



# Gene-Editing—Is the Quest to Alter a Patient's Genome Ethical?

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Gene-editing—the ability to alter a patient's genome—aims to repair deleterious genes in order to improve patient outcomes. Recent biomedical and social science research, however, has exposed many biological and ethical hurdles that compromise its merits. While gene-editing holds promise to treat many detrimental diseases, it should be approached with caution as it could have unforeseen consequences that should be investigated with further research.

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In 2015, a group of Chinese researchers reported replacing a mutated gene that encodes the  $\beta$ -globin protein, a gene responsible for the development of  $\beta$ -thalassemia, in pre-implantation human embryos.<sup>1</sup> While only 4 of the 86 embryos contained the replaced DNA, this discovery heralded the possibility of removing mutations and making epigenetic changes to the genome that could protect humans from diseases. It also adds a new level of complexity to decisions regarding changing the fate of future generations, a question that haunts many parents and policy workers today. With this advancement, expectant parents may have the ability to protect their children from certain diseases while also introducing them to novel, unanticipated ailments. Such advancement could thus blur the boundary between disease prevention and acceptance of genetic diversity.

My father once told me the story of how a deaf girl grew up to become a professional clarinet player. Because of a recessive mutation, she had to learn to connect the sign language therapist's motions with the cues from the individual with whom she was communicating to understand the people around her. With no friends to play with, she often contemplated what would happen if she did not have the mutation.

My father asked, "If you were her parent, would you amend the gene responsible for her deafness?"

As a mere ignorant adolescent, I responded energetically, "Of course!"

My father eyed at me closely and hesitated. Then he said, "Let's return to that response later."

My father then continued with the story. One day, when the girl turned on the TV, she noticed that Julian Bliss, a British musical prodigy, was performing Mozart's Clarinet Concerto. With her eyes on

the screen, she observed how Julian swayed his clarinet and regulated his breathing to convey the emotions dictated in the sheet music. She suddenly understood that she could interpret and perform music without hearing it. Since then, she has won five gold medals across various music competitions.

To this day, I have pondered the implications of this story and the ethical and policy questions raised by the discovery made by the Chinese researchers. Should parents have the ability to alter their children's DNA? Should people have the opportunity to remove a deleterious mutation? While gene-editing may alleviate patients from diseases, further research is needed to justify the potential benefits and consequences as it could introduce additional mutations, produce unintended side effects, promote social prejudice and prevent social inclusion, encourage economic inequality and change the course of human evolution.

While gene-editing may remove deleterious mutations, it may also introduce additional, unintended mutations. In 2015, Liang et al. discovered a surprising number of unintended mutations in human tripronuclear zygotes after replacing the gene responsible for  $\beta$ -thalassemia using a gene-editing technique known as CRISPR/Cas9. This represents a subset of unwarranted mutations as they only sequenced the exome, or the protein-coding region of the genome.<sup>1</sup> Moreover, in 2013, Fu et al. discovered these mutational frequencies can range from 0.1% to more than 60%. These unintended sites may harbor up to five mismatches and can be mutagenized comparable to or higher than on-target sites.<sup>2</sup> While the prognostic effects of these mutations are unknown, even low-frequency mutational events could be perilous if they have unwarranted effects, such as encouraging carcinogenesis, which could cause patients to suffer from unforeseen diseases. Although the human embryos being experimented on are not allowed to survive beyond 14 days and the gene-correcting efficiency of such techniques has improved to 75%<sup>3</sup>, with countries such as the U.K. being recently granted the opportunity to perform gene-editing in human embryos and other nations having little oversight over the reproductive use of gene-editing<sup>4</sup>, unfortunate outcomes via these unintended mutations could increase, thus compromising the benefits of gene-editing.

Even if gene-editing could accurately repair the defective gene and does not introduce novel mutations, the repaired gene could have unintended side effects. In 2002, Tyner et al. discovered, while generating mice with different combinations of the mutant and normal copies of the *TP53* gene, those that are heterozygous for the mutant gene displayed greater cancer resistance compared to the wild-type mice, despite having an early onset of reduced longevity, osteoporosis, generalized organ atrophy, and diminished stress tolerance.<sup>5</sup> Furthermore, given our limitations to understanding disease pathways and the complexity of gene-environment interactions, even if one gene is accurately repaired for one disease, it may predispose patients to other diseases. Because of the complex roles genes play in biology, further research is necessary to elucidate these pathways even after a gene is repaired.

At the same time, the unforeseen opportunities for gene-editing may also promote social prejudice and prevent social inclusion. Given that gene-editing may treat an array of diseases, patients may use this technique to overcome serious health challenges. However, this technology also raises a more troubling issue: parents may be encouraged to produce "designer babies" in countries that have little oversight over the reproductive use of gene-editing. These parents risk disappointment as they cannot completely control their children's future and miss out on their children's personal growth as they overcome their disabilities. By allowing parents to design babies that match their desires, society is reducing social inclusion because parents do not view certain traits as attractive. In addition, by offering parents the autonomy to dictate the future of their children, society may undermine the life

satisfaction these children have should they possess a genetic disability. In 1999, Albrecht et al. discovered that more than half of the respondents with disabilities reported having an 'excellent' or 'good' quality of life.<sup>7</sup> Thus, altering the DNA of those with disabilities may cause greater life dissatisfaction. Moreover, since people overestimate how severely health impacts their happiness compared to other factors, such as economic or social support, gene-editing may not have a huge impact on life satisfaction at all. In 1978, Brickman et al. made a discovery that while comparing to people who were paralyzed with those who had won a state lottery, although those who had accidents ranked their happiness lower, both groups predicted their future happiness would be roughly equal and those who were in an accident attained more of their happiness from everyday activities.<sup>8</sup> Gene-editing, therefore, may not only reduce social inclusion, but also undermine the psychological well-being of children and adults with disabilities.

Gene-editing may also promote economic inequality. Although it is unknown how long it would take to refine gene-editing technologies and how much it would cost in the future, given the costs of previous genetic testing techniques, such as preimplantation testing and prenatal screening, which can range from under \$100 to more than \$2000, depending on the nature and complexity of the test<sup>8</sup>, those with higher income are more likely to exploit gene-editing, thus encouraging a society in which disability is even more closely linked to economic inequality rather than an accepted part of a diverse and inclusive society.

Furthermore, gene-editing may change the course of human evolution. Although some genetic variations appear to be deleterious in one environment, they may be beneficial in another location. For instance, although individuals with one copy of the mutant sickle-cell gene experience some effects of sickle-cell anemia, they have some protection against malaria. Thus, the frequencies of sickle-cell carriers are high in malaria-endemic areas. If individuals who have sickle-cell anemia wish to replace the sickle-cell gene with the normal hemoglobin gene, with subsequent generations, the frequency of the sickle-cell gene would decrease, thus decreasing the protective effects the human population could have against malaria. Given that gene-editing could cause the reduction of genes that could protect humans from certain diseases, it should be approached with caution as it could have unforeseen consequences.

Thus, while gene-editing has substantial potential to alleviate suffering, it also introduces many biological and ethical issues that must be addressed responsibly. Until we have fully elucidated the genetic, social, economic, and evolutionary consequences of gene-editing, and until we have policies that regulate its uses, this new scientific breakthrough should not be deployed beyond the lab or brought to any clinic.

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