post treatment would be the baseline QOL of subsequent generations without them needing treatment at all. SCD Expert A explains this reasoning: *"theoretically, the idea is that every person who gets heritable gene editing is [...] patient, zero, but in a positive way, right? They would [be]* ***patient zero or patient X in the sense that it ends with them****"*.

Dr. Helen O'Neill adds on to this saying: *"the benefit of correcting a mutation [...] is that you do remove it from the germline. And so that fear of passing things on is removed to an extent. As opposed to[...] perpetuating a carrier status"*. Although, Dr. O'Neill mentions there would be costs associated with monitoring edited individuals, as detailed in my literature review, the cost of lifelong treatment for SCD creates financial burden that can have a long-term impact on overall socio-economic mobility. When you take this into consideration, Dr. O'Neill says, HGE could pose to be far more equitable and sustainable for families:

> *"in terms of actually the price point for preventing versus treatment, ongoing lifelong treatment, and then a single one-and-done trial,* ***heritable genome editing could mean far greater equity****, especially if it prevented the transmission or heritability of a condition in families thereafter"*

5.5 Accessibility

In this section, I will outline the anticipated barriers to access as well as possible solutions. The common themes across responses include that the main barriers to access would be the establishment of infrastructure required for heritable gene editing, such as In Vitro Fertilization (IVF) clinics, as well as high prices due to corporate profiteering.

The topic of IVF clinics being a substantial consideration was not discussed in the literature review I conducted, and was not something I had understood as being a necessity prior to conducting my research talking to experts. However, it was one of the most common factors mentioned as a barrier to accessibility, as well as regulation as the next section will detail. During IVF, the egg is extracted from the women's ovaries and fertilized with sperm in a laboratory, the resulting embryo is then returned to the women's uterus to grow to term (NHS). The heritable gene editing process of genetically modifying the embryo and subsequently implanting into the uterus would also utilize the IVF process. According to Dr. Ryan Clarke, the added cost of performing the germline editing would actually be *"very little"*, and Dr. Helen O' Neill agrees:

*"Germline genome editing is cheap. **It's actually cheap**. You're applying something to an embryo, a bunch of enzymes, [...] that's the one benefit of CRISPR; it is very cheap. It is a nucleus and some guide design tools. Doesn't require expensive equipment. The components themselves aren't expensive."*

So if the technology itself is not expected to be expensive, what regulators and researchers alike, in the words of Dr. Clarke, expect to be the *"big cost driver"* when it comes to making the technology accessible on a global scale would be the establishment of the necessary infrastructure, such as IVF clinics. As Dr. Musunuru explains:

"they're always gonna be the IVF costs, and that isn't cheap [...] embryos don't come from nowhere, right? [...] you have to get eggs from mom and that involves getting treatments and collecting the eggs, that's a surgical procedure [...]Sperm are much easier to obtain for the

obvious reasons. And then you actually have technical skills keeping those cells alive, keeping them in good condition ,and then actually doing like the micro needle injections of different components"

Regulator A agrees that one of the most pertinent accessibility barriers is whether these fertility centers are *"already in place"* there. Dr. Kelly Ormond adds on to these considerations, saying it is not just the presence of these clinics, but there is so much more to discuss when it comes to accessibility, especially regarding the geography: *"the geography of how healthcare happens is also another place where we're going to see differences, because many of these treatments really are going to come out of these large academic centers, right that are usually are located in cities"*. There are many logistics at play with this consideration, such as the fact that people would need to travel to these locations in order to receive treatment. And as Dr. Kelly Ormond continues to explain, it's not a "one and done therapy" in the way that people discuss it as being:

"[..] it's not that simple. Because the things that lead up to when you get it and how they have to, you know, in many of these cases, take some of your cells and then they need to culture those cells and then they need to [put] them back [...] all of these things are going to require people to take time off to drive long distances to you know, be in the hospital for a while [...] I think we often aren't discussing beyond just the cost of the treatment, let alone the cluster of all the hospitalization and the medical care that goes along with that right. So this is gonna drive inequity as well, ***we might solve the cost of the drug problem, but we're still going to have all of these other challenges too****."*

On the topic of the issue regarding the cost of the actual treatment, Regulator B's core issue lies with how the treatment is discussed versus how it is implemented. While they do not want to claim that all researchers are dishonest, they do have the view that the racialized discourse around gene editing treatment for SCD is very intentional on the part of pharmaceutical entities: *"it's not coincidental that sickle cell strikes moral gold [...] it strikes moral gold because it falls into this [claim] we're saving the black people of the world [...] and so it allows for this sort of morally impregnable conversation, like who could fault us for that"*?

