

# Genome Editing: Learning from Its Past and Envisioning Its Future

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## Abstract

With the technical possibility of genome editing, we have reached a new phase of transforming human beings and even altering our genetic legacy. Genome editing constitutes new responsibilities in many fields. Science and society have never been as dependent on each other as they are today. We must also learn from the past episodes of eugenics and we need to investigate fraudulent practices and cases of failure in scientific research that have often occurred due to merciless scientific competition, profit-seeking commercial interests, or individual pride. Genome editing raises numerous legal questions, such as: Would it be possible to make a legal difference between specific versions of gene editing? Who decides on what is considered a disease or an anomaly, a condition, or a variation? Which diseases are worth being corrected or treated and which ones are not? What kinds of social implications will gene editing bring about when it becomes widely available? Some normative distinctions have already been made in the case of gene therapy: separating somatic from germline interventions. But this distinction has not yet been analyzed in the light of the most recent editing practices. Genome editing also realigns the structure of ethical debates. It makes us rethink the concept of discrimination and scrutinize its cases in the field of assisted reproductive procedures. It revolutionizes the concept of medical treatment. It may increase or reduce inequalities based on health conditions. It may lead to numerous new rights in the field of genetics. Good genome editing practice can only be achieved through the close cooperation between the natural and social sciences. The present paper will endeavor to examine this new form of dialogue.

## Keywords

genome editing – eugenics – research ethics – governance – genetic interventions

## 1 Introduction: What Can We Learn from the Past?

The first draft sequence of the human genome was reported 20 years ago in the scientific journals *Nature*<sup>1</sup> and *Science*.<sup>2</sup> Back then, in 2001, the 21st century was already being heralded by many, optimistically, as the century of biology. Nevertheless, unlocking the secrets of the human genome has brought not only scientific success but also numerous ethical issues. In other words we reached a new phase of the textuality of genetics, as we use letters to describe gene sequences, and scientists refer to the codes obtained this way and eventual mutations using letter codes. This marks the beginning of genetic literacy as well.

In ethics debate on genetic interventions, reference to *eugenics* still play a crucial role even though this term has been used in many different contexts. The term *eugenics* was used by Francis Galton as early as in 1883.<sup>3</sup> It has gained several connotations over time and has been misused in ways that led to great human tragedies, but it was also seen by many as a progressive approach. Since the beginning of the 20th century, though in different waves, sometimes wandering astray and with numerous detours, human genetics has been growing vigorously and, thanks to the Human Genome Project, it has influenced almost all areas of medicine.

In human imagination, fantasy and literature, artworks related to this topic, and which still shape our thinking, had appeared long before modern genetics started to flourish. The first example to mention can be Mary Shelley's *Frankenstein*, written in 1818, which still serves as a reference in ethical debates. Since then, all irresponsible experiments on human subjects have been associated with the term 'Frankensteinian'.

Huxley's *Brave New World*, his modern classic that has been translated into many languages, was published in 1932. The list may be continued with the "Geneticists' Manifesto," an influential proclamation written in 1939.<sup>4</sup> Eugenics, experiencing a revival before the war, covered almost all areas of life, including psychiatry, child education, reproduction, sterilization and selective

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1 International Human Genome Consortium, 'Initial Sequencing and Analysis of the Human Genome', *Nature* 409 (6822) (2001) 860–921.

2 C.J. Venter, M.D. Adams, E.W. Myers, P.W. Li, R.J. Mural, G.G. Sutton, H.O. Smith, M. Yandell, C.A. Evans, R.A. Holt, et al., 'The Sequence of the Human Genome', *Science* 291 (5507) (2001) 1304–1351.

3 N.W. Gillham, 'Sir Francis Galton and the Birth of Eugenics', *Annual Review of Genetics* 35 (2001) 83–101.

4 L. Darwin, The Geneticist's Manifesto, *The Eugenics Review* 31 (4) (1940) 229–230, available online at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2962351/pdf/eugenrev00238-0033.pdf> (accessed 30 March 2021).

murder of people under the name of euthanasia. Selective murder and interventions committed in the name of eugenics cast dark shadows over genetics and still urge caution. However, the discovery of the double-helix structure of DNA by James Watson, Francis Crick and Rosalind Franklin in 1953 brought new momentum to the development of genetics.

