Chapter 4
Therapeutic Genome Editing

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Abstract Efforts to cure single gene disorders by replacing the responsible genes using stem cell transplantation and gene transfer have been pursued for decades. These approaches, however, have been confined to serious diseases due in large part to their toxicity. Somatic gene editing (SGE), which repairs undesirable variants, is changing the landscape. It may well have fewer side effects than prior technologies. Thus, it is possible to consider using this approach to address a much broader array of a single gene variants, including treating milder genetic disorders and even improving function in otherwise healthy people. With these possibilities in mind, we discuss three implications of SGE. The first is the complexity of distinguishing between therapy and enhancement as well as the multifaceted debate about the acceptability of the latter, noting that many in the public are opposed to what they see as unfair advantage. The second, which previously has received little attention, is the tremendous price that is likely to be charged for SGE, which makes the debate about enhancement almost moot because even the needs of the most seriously ill will almost surely not be met, raising serious concerns about equity. The last is ensuring adequate regulation and governance of somatic gene editing.

Keywords Single gene disorders · Somatic gene editing · Gene editing regulation · Governance · Enhancement

Thousands of genes have variants that can contribute to disease. Some of these changes have major phenotypic effects, causing so-called single gene disorders, such as sickle cell (SS) disease, cystic fibrosis, and Tay-Sachs disease, to name just a few of the thousands that are known. Other variants have little phenotypic effect on their own but contribute in combination with many other genes to the development of complex disorders such as hypertension, obesity, and Type 2 diabetes. The advent of technologies such as Zinc finger nucleases, transcription activator-like

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effector nucleases, and CRISPR-Cas9 and their progeny holds out the prospect of promoting health by making it possible to edit or change these variants to their non-pathogenic forms.(National Academies of Sciences, Engineering, & Medicine, 2017) In this essay, I will focus on the ethical issues raised by using these technologies to alter genes after the person is born. Editing gametes and embryos with the intention of bringing the altered child to term, so-called germline gene editing, is potentially both more powerful and more ethically fraught,. (National Academies of Sciences et al., 2017; National Academies of Sciences, Engineering, & Medicine, 2020) Germline modification is also addressed in Chaps. 3 and 6.

Efforts to "fix" diseases caused by pathogenic variants by replacing them have been underway for decades. Early examples include what were then called "bone marrow transplants" (now more commonly called stem cell transplants) to treat disorders such as severe combined immunodeficiency (SCID) by replacing the child's immune system. (De La Morena & Gatti, 2011) These were followed by numerous trials of gene therapy or transfer, which sought to replace only the affected gene. (Gostin et al., 2014) Some disorders for which this approach now appears to be effective include spinal muscular atrophy, a rare form of retinal dystrophy, some lipid disorders, (Cring & Sheffield, 2020) and, quite recently, ornithine transcarbamylase deficiency. (Kaiser, 2021) These efforts provide powerful lessons about the challenges posed by the development and use of therapeutic genome editing.

The role of risk, however, has loomed large in ethical analysis of these approaches. Some of these technologies have been limited by their toxicity. Stem cell transplantation (SCT) has largely been limited to single gene disorders from which children would otherwise die in childhood, such as SCID. By contrast, this approach has been much less commonly used to treat sickle cell disease (SS) even though this disease causes enormous suffering and involves only a single base pair change in stem cells that are readily accessible. This reluctance is due in part to the fact that survival into adulthood is more common, concern about the side effects of SCT, and the availability of other partially effective interventions, such as the use of urea to promote production of fetal hemoglobin. (Jones & DeBaun, 2021; Krishnamurti, 2021) Some advocate for using SCT to treat SS, (de la Fuente et al., 2020) citing improvements in of stem cell transplantation with marrow ablation over the years, but the remaining risks still make technology less palatable to many.

Efforts to replace single genes, so-called gene therapy or transfer, raise a different, but related set of risks. The first are the risks of delivering the "new" gene to a place where it can usefully function. Replacing a gene that is expressed to create a needed enzyme or hormone, as is the case in SCID caused by adenosine deaminase deficiency, is more likely to be effective than one that contributes to the formation of structures like the heart or bone. (Fox & Booth, 2021) Delivery of wild type FGFR3,(MedlinePlus, 2021) for example, will not repair the skeleton of a person with achondroplasia. Accessibility of the target organ also matters – the bone marrow is easier to reach than the central nervous system. Typically, a vector, such as an altered virus or a lipid nanoparticle, is required to ensure that the gene reaches its target without being degraded. These vectors, however, can elicit serous immune responses, as was tragically observed in the case of Jesse Gelsinger, who died

during an early phase I trial of gene transfer to treat ornithine transcarbamylase deficiency. (Wilson, 2010) And a number of cases have been identified in which patients treated with gene transfer have subsequently developed cancer, apparently attributable to the intervention. (Jones & DeBaun, 2021; Marwick, 2003) Misdirected integration of genes, so-called off-target effects, have also occurred, interrupting functional genes, rendering them inactive or altering their regulation.

Many of the efforts at gene replacement/therapy have focused on children in an effort to prevent the progression of disease. For such trials to be acceptable, however, there must be a commensurate possibility of benefit to the children or to others like them. (Office of Human Research Protections, 2021) Thus, some trials are being conducted in adults who can make their own decisions about the balance between risk and benefit. The Jesse Gelsinger case mentioned above was a powerful lesson about both the challenges of obtaining truly informed consent and concerns about the appropriate conduct of clinical trials. (Gelsinger & Shamoo, 2008; Wilson, 2010).