However, the *"market reality"* is a price tag in the millions. And to this, Regulator B asks how companies plan to accomplish the goal they build a platform upon of helping the *"neediest people of the world"* without any mechanism for how to accomplish this: *"the disconnect was never breached"*. Dr. Das spoke about asking a similar question to physicians and scientists, with the response she received being that it will *"initially be expensive"* but that it would be *"subsidized"* later in life as it becomes more widely used. While she recognizes that this is usually how it happens, she questions whether it is the best way it can happen, describing the concept as a ***"futuristic promise that one day you will be free of suffering".*** Tesha Samuels details the deeper impact here, for the sickle cell community, and in particular African Americans with sickle cell disease:

*"It's almost like **dangling a carrot** in front of this sickle cell community, because a lot of us, in large part, come from backgrounds [of] primarily African American descent. [We] are the stories that are really that you see in front of you even though it's a disease that can affect middle eastern, Indian you name it. [...] when you dangle the carrot, it's almost like this is this **promise of a cure [but] by the way it's $3 million.**"*

Dr. Ben Hulburt criticizes the pricing structure as basically *"pay up or die"*, expressing his belief that believing that the system is *"built"* to ensure people of lower income levels, and even people of moderate income levels, would not have access:

"there's something perverse about recognizing that we have the means, in principle, to deploy what are effectively cures in a possibly economically manageable way for many, many, 100s of 1000s of people who suffer with diseases like sickle cell disease in the Global South, but we're not going to do it."

Despite his criticism, Dr. Hurlbut also emphasizes that the situation regarding corporate profiteering is multi-dimensional, explaining how this area of research is a very expensive one to be in, and as a result there are companies *"on the verge of closing up shop"* due to running out of money: *"I mean, it's a very expensive, and there's a lot of risk involved. And so I don't want to belittle that at all"***.** To this, Dr. Ryan Clarke talks about how for many companies, the

risk-benefit calculation becomes one in which cost-effectiveness is not prioritized. He provides more insight from a company perspective:

"In a company perspective, unfortunately, a lot of the time, the risk and benefit has to do with, like, potential dollars associated with how much it'll cost to get something to the clinic, then how much will the drug cost afterwards? [...] will the FDA ever approve this? How expensive is it going to be to turn it into a process that can be commercialized? And then hopefully, it would also be like, how big is the addressable patient population? Is it too expensive? Are we going to make money because it's a one and done treatment? And I'm not saying that those are the right things to think about, because I disagree with a lot of them, but I've just seen what sort of calculus you know, investors, or elite or like executive teams will have to do."

In addition, there is also the essential aspect of getting the technology to actually work in a way that is both safe and effective. As we have learned from the insight into the regulatory process that Dr. Kiran Musunuru provided, this is a very long, extensive, and expensive process, ranging in the millions regarding the cost a company would have to invest. And because the technology is so novel, Dr. Clarke describes that these companies have to *"invent so many steps along the way"* which compounds additional costs.

Part of the issue, as Regulator B describes, is that *"science is no longer public science"*, but rather a *"heavily privatized science"* with profits as the motive as opposed to public good. In regards to germline gene editing within the United States, the research of this technology currently has no choice but to be driven solely by private or corporate entities. As a reminder, germline editing research (modifying the germline without implanting the embryo) is legal in the United States. Heritable gene editing, the focus of this paper, involves germline editing, but would be the next step of implanting an embryo with a modified germline into a uterus. This has not yet been legalized. However, they are very closely connected, as scientists will have to establish substantial research on editing the germline before it could ever progress to heritable

research. This also means that the regulation of germline editing will have a direct impact on the research and future accessibility of heritable gene editing if legalized. As mentioned in this paper's earlier review of the current regulatory landscape, although the United States allows for germline editing research, they restrict the use of any public funding for it. As we have seen with the current gene editing treatments, the exorbitant price tag can at least be partially explained by how much money has to be invested by companies. With the prohibition of any public funding for germline research, the financial risk is not only still present but heightened, as SCD Expert B explains:

"within the US context, regulators have put restrictions on [germline] genome editing so people cannot get NIH funds or federal funds to support research to do [germline] gene editing. So that's kind of like the current restriction [...] you got your own money, go up and do your own thing or got a benefactor that's giving you money"

For Dr. Das, this is a problem, because she believes that *"what funding looks like would tell us how equitable it will be in the future"*. She emphasizes that not all scientists are motivated by profits. There exist people who do research for the purposes of helping people– but they do not have the resources to do so. In her view, there needs to be public investment by the government into researchers with these goals because *"the state has responsibility for the sort of disability that is in the blood…**they say our blood is disabled**"*. Who is funding the research can speak to its expectations to help the people it claims are the center of its ethos once developed:

*"What if we insert social justice into that researching process? You are going to be gene editing, and mind you, be careful that this is a disease that you guys have said affects marginalized communities. So **what is the model of research that should be allowed**? Is it corporate funded research for gene editing or public funded research for gene editing?"*

Dr. Ryan Clarke also believes there are researchers that have equity as a genuine goal. His company, although in the early stages, is making progress in their development of a somatic

gene editing technique that will make the process more efficient and therefore more cost-effective, a goal that he expressed his company is committed to. He also acknowledges that are other researchers that share this similar aspirations:

"People are thinking like, what's the next wave of innovation, and ***they're finally starting to pay attention to cost****. And that being a part of your technical value proposition […] I'm seeing many more waves of newer entrepreneurs and technologies coming out that are like a core part of their thesis. And I hope that that just means that the price tags will be coming down soon."*

While Dr. Musunuru shares a similar thought that the *"burden"* is on scientists to make the technology *"better, faster, cheaper"* in order to make it more accessible, Dr. Helen O'Neill shifts the discussion of accessibility to a new direction: *"if you don't know something exists, you can't get access to it"*. She emphasizes a need for education so that people are knowledgeable about whether they carry the gene and their treatment options. Especially regarding the possibility of heritable editing, she says "time is everything" because people should be educated about their options before their decision to have children, in order to make informed choices. She describes it as a *"key step"* in ensuring equity of access because *"to know your place at the table, you have to know the table exists"*.