Gene editing and embryo research would have not been possible without the development of the in vitro fertilization. Louise Brown in 1978,<sup>5</sup> the first human to have been born after conception by in vitro fertilization and embryo implantation. Following the first in vitro interventions, the Human Genome Project<sup>6</sup> and the first cloned mammal, Dolly the Sheep,<sup>7</sup> was born the same year, although her birth was officially announced only in 1997. Cloning made biotechnology's achievements tangible and, as a result, 1997 became the golden age of setting standards for bioethics. The Oviedo Convention,<sup>8</sup> UNESCO's Universal Declaration on the Human Genome and Human Rights,<sup>9</sup> was adopted. The movie *Gattaca*,<sup>10</sup> which foresaw a caste system of society based on genetic traits, was also released that year. From then on, news stories on genetics have been published on an almost daily basis and ranged from the announcement of the first draft of the human genome to the *en masse* emergence of biobanks.

Naturally, there have always been periods of setbacks, failures, and ethical fiascos. After Jesse Gelsinger, a young participant in the first gene transfer trial, died in 1999,<sup>11</sup> at least for a decade gene therapy had become a black label. Researchers failed to inform Jesse about the earlier patients' side effects or

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- 5 L. Brown, 'Louise Brown on 40 Years of IVF: "I Was the World's First IVF Baby, This is My Story"', *The Independent* (2018), available online at <https://www.independent.co.uk/life-style/health-and-families/ivf-baby-louise-brown-story-test-tube-world-first-40th-anniversary-a8455956.html> (accessed 18 March 2021).
  - 6 Starting on 1 October 1990 and completed in April 2003, the HGP gave the possibility for the first time, to read nature's complete genetic blueprint for building a human being.
  - 7 The birth of Dolly was important because she was the first mammal to be cloned from an adult cell. Her birth proved that specialized cells could be used to create an exact copy of the animal they came from.
  - 8 Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, *ETS No. 164*.
  - 9 UNESCO, Universal Declaration on the Human Genome and Human Rights, available online at <https://unesdoc.unesco.org/ark:/48223/pf0000110220.page=47> (accessed 30 March 2021).
  - 10 *Gattaca* is an American dystopian science fiction film written and directed by Andrew Niccol.
  - 11 M. Rinde, 'The Death of Jesse Gelsinger, 20 Years Later', *Distillations* (4 June 2019), available online at <https://www.sciencemuseum.org/distillations/the-death-of-jesse-gelsinger-20-years-later> (accessed 28 March 2021).

about the fact that two lab monkeys were killed by the high doses of adenoviruses. For a long time, his case has been an alarming reminder for supporters of gene therapy. In the field of another promising therapy, the embryonic stem cell research by the Korean Hwang Woo-Suk turned out to be fraudulent.<sup>12</sup> There was a tremendous pressure on him to make Korea the first country where embryonic stem cell therapy became possible. All these cases raised numerous ethical concerns. Hwang recruited his assistants to be egg donors; his lawyer was a member of the ethics committee that reviewed his research, and he was under great social pressure to make South Korea the world's leader in embryonic stem cell research.

In 2016 Karolinska Institutet had to face also serious consequences when it turned out that their employee, Paolo Macchiarini conducted a series of fatal trachea surgeries combining it with some stem cell technologies.<sup>13</sup> These scandals are cautionary tales about how cutting-edge technologies combined with fame can distort ethical principles not only on an individual but also on institutional and national level.

## 2 Gene Therapy and Gene Editing

In the field of genetic based therapy, we reached the latest stage of progress a few years ago, but this might be one of the most significant milestones so far. In fact, having a vast knowledge of the genetic background of certain human diseases, of stem cell research and of cell reprogramming is not enough if we cannot apply these technologies to cure people or eliminate certain biological threats. Without clinical application, these remain only interesting scientific achievements to be published; however, clinical applicability is crucial for mankind.

This is the area in which gene editing provides opportunities, by correcting the gene segments responsible for a predisposition to diseases. Although it is similar in many ways to gene therapy, gene editing opens new horizons. The most well-known gene editing technique is CRISPR.<sup>14</sup> The term CRISPR

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12 D.B. Resnik, A. Shamoo and S. Krinsky, 'Fraudulent Human Embryonic Stem Cell Research in South Korea: Lessons Learned', *Accountability in Research* 13 (1) (2006) 101–109, doi: 10.1080/08989620600634193.

13 Available online at <https://www.theguardian.com/science/2016/sep/06/two-nobel-prize-medicine-judges-fired-stem-cell-doctor-scandal-paolo-macchiarini>.