Gene editing, typically using CRISPR or related technologies, holds out the promise of treating genetic disorders by repairing the pathogenic variant directly while avoiding some of the risks of SCT and gene transfer. Bone marrow ablation is not always needed and if necessary, can often be less intense. Many of the adverse immune responses may also be avoidable. In fact, some experimental efforts to edit genes are being conducted *ex vivo*, or outside the body. This involves removing stem cells from the bone marrow, treating them, and then reinfusing them into the patient. Trials are under way to treat SS, beta thalassemia, Leber congenital amaurosis, and transthyretin amyloidosis using gene editing, as well as HIV (Saha et al., 2021).

If it turns out that gene editing poses little risk to the individuals whose genes are altered, questions have already been raised about whether this technology should be used to edit somatic, or body, cells to treat less serious disorders or even to enhance normal human function, raising problems both of line drawing and equity. While the public in general is more supportive of gene editing to treat diseases than to address non-medical traits, (Delhove et al., 2019; Howell et al., 2020; Riggan et al., 2019) the distinction between therapy and enhancement may not always be clear, an issue also discussed in Chap. 13. A classic example used to explore this issue is the use of erythropoietin (Epo), a hormone used to increase red cell production in patients with anemia, but which athletes can use to increase their endurance.

In an effort to place some boundaries around the use of somatic gene editing, many commentators have argued that this technique should be used only to relieve symptoms or to bring the individual to normal human function. (National Academies of Sciences et al., 2017) Using the admittedly fluid concept of normality as a limit has been attacked from many directions. John Evans argues that, once begun, gene editing has no clear boundaries or stopping points, creating a risk that expansion of use will continue unabated. (Evans, 2020, 2021) Others challenge the notion that enhancement is undesirable *per se*, arguing that people appropriately do many things to improve their own life experiences and those of others, usually family members, around them. After all, parents are supposed to enhance the lives of their children, and the job of educators is to enhance the understanding of their students.

Indeed, a few argue that parents are morally obligated to use genetic interventions to enhance their children. (Savulescu, 2009) For most people, however, the question is how to distinguish between acceptable and unacceptable interventions. (Juengst et al., 2018) One line of inquiry that has been instructive is the longstanding debate in sports, also addressed in Chap. 15, where a rough line has been drawn to exclude interventions that confer advantage without effort on the part of the athlete. Thus, just as use of epo is forbidden in many sports, so too would gene editing to increase the production of erythropoietin be banned. (Juengst, 2020; Murray, 2018).

These questions about treatment versus enhancement pale in comparison to issues of access given the likelihood that these interventions will be more available to those with more resources, thereby widening the gaps between haves and have-nots even further. This is particularly the case given the price of gene editing, which will dramatically constrain the availability of these interventions. The current price for gene replacement/therapy for spinal muscular therapy, for example, exceeds $2,000,000 for a single dose, with no guarantee that further doses will not be required. Since gene editing trials are so new, little information is available about what price will be charged for these interventions if these trials prove effective, but it appears certain that the price will be quite high. (Irvine, 2019) And yet the number of people with serious disorders, ones that cause early death, serious morbidity, or lifelong onerous or expensive intervention, that are potentially amenable to gene editing is quite high. To pick just a few out of thousands of candidates affecting people in the US, ~16,500 have PKU, ~10,000 have urea cycle defects, 10,000–25,000 have spinal muscular atrophy, and almost 100,000 have sickle cell disease. Assuming a conservative price of $2,000,000 per dose, treating all these patients would cost over thirty billion dollars in the US alone. This sum is an underestimate in that many other disorders would also be candidates for editing, and the potential need worldwide will be even greater. The World Health Organization estimates that 300,000 babies with severe hemoglobin disorders are born every year around the world. (World Health Organization) It is notable that representatives of Médicins Sans Frontières attended the Paris meeting of the first international genome editing committee. (National Academies of Sciences et al., 2017) Some of the price would be offset by the ability to forgo future treatment, (Chapman et al., 2021) assuming 100% efficacy and no need for retreatment, but the potential price remains prohibitive. Thus, whether these interventions should be devoted primarily or exclusively to treating those who have severe, life-limiting disorders is a pressing question of equity, for which the current unequal distribution of COVID-19 vaccine around the world provides a powerful parallel.

On balance, it seems reasonable to suggest that somatic gene editing when effective should be used to treat individuals who are ill, acknowledging the inherent vagueness of these categories, and that use for other purposes should be disfavored due to the lack of resources needed for patients. Clearly, ongoing efforts to obtain public input on how to deploy these interventions are critical. (National Academies of Sciences et al., 2017; Scheufele et al., 2017) But it is also important to consider how to ensure that these tools are actually allocated appropriately because violating ethical norms and public consensus threatens the fabric of society. Some

mechanisms that have been proposed are the traditional tools of regulation and licensure, perhaps augmented innovatively by a lottery to allocate interventions among those are eligible. (Mehlman, 2018) Others have taken a broader view of the needed governance structures. (Jasanoff et al., 2019; Marchant, 2021) All of these approaches have limitations and their implementation varies widely around the world, so ongoing monitoring is needed.

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