While Dr. Ben Hurlbut acknowledges the process of accessibility will be a difficult one, he believes its possibility would hinge on society's ability *"think creatively about how you could take something that is a good thing, and make it available to people who are deserving of that good thing, in the way a good society does"***.** Dr. Andy Greenfield, who sits on the National Academies International Commision on Heritable Gene Editing, says this was a priority in their discussions: *"No one wanted to see on our commission, you know, an incredibly expensive, but safe and effective intervention in the heritable space, which was only affordable to a tiny minority [in] countries like the UK in the US. And an even tinier minority of the world"*.

As discussed earlier in this section, one of the primary barriers to accessibility for different parts of the world would be the lack of existing infrastructure such as IVF clinics. In response to the question of what strategies are being considered to make the technology accessible, Dr. Greenfield believes it would have to be an international investment into the improvement of lives globally. He describes that investing US dollars or Euros into the establishment of infrastructure such as IVF clinics in developing countries would be more economically sensible because the *"dollar would go a lot further"*, and would be able to accomplish more regarding development than in the United States, where $10 would go as far as to *"buy a coffee"*:

> ***"****There there might be ways of actually making progress here that involves kind of careful, smart investment by rich countries into the global South, allowing them to develop an infrastructure that would that would support technologies such as IVF, which of course IVF is probably not available to the vast majority of people in many countries, not affordable and so it would have to involve the development of infrastructure for IVF. And then also the development of infrastructure for genetic testing of embryos, editing of embryos, safety assessments, you know, these are all things that you can't really cut corners on. Any clinic that decides that it can do this can offer this as a service, we need to demonstrate that they're competent, competent in all of those different aspects of heritable genome editing, and there are many options that they have to demonstrate competence, but all of that can be taught and can be, can be trained and can be developed, given the right the goodwill and good money. But it will require both; I think it's something that will be a slow process of collaboration [...]* ***A roadmap of collaboration and investment. It's a long term roadmap, but it could work.*** *It could work"*

One consideration of his regarding this method, however, is how to *"build bridges of collaboration"* without being *"patronizing or paternalistic"* to these countries. The only way to mitigate this, he says, is to assume nothing about what these countries would want, but instead establish a *"two-way dialogue"* and communicate with the *"groups, societies, and professionals"* in those countries. Because as the next section will explore, there is a political, historical, religious, and cultural context that will be a factor in every country, and this context is

what will shape their views and regulation regarding heritable gene editing. As Dr. Greenfield highlights:

"No population wants to be told that this is how we're going to deal with this particular disease. They will need to decide whether that is an acceptable solution. And so we have to listen to that. And it might be that some countries, particularly those that have a particular faith, may turn around and say: No, thank you."

5.6 Contextualizing Regulatory Landscape

In this section, experts will discuss examples of the cultural, historical, religious, and political components that will be a factor in countries when it comes to regulation or public reception to HGE. Key considerations discussed in this section are the challenges regarding establishing universal regulation, the reliance of HGE regulation on existing IVF laws in respective countries, and the importance of respecting cultural attitudes towards the technology.

As discussed in my literature review, there is some consensus currently regarding regulation towards heritable germline editing. There is global attention on HGE and how it should be regulated. This is what motivated World Health Organization to release its guidelines, as SCD Expert B points out:

"On a global context, like the World Health Organization has come out with policies and guidelines, various countries have come out with views [...] there [is] clearly a recognition, both in a US context and in a global context. That we need to have principles in place to protect the public with regards to risk"

However, as multiple experts highlight, establishing a consensus on laws regarding HGE will be difficult in practice due to the complexity of different values and beliefs present on a global scale. Dr. Andy Greenfield is hopeful that there will be a *"voluntary code of conduct"* that countries can choose to adhere to that will signify their commitment to the *"safe and acceptable use of heritable gene editing"*. While this could establish a commitment between participating countries, his concern lies within the consequence of countries choosing not to agree:

"You only have to switch on the TV, to see what's going on in the world, to see that it's very difficult to mandate countries to do anything that they don't want to do [...] I'm sure, countries who feel like they don't need to sign up to that kind of set of guidelines. They want to go their own way and do their own thing. The danger there, of course, is that they could then be a race to the bottom so that you'd start getting reproductive tourism and individuals would go to those countries that had very [relaxed] regulation. Whether it was safe or not, will be unclear. Yet they would go there hopefully to get some kind of treatment which they think [would] work and it might not work and these are the kinds of things that we wanted to avoid."