14 CRISPR is the abbreviation of the term Clustered Regularly Interspaced Short Palindromic Repeats. The discovery of the type II prokaryotic CRISPR "immune system" has allowed for the development of an RNA-guided genome editing tool that is simple to use.

was first used by the Spaniard Francisco Mojica in 2000 and it is an acronym that refers to the organization of short, repeated DNA sequences found in the genomes of bacteria. Although several journals rejected his publication as not interesting or required more laboratory proof, finally in 2005, he and his colleagues managed to publish his paper.<sup>15</sup> CRISPR is based on the molecular defense system in bacteria. It was known that the CRISPR defense system is found in many bacteria, but only much later was it discovered that it can be used as genetic scissors.

To use a more illustrative metaphor, gene editing works a bit like Microsoft's "replace text" feature. After writing a long text, it is not uncommon that we change our minds and decide to replace an expression with another that fits better. The replace text feature can be very useful in these cases. It searches through the text for the words to replace and it replaces them with one click. In any case gene editing unlikely "gene manipulation," or "gene engineering" is a friendly term that is followed by international curiosity and hope rather than fear.

The *enfants terribles* of DNA research, James Watson and Francis Crick, were famous for their cheekiness and vast self-confidence, which made it easy for them to overcome obstacles and failures. Their colleague, Rosalind Franklin, who did not receive the Nobel Prize, was much more reserved, just like Doudna. These women were aware of their knowledge and capabilities, but they always had to protect these values from others.

Studying RNA did not seem to be a good avenue for success in comparison with the fashionable DNA. But studying RNA led to the revolutionary technique of gene editing.

In 2020 Jennifer Doudna received the Nobel Prize in Chemistry for inventing the CRISPR gene editing technology together with Emmanuelle Charpentier. While most researchers were busy studying the DNA after the Human Genome Project was completed, Doudna chose to turn her attention to the relatively neglected RNA, and now we know that this decision brought her high returns. The groundbreaking article on the structure of RNA she coauthored was published in *Science* in 1996.<sup>16</sup>

The other key figure in the development of gene editing technologies, Emmanuelle Charpentier, was also an outsider at the beginning. Doudna and

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15 F.J.M. Mojica, C. Díez-Villaseñor, J. García-Martínez and E. Soria, 'Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements', *Journal of Molecular Evolution* 60 (2) (2005) 174–182, doi: 10.1007/s00239-004-0046-3.

16 J.H. Cate, A.R. Gooding, E. Podell, K. Zhou, B.L. Golden, C.E. Kundrot, T.R. Cech and J.A. Doudna, 'Crystal Structure of a Group I Ribozyme Domain: Principles of RNA Packing', *Science* 273 (5282) (1996) 1678–1685.

Charpentier were famous and respected researchers on their own, and they did not meet until 2011, when they realized their common interests at a microbiology conference in Puerto Rico.<sup>17</sup>

In the field of RNA research, the Hungarian Katalin Karikó played a pioneering role in developing the Messenger RNA based vaccine technology. Karikó was also an outsider most of her life, and her research interests have also frequently departed from the mainstream.<sup>18</sup>

### 3 Application of the Technology

Even the most talented researchers and inventors cannot implement their technology without proper translation into innovation. This process of innovation requires both ethical and business skills. In the United States it was the engineer and public intellectual, Vannevar Bush, who first promoted the idea that centers of innovation should be located at universities and their scientific laboratories, as well as in a number of smaller for-profit research labs, as opposed to the mega-laboratories created by the state (as it had been in the case of developing the nuclear bomb). Basic science, as opposed to applied science, needs to be supported by the state, as it is the ultimate source of innovation. This model of financing scientific laboratories by the state proved to be very successful in the United States. This is especially salient in the world of biotechnology, where it is essential to have a sharp sense of business, good timing, and preparedness to file patent claims — it is not enough to be a good scientist, one has to be able to protect scientific knowledge.

In July 2019 an Afro-American woman suffering from sickle-cell anemia volunteered to undergo gene therapy made possible by the CRISPR-Cas-9 technology.<sup>19</sup> At first stem cells were extracted from her blood, then these cells were treated by gene editing, and finally the blood was infused back to her body. Emmanuelle Charpentier's CRISPR Therapeutics company conducted

17 K. Krämer, 'How CRISPR Went from Niche to Nobel', *Chemistry World* (15 October 2020), available online at [www.chemistryworld.com/features/how-crispr-went-from-niche-to-nobel/4012604.article](http://www.chemistryworld.com/features/how-crispr-went-from-niche-to-nobel/4012604.article) (accessed 20 September 2021).

18 In 1995 she even lost her research job at the University of Pennsylvania, but she never gave up and never slowed down. Many years later she became the vice president of BioNTech, the company located in Mainz, Germany, that has become famous for developing the first mRNA-based vaccine against the SARS-Cov-2 coronavirus.