Dr. Helen O'Neill brings the consideration of a country's existing legislation on IVF into the conversation. *"What people tend to forget when they talk about heritable genome editing, is that governance is very powerful and very strong when it comes to clinical IVF"*. Because of the existing regulation, she explains that *"any governance pertaining to heritable genome editing would need to also comply with the governance that's already associated with IVF and assisted reproduction"*. When this fact is taken into account, the difficulty in creating uniform legislation for HGE on a global scale is put into perspective, because there is no *"single unifying law"* or *"global coverage"* when it comes to IVF practice. In fact, many countries have a cultural or historical context that inform their regulation to varying degrees:

"when you look at the likes of the US for example [...] sex selection of embryos, you can select the sex of your embryos in the States and that is fine. In the UK and the rest of the world [...] that is illegal, because there is a fear that people might [have] a bias towards usually male embryo selection. Another example is in the biopsy or testing methods that we use to analyze embryos. So for example, in the majority of the world we can test embryos for aneuploidy or single gene disorders. But for example, in Germany, you can't do certain types of genetic testing, and that has again historical roots to the fact that Germany is quite conscious of its tricky history when it comes to the Holocaust. And so ***when you don't have uniformity of existing clinical situations and the laws that govern them, then it's actually hard to imagine a scenario where you'd have uniformity*** *when you introduce new scientific practices that would also require governance and compliance."*

On this topic, Dr. Greenfield brings up how what is considered "human dignity" will be a point of contention in which each country will have to decide whether altering the genome will

"compromise" human dignity. Similar to Dr. O' Neill, he also uses Germany as an example: *"in Germany even any kind of research on a human embryo is not permitted, because they would consider that to be incompatible with human dignity".* In the German constitution, as he goes on to explain, human dignity extends the prevention of anything that would be considered *"instrumentalizing"* a human. And for Germany, research on a human embryo would fall under this category.

But Germany is not alone in their reservations regarding IVF, and consequently HGE, technology. As Dr. Kelly Ormond, points out, there is a religious component at play that will be a factor for many countries deciding whether HGE will be acceptable: *"what we're hearing from populations is that this feels like we're messing with nature, we're doing things that only God is supposed to do"*. Ultimately, she says, the ***"cultural trust in science"*** will impact its acceptance. For Dr. O'Neill, this cultural context is essential to consider, because she warns the same practice in different contexts can have completely different implications. In an example, she explains two different receptions of IVF between the UK and India:

"[...] when it comes to ethical expectation or acceptance [...] the culture is so important. So the world's first IVF baby, Louise Brown, was born 40 years ago, and it was Bob Edwards and Patrick Steptoe. They went on to win a Nobel Prize. The world's second IVF baby was born in India to an Indian doctor, who, nine months later committed suicide because he was attacked by the press, by the public, by his native people in India who said what he's doing [is] a monstrosity [...] ***the exact same technology in a different location in the world can either be embraced or fully rejected****."*

Dr. Das offers a cultural perspective from her role as a researcher in India. Das speaks about how, in India, the culture is a very *"communal society rather than the western model of [an] individualistic society"*. Within that culture, taking care of a child is considered a very collective responsibility. She says, although they are still attentive to the suffering that individuals with SCD experience, *"a child is thought of as a gift from their supernatural power*

that they believe, their gods". She recognizes that establishing international regulation will be difficult, but emphasizes that it cannot be something that is forced upon any society:

"I feel like gene editing would have so many different loops or hoops to jump through because ***it's implementation cannot be an imposition ever****, because there will be many, many [...] cultural translations, sometimes political translations, economic translations, gender based translations that will be required for its implementation, but we will only know in the future how communities react to it"*

Dr. Das expresses her belief in the potential for HGE, but that it must coincide with *"decolonizing"* gene therapy research.. She says that scientists will need to display *"humility"*, and be able to reckon with the possibility that HGE may not be what some SCD communities in certain cultures or countries are invested in. It should be a community decision, she says, whether a "cure" is even a priority, because maybe the priority for sickle cell communities in these societies is simply *"access to portable water"*, and that is where they want to invest their resources. The idea of societies determining where to invest resources was also brought up by Dr. Kelly Ormond: *"What's your problem? You pick your problem. Where are you gonna put your resources? It's a matter of resource allocation [...] It's up to them what they decide. [...] there are all sorts of considerations that are due."*

On similar grounds of "decolonizing" gene editing research, SCD Expert B talks about in the practice of biotechnology companies operating in low income settings, there should be *"collaboration with scientists in those settings"* and involvement of the professionals that are both knowledgeable in the science but also of the communities and countries they work and live in. This collaboration is both essential and possible because, as SCD Expert B explains, there is already an effort in some of these countries to bring technologies like gene therapy to the forefront:

"There are a couple of countries that are really pushing and moving forward. Tanzania, Uganda [are] doing a lot of work around how to bring forth bone marrow transplant, stem cell transplant, and gene therapies within their countries and their settings today. So there's work going on in that area"

While international discussions surrounding how HGE should be practiced can still be had and should still be had, there are many factors at play regarding how the technology would be implemented in certain countries, if implemented at all. There cannot be an imposition of the technology, communities need to be listened to in their choice of whether they feel HGE is even a necessity for them. At the same time, there are also communities that could be open to implementing the technology, and collaboration with these researchers when operating in these settings is essential to implementation that can take into account the social and political climate of a country.

6.0 Policy Recommendations

Based on my findings, I have developed 4 policy recommendations that encompass the themes present in my data: 1) Public Funding for Cost-Effective Research 2) Precise Language when Drafting Regulation 3) Mitigating Risk through Diversity in Research 4) Communication with Stakeholders at Multiple Levels. These considerations, and in particular the methods in which I will detail they should occur, were not discussed in the previous literature I have reviewed regarding the implementation of HGE for sickle cell disease, but through my findings I hold them as essential to aiding in the safe and ethical use of HGE if this research is pursued.

6.1 Public Funding for Cost-Effective Research

The first recommendation would be the ability to obtain public funding for germline research. At least currently within the United States, there is no option for the research to be publicly funded. As multiple experts said, this restriction could lead to the research becoming both heavily privatized and the resulting technology being profit-driven, catering to a wealthy minority as opposed to a more widely accessible public good. In particular, allowing for public funding, such as grants or research subsidies for research with a goal of being cost-effective and affordable can give means to researchers who already have this as a priority, and incentivize others to do the same. However, it cannot be enough for a company to only claim this will be a priority, because as pointed out in my findings by Regulator B, companies will use this kind of "moral capital" to their benefit, with no plan to actually make this happen in practice. If companies market their product as something meant to benefit impacted and marginalized communities as part of their value proposition, they should be required to outline the methods in which they plan to make their product accessible prior to receiving funding, so that those communities can actually benefit. There would also need to be accountability in the follow-through, as determined by key indicators such as its pricing in the market. This would inform enforcement with repercussions such as owing the money back and cessation of future funding if they do not follow-through with their the goal of accessibility .

6.2 Precise Language when Drafting Regulation

I will now detail key elements that need to be considered when drafting legislation or other policies meant to regulate the implementation of gene editing treatments. For example, framing the use of HGE as a method for preventing SCD, and avoiding problematic language

that could negatively center or stereotype any group of people as highly defective groups requiring “fixing” via heritable treatment. The importance of this is supported by the story shared by Dr. Das, regarding the shift in conversation she witnessed from treating sickle cell disease to treating the tribal communities in India with “many disorders". Rhetoric that focuses a group of people as being the focus of HGE can be alarming because it negatively paints the people as the targets as opposed to the disease, and historically this rhetoric has had dangerous implications. When it comes to heritable editing in particular, regulators will need to pay close attention to ensure that the language used does not further marginalize already underrepresented or negatively perceived groups. This includes making distinctions between wording such as treatment versus prevention, because another aspect of language that was highlighted by Dr. Kiran Musunuru and Dr. Ben Hurlbut, is that there is no treatment in the sense that the individuals have not been born yet, and therefore do not yet have disease to be treated, but rather prevented. This consideration, alongside the importance of not framing any group of people at the targets of HGE, are what inform my recommendation that the goal should be framed as *preventing* sickle cell disease, and not *treating* any one group of people.

6.3 Mitigating Risk through Diversity in Research

Another recommendation has to do with the mitigation of risk. Clearly, there is still a lot more research that would need to be conducted with both germline and heritable gene editing before it could be implemented in any capacity. The first step in ensuring that the utilization of CRISPR for combating disease remains equitable is requiring researchers to gather a diverse sample set. Sickle cell anemia has been one of the most studied conditions when it comes to application of the CRISPR technique. However, despite Black Americans accounting for 93.4%

of sickle cell anemia hospitalizations, they make up less than 2% of the sample for genome-wide associations studies (Popejoy and Fullerton, 2016). When there is sampling bias akin to what is currently observed, the ability to generalize the results of these studies is compromised (Landry et. al, 2018). Translating care to populations underrepresented in these studies now runs the risk of the sample bias implementing bias within clinical applications. An example of this comes from a study where genetic tests for hypertrophic cardiomyopathy inaccurately determined some variants, variants primarily found in Black Americans, as harmful (Jooma et. al, 2019). The conflation of this variant as being harmful was a result of Black Americans not being included in the original study, and the significance of misclassifications such as this come into focus when taking into consideration the social stigma and financial implications of mistakenly being considered at risk for heart disease. Alternatively, and perhaps even more dangerously, critical variants have the potential of being overlooked if they are not as prevalent or absent in a population with European-ancestry (Wojcik et. al, 2019). The gravity of this is especially pertinent in regards to the HGE technology, because there is much at stake when it comes to the manipulation of genetic code.

Many of the gene editing interventions that are currently either on the market or in research focus on SCD– a disease that primarily affects minority populations, particularly those of African descent. Heritable gene editing in the context of this paper, would also have sickle cell disease as the focus. Thus it is imperative that when seeking to achieve a comprehensive understanding of what these risks could be and how they can be mitigated, there is diversity within these research samples that allow for these findings to be applicable to the entire population, and especially those in which the burden of disease often falls upon. Because as Dr. Kelly Ormond warned, how can researchers even determine risks, such as unintended changes, if

they *"**don't have a clear sense of the normal variation between people from different populations"**?* Having diversity in clinical trials is a necessity for mitigating risk in what will be the primary demographics of this technology.

6.4 Communication with Stakeholders at Multiple Levels

The third recommendation has to do with detailing how communication will occur between researchers, regulators and stakeholders. First I will recount how risk and other aspects of the research should be communicated through the informed consent process. In particular, reforming the informed consent to one that prioritizes the needs and values of individuals with sickle cell, focusing on their perspective as opposed to recounting legal liabilities. The consent process should also acknowledge concerns of marginalized communities regarding distrust with medical institutions, and address these concerns through complete transparency at every stage of the process.

How this transparency happens was arguably the most common necessity discussed by the experts. This would need to occur on both a national and international scale. On a national scale, this means community outreach and education through trusted and established organizations. In addition, the faces behind the scenes– in both the regulatory and research space– attending these SCD events is an interaction Tesha Samuels feels will be a necessary component in communities being able to foster trust. It is essential that these discussions include information that is relevant and current, because a concern cited by experts like Dr. O'Neill, is that the discourse regarding the developments in the technology is not up to date, and this can impact public perceptions because they are not obtaining complete information. Additionally, as Dr. Das expressed, researchers and regulators cannot ethically operate under the assumption or

false justification that the community does not have enough technical literacy, because as we heard from both SCD Experts, alongside Tesha Samuels, many individuals in the community are knowledgeable of these emerging interventions being discussed and want more information– and interaction– from the people behind it.

On an international scale, making heritable gene editing accessible across the world would require a *"roadmap of collaboration and investment"*, as Dr. Greenfield described it. However, before even getting to that point, there should be diversity of perspectives within international regulatory bodies regarding respective stances on HGE. While these international regulatory bodies on gene editing and even HGE already exist, one criticism brought up by participants, such as Dr. Ben Hurlbut, was the lack of diversity in who was being represented in these discussions. Addressing this moving forward would involve bringing in perspectives of the many stakeholders here, such as the parental one, those with SCD, and representatives from developing countries. While an international consensus would have merit, such as the prevention of medical tourism, the case of HGE is subject to so many different socio-political factors that will be different in every country. Therefore, an international consensus on how the technology should be implemented- and whether it should- even be implemented, would be difficult to reach if possible. However, cultural values should be respected, and no country should be forced to either engage or not engage with HGE– given that it has been thoroughly researched and being conducted in a safe manner, if conducted at all. However, for countries who are interested in establishing the technology, diversity in these international forums is necessary for another reason: broadening the general baseline understanding of what is considered equity. In reference to the words of Regulator B, the conversation of what equity should look like cannot be had without a diversity of perspectives to reimagine what equity could be.

6.5 Summary of Findings

The findings of this paper pay close attention to elements like the source funding for gene editing research. Allowing for public funds towards research with the goal of being cost-effective could enable researchers that already have these goals to perform their work, but also incentivize others to do the same. There should be accountability with ensuring that the mechanisms and strategies for accessibility are being detailed by researchers, and are aligning with the follow-through of how the technology is being implemented in practice. There was also an emphasis on precise language when drafting legislation. Due to the gravity of the technology, this paper explains why rhetoric is important, and subtle differences in rhetoric can still have dire implications that will need to be carefully considered by regulators when drafting regulation. In particular, regulators should avoid rhetoric that involves *treating* a group of people, but rather employ rhetoric that focuses on *preventing* disease.

Recommendations also discuss the current landscape of genome research and how the communities that would be at the forefront of this technology are currently vastly underrepresented in genome research. This can have dangerous implications when it comes to factors like understanding the risks posed, because if these black and brown communities are under-represented, researchers cannot truly understand how the variations between groups can impact the level of risk. There needs to be more engagement with these communities in both a clinical setting, and otherwise. As the final recommendation gets into, there are ways in which community engagement and education has to occur, such as centering their needs and what they wish to see from the technology in the consent process, as opposed to the idea of "consent" being to outline everything that could go wrong and then giving these individuals a box to check. There

is an awareness in these communities about topics such as HGE, and there is a willingness to learn that needs to be meet with the provision of current educational resources, and interactions with those “behind the scenes”, such as the researchers and regulators.

Accessibility on an international scale requires a level of investment into these areas that do not currently have the infrastructure. While this would be ideal, I cannot make any claims as to whether this kind of investment will be a priority for either side in the future. Countries may decide they do not want that kind of investment due to their own beliefs regarding the morality of HGE. What my policy recommendation does recommend, is a diversity of perspective on an international scale. This should be a priority in the already established gene editing, and in particular heritable gene editing, governing entities in which they are currently under-represented, as well as future regulatory entities that arise. Countries should have the final say in whether this technology is something they wish to pursue, given the evidence of substantial research and safe outcomes. In particular, these diverse perspectives can aid in discussion of equity, because broadening the idea of who gets a seat at the table is essential to broadening the imagination of what equitable solutions could look like in the future.

7.0 Limitations and Future Research Considerations

The primary limitation in my study is that germline gene editing research is heavily restricted in most countries, and heritable gene editing is not yet legalized in any. This means the discussion in my findings regarding potential costs, risks, and benefits are largely speculative, or based upon current knowledge from somatic gene editing, because there is no data from case studies with heritable gene editing to draw from. The only exception would be the case in China regarding Dr. He Jiankui editing embryos to be immune to HIV, but there is no publicly available

information about the success of the editing or its current impact on the children. I predict that as germline research becomes more substantial in the countries where it is legal, and perhaps potentially legalized in more, the availability of information will change. This will allow future research conducted on this topic to add upon or alter the findings discussed in this study with data from germline research.

8.0 Conclusion

In my paper, I have explored the potential for heritable germline editing to create accessible and sustainable solutions for those with sickle cell disease. Because millions of individuals around the world suffer from the disease, many of which from low socio-economic backgrounds, I found it necessary to investigate previous claims that HGE can be a method of creating long-term and equitable solutions for these communities and populations.

Through my literature review, I aimed to understand the controversial nature of HGE, and how this has influenced the regulatory landscape. Themes and terms that were present in my review also came up in my discussions with experts, such as concerns around "playing God" or the decision-making process regarding what conditions would constitute a need for HGEg. In addition to examining and attempting to address these concerns through my policy recommendations, findings of this paper also brought new considerations into the discussion, such as the implications of funding for accessibility, as well as a primary barrier to accessibility and universalizing regulation being the IVF process.

The most instrumental finding that this paper details, however, is the necessity for community engagement at truly every stage: from the research, to the regulation, to the implementation. Sickle cell disease stakeholders need to be engaged in a meaningful way, in a

way in which they are not being communicated with currently. It is their stories being told, their lives on the line, and there should not be a decision making process in which they are not at the center. SCD Expert A emphasizes that space needs to be given for these conversations, and *"regulatory boards ought to be part of them so that they can hear and understand and also describe their concerns"*. They hope to avoid what often happens with scientific development, which is the realization of *"Oh, wait, we should have done this earlier"*. Professor Ben Hurlbut shares a similar sentiment regarding the importance of having conversations surrounding heritable gene editing at these early stages:

"I think that it's really important to have conversations like this one that we're having now and that [it] should be much more widespread. Because if we have those conversations in 15 or 20 years, when the horse is out of the barn we'll say, 'Wow, wouldn't it have been better if we had thought about this before?' [...] ***It's actually very easy to look back and think about what should have been done. It's very difficult to do anything about it****."*

My goal and aim for this paper is to look forward and do that hard work of defining what the future reality of heritable gene editing should look like, while we are still in these early stages– and while we still have the ability to do so. For Tesha Samuels, her goal is for people to finally be heard, and their pain finally addressed:

"My hope is that everyone that has ever been in this kind of pain, felt unheard, have been ostracized, isolated, I mean, life with this illness has been so difficult [...]There are people who are suffering chronically. And so this treatment could potentially change millions of lives by just, you know, editing a particular gene. I want everyone to experience it because the life that I'm living now is unlike anything I would have ever imagined. [...] It'll be six years for me. March the 13th. And so I'm just thankful every single day for this, ***it is almost like a new birth for me****. It's like, who is she now? [...] Watch out world, because here I come. Everything that I thought that I wouldn't go into, [that] I wasn't gonna be able to do. I'm trying to go full force with it…for everyone that is my hope"*

Appendix

Table 3: Interview Questions for Regulatory Officials

Regulators
Development of Governance ● What considerations are taken into account when developing regulations and governance surrounding gene editing technologies such as CRISPR-Cas9 ● How can regulatory frameworks ensure that the benefits of gene editing technologies are distributed equitably among diverse populations, particularly in the case of sickle cell anemia?
Equity and Access ● What strategies are being explored to make sure that vulnerable or underserved communities have timely access to gene editing treatments? ● What are the ongoing assessment of benefits — In particular, how can heritable gene editing address potential socioeconomic disparities and health equity, particularly in the case of diseases like sickle cell anemia?
Risk Assessment and Mitigation ● What are the ongoing assessment of benefits — In particular, how can heritable gene editing address potential socioeconomic disparities and health equity, particularly in the case of diseases like sickle cell anemia? ● What are the ongoing assessment of risks — In what ways can heritable gene editing worsen both health and/or social inequality if not properly regulated? ● How do you recommend balancing the pursuit of scientific innovation with a cautious approach to mitigate potential risks, especially in the early stages of implementing gene editing technologies?
Public Engagement ● Considering diverse cultural and societal perspectives, how can regulators contribute to shaping ethical guidelines that respect various values and beliefs regarding heritable gene editing, especially when addressing diverse communities affected by sickle cell anemia? ● What role does, or should, community engagement play in the development and implementation of gene editing technologies, especially in regards to communities disproportionately affected by sickle cell anemia? How can it be done in an ethically sound manner? ● Given the vulnerable populations affected by sickle cell anemia, how can the informed consent process be tailored to effectively communicate with the public about the

benefits and risks of gene editing?
Future Regulatory Landscape ● Where do you foresee the regulatory landscape for heritable gene editing heading in the near future, in terms of progression or challenges, especially concerning its use to address health disparities in diseases like sickle cell anemia?

Table 4: Interview Questions for Gene Editing Scientists

Gene Editing Scientists
Overview of Research ● Can you provide an overview of your current research using CRISPR-Cas9 technology ● Does your research specifically aim to address health disparities in any way? If so, how? ● Have you currently, or in the past, done any research regarding the use of CRISPR-Cas9 gene editing for sickle cell anemia? If so, what did the research entail?
Potential of Germline Engineering ● Considering ethical concerns, how do you see the potential use of heritable gene editing in addressing health disparities such as sickle cell anemia? ● What advancements in CRISPR technology do you foresee that could contribute to minimizing off-target effects in gene editing?
Equity and Accessibility ● How can the application of heritable gene editing be conducted in a manner that ensures equity in healthcare outcomes? ● Are there any efforts being made to make CRISPR-based treatments accessible to communities impacted by sickle cell anemia?
Risks vs. Benefits ● What are the ongoing assessment of risks and benefits associated with heritable gene editing technologies, and what factors should be considered when determining an acceptable level of risk? ● How do you recommend balancing the pursuit of scientific innovation with a cautious approach to mitigate potential risks, especially in the early stages of implementing gene editing technologies?
Sustainability of Approaches ● How do you envision the integration of gene editing technologies into standard

healthcare practices in a sustainable manner?
Community Involvement in Research ● Given the unique challenges faced by individuals in vulnerable populations affected by sickle cell anemia, how can the informed consent process be tailored to ensure true understanding and voluntary participation in gene editing interventions? What considerations are crucial for obtaining informed consent? ● What role does, or should, community engagement play in the development and implementation of gene editing technologies, especially in regards to communities disproportionately affected by sickle cell anemia? How can it be done in an ethically sound manner?

Table 5: Interview Questions Sickle Cell Disease Researchers

Sickle Cell Disease Experts
Current Landscape of Sickle Cell Disease Research ● Can you provide an overview of the current state of sickle cell anemia research, particularly in terms of available treatment options and their impact (benefits and challenges) on patients? ● Of the challenges sickle cell anemia poses in terms of both research and treatment, and how might heritable gene editing address them differently from current treatments?
Potential for Germline Gene Editing ● In your opinion, what role can germline gene editing play in addressing the hereditary nature of sickle cell anemia and reducing the prevalence of the disease in future generations? ● From a researcher's standpoint, what potential risks or ethical considerations should be taken into account when exploring heritable gene editing as a treatment option for sickle cell anemia?
Sickle Cell Community ● How do you involve and engage communities affected by sickle cell anemia in your research and what is the impact of the disease on their lives? ● What are the patterns you have observed regarding which demographics are affected by sickle cell disease? ● Based on your interactions with the sickle cell community, how knowledgeable are individuals affected by the disease of gene editing as a potential treatment, and what perceptions, concerns or hopes have they expressed?

• Considering the global prevalence of sickle cell anemia, how might heritable gene editing interventions impact the worldwide burden of the disease, and what challenges and opportunities does this present?
Equity and Access: • How can regulatory frameworks ensure that the benefits of gene editing technologies for sickle cell disease are distributed equitably among diverse populations, including those who may be more disproportionately affected by the disease? • Considering the specific challenges faced by vulnerable or underserved communities affected by sickle cell disease, what strategies do you think should be explored to ensure these communities have fair and timely access to potential gene editing treatments?
Risk Assessment and Mitigation: • In the context of sickle cell disease, what are the primary concerns or risks associated with the use of germline gene editing, and how do you think regulatory bodies should address these concerns to safeguard the well-being of patients? • How can regulatory frameworks specifically contribute to minimizing risks and ensuring the safety of patients with sickle cell disease who may undergo gene editing procedures?
Long-Term Outlook • Looking forward, how do you envision the role of gene editing, in particular heritable gene editing, evolving in the treatment landscape for sickle cell anemia, and what milestones or challenges do you anticipate in the next decade?

Table 6: Interview Questions for Tesha Samuels

Tesha Samuel's Questions
Treatment Journey • Can you share your journey leading up to the decision to undergo gene-edited treatments for sickle cell anemia, including any considerations or factors that influenced your decision? **Personal Experience Post-Treatment** • How has your life changed since undergoing the gene-edited treatments for sickle cell anemia? Can you describe any improvements in your health or overall well-being?

- Can you speak to any challenges or setbacks you encountered during the treatment process or in the aftermath, and how you navigated those challenges?

Community Engagement

- What motivated you to become an advocate for sickle cell disease, and how has your personal experience with gene-edited treatments shaped your advocacy efforts?
- What kind of support or advice would you offer to individuals who are considering or undergoing similar gene-edited treatments?
- How do you feel regulators (i.e FDA or public health officials) can effectively communicate with the sickle cell community about the benefits and risks of gene editing?

Perspectives on Hereditary Gene Editing

- Given your experience with gene-edited treatments for sickle cell anemia, how do you view the prospect of hereditary gene editing (genetic modifications that are passed on to subsequent generations) as a potential means to prevent or address the disease in future generations?
- How do you perceive the broader sickle cell community's views on hereditary gene editing, and what discussions or concerns have you encountered regarding the potential implications of hereditary interventions?
- As someone who has undergone gene-edited treatments, how do you personally balance the promise of innovative gene editing technologies with the ethical considerations, particularly when it comes to interventions that may affect future generations?

Future Hopes and Expectations

- Looking ahead, what are your hopes and expectations for the future, both personally and for the broader sickle cell community, as gene editing technologies continue to advance?

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