19 R. Stein, 'CRISPR Revolution: In a First, Doctors in U.S. Use CRISPR Tool to Treat Patient with Genetic Disorder', *NPR* (29 July 2019), available online at [www.npr.org/sections/health-shots/2019/07/29/744826505/sickle-cell-patient-reveals-why-she-is-volunteering-for-landmark-gene-editing-st](http://www.npr.org/sections/health-shots/2019/07/29/744826505/sickle-cell-patient-reveals-why-she-is-volunteering-for-landmark-gene-editing-st) (accessed 20 September 2021).

the clinical trial with great caution. The patient's first reaction to the CRISPR injection was a shock, she could not catch her breath and even her heart stopped temporarily, but soon after that she got better and recovered. The CRISPR technology proved to be successful. But CRISPR is not the only technology applied for gene editing.<sup>20</sup> The discovery of zinc finger nucleases (ZFN) in the 1980s<sup>21</sup> has already raised hope for gene editing. A similar technology was called *transcription activator-like effector nucleases* (TALENs). TALENs as a gene editing tool was still time and cost intensive and there were some limitations in its use.<sup>22</sup>

Today we can also think about the use of RNA editing technologies.<sup>23</sup> In 2018 the US Food and Drug Administration approved the first therapy using RNA interference technique in which a small piece of RNA is inserted into a cell. Researchers at the Wyss Institute for Biologically Inspired Engineering at Harvard University and Harvard Medical School (HMS) have created a new gene editing tool called *Retron Library Recombineering* (RLR) that makes editing task easier as RLR generates up to millions of mutations simultaneously.<sup>24</sup>

Time to time not only scientists but artists would like to go ahead with the application of a new technology. There have been people who tried CRISPR themselves; for example, Josiah Zayner, who injected himself with CRISPR at the SynBioBeta conference in 2017, trying to disable his myostatin gene to boost muscle growth in his arm. The idea of genetic modification has also become part of art is shown by numerous artists who use genetic interventions as inspiration or for further reflection. Nontraditional gene editing may pose future challenges to governance.<sup>25</sup>

20 See <https://www.synthego.com/blog/genome-editing-techniques#4-gene-editing-techniques-tools-to-change-the-genome>.

21 A. Klug, 'The discovery of zinc fingers and their development for practical applications in gene regulation and genome manipulation', *Quarterly Reviews of Biophysics* 43 (1) (2010) 1–21, available online at <https://www.cambridge.org/core/journals/quarterly-reviews-of-biophysics/article/discovery-of-zinc-fingers-and-their-development-for-practical-applications-in-gene-regulation-and-genome-manipulation/D25ADFAFC0F47D14E52E36BF5A27FCDE>.

22 A. Mah, *Genome Editing Techniques: The Tools That Enable Scientists to Alter the Genetic Code* (2019), available online at <https://www.synthego.com/blog/genome-editing-techniques#4-gene-editing-techniques-tools-to-change-the-genome>.

23 S. Reardon, 'Step aside CRIPR, RNA editing is taking off', *Nature* 578 (2020) 24–27.

24 L. Brownell, *New gene editing technique enables millions of genetic experiments to be performed simultaneously* (2021), available online at <https://wyss.harvard.edu/news/move-over-crispr-the-retrons-are-coming/>.

25 M.J. Mehlman and R.A. Conlon, 'Governing Nontraditional Gene Editing', in: I.G. Cohen, N.A. Farahany, H.T. Greely and C. Shachar (eds.), *Consumer Genetic Technologies* (Cambridge: Cambridge University Press, 2021), pp. 145–156.

#### 4 The Role of Research Ethics in Developing Gene Editing Techniques

While innovation is competitive in case of life sciences human applications requires additional ethical assessment that is of course might be frustration and time consuming, but still cannot be ignored. In November 2018, a Chinese researcher, He Jiankui, revealed the birth of the first gene-edited babies, Nana and Lulu.<sup>26</sup> The babies' names, of course, are pseudonyms; the twins' birth-place and their real names are unknown. He Jiankui's glory did not last long, as even the Chinese authorities have since distanced themselves from experimental interventions in human subjects. It seems that the first announcement of a new biotechnological method is often scandalous, and the research results are surprising. Racing to be the first always involves keeping secrets from competitors. However, He Jiankui was not in a competitive position, as scientific consensus at the moment is against this kind of intervention; besides, the intervention was not even justified.

He Jiankui announced his work on gene editing at the Second International Summit on Human Genome Editing, in Hong Kong, on November 25, 2018. He expected a huge scientific success, but not long after the announcement several experts on bioethics suggested that such a surprising transformation could only occur if ethical approval procedures were ignored. It turned out that transparent ethical procedures indeed did not take place. Human gene editing, like many other biotechnological innovations, involves terminological novelties, too. In this case, changing the previous terms *genetic manipulation* or *genetic modification* to *gene editing*, also changed the connotation and suggested a much smaller intervention or correction with a better result.

In all, 22 embryos were gene-edited, and 11 embryos were used in six implantation attempts before Nana and Lulu were born. The procedure can raise many kinds of ethical concerns. One of them was the result they wanted to achieve by gene editing. The intervention's goal was to confer genetic resistance to HIV.

Dr He claimed that he received approval from Shenzhen Women and Children's Hospital, but he failed to obtain authorization from his university or the four other hospitals from which some of the gene-edited embryos came. Even though the couples participating in the experiment were informed, the focus of their consent was much more on the copyright of photographs of the unborn babies than highlighting the novelty of the procedure. Is it appropriate

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<sup>26</sup> BBC News, 'He Jiankui Defends "World's First Gene-Edited Babies"', *BBC News* (28 November 2018), available online at <https://www.bbc.com/news/world-asia-china-46368731> (accessed 30 March 2021).

to ask for the public's help in the acceptance of a scientific announcement instead of going through prior professional challenges? He made an attempt to publish his results in a scientific journal a few days before the Hong Kong Summit.

The public knows relatively little about the birth of Nana and Lulu. The mother gave birth by emergency cesarean section. The twins' birthplace was not made public; all we know is that He Jian-kui left by plane to be there at the time of their birth. The goal of the procedure was to make the babies resistant to HIV. Therefore, on one of the babies' genes, the so-called CCR5 located on chromosome 3, He artificially created a CCR5 $\Delta$ 32 allele, with the help of the CRISPR "scissors."<sup>27</sup> In order to contract HIV, it is necessary to have a functioning CCR5 gene. Therefore, the aim of the experiment was to alter the function of this gene.

As a result of the international outrage following the incident, the case was also subject to court proceedings. That is how it emerged that a third child was also born. A court in Shenzhen found that He and two collaborators forged ethical review documents and misled doctors into unknowingly implanting gene-edited embryos in two women. The twins were born in November 2018, but it has not been made clear when the third baby was born; in fact, no information at all has been provided about the third child. He was sentenced to imprisonment and fined 3 million yuan (350,000 £). The Chinese government tightened its regulations on genome editing in humans. Experts from all over the world agreed that there are safer and more effective ways to prevent HIV infections. The experiment was deemed irresponsible, premature and unjustified, because it exposed the babies to risks associated with gene editing without any benefit.<sup>28</sup>

Responsible research requires risk assessment that takes into account the expected benefits, as well as the short- and long-term risks. In the case of a genetic intervention this assessment needs to consider some ripple effects, including epigenetic consequences. Modifying the genetic make-up of minors may also have a broader social impact, such as the commodification of human beings. A pre-implantation alteration of traits that do not serve any lifesaving

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27 Myles W. Jackson published a rather interesting book on the history of CCR5 gene and Delta 32 allele, which is of great importance for both understanding how HIV infections develop and curing them. See M.W. Jackson, *The Genealogy of a Gene* (Cambridge, MA: The MIT Press, 2015).

28 K. Musunuru, 'Opinion: We Need to Know What Happened to CRISPR Twins Lulu and Nana', *MIT Technology Review* (3 December 2019), available online at <https://www.technologyreview.com/2019/12/03/65024/crispr-baby-twins-lulu-and-nana-what-happened/> (accessed 30 March 2021).

or compelling medical purpose ultimately instrumentalizes the human being to serve the researchers' ambition or the parents' desire, or both.

## 5 Professional and Ethical Responses

Jian-kui He's announcement was so unexpected that the Nuffield Council's report titled *Genome Editing and Human Reproduction: Social and Ethical Issues*,<sup>29</sup> published in 2018, discussed the application of genome editing to the field of human reproduction only theoretically and in a futuristic way. It analyzed the, as yet, hypothetical situation when genome editing becomes routine and safe, and can be used among the assisted reproductive technologies available to women and men. This would mean that certain disadvantageous human characteristics, mutations, or susceptibility factors can be knocked out before the embryo is inserted into the womb. As a result, even those fetuses can be brought to life that previously did not have a chance to survive or to develop into a healthy child. In certain cases, even infertility, or other obstacles that make reproduction impossible, can be treated through genome editing. If genome editing works safely, it might lead to the possibility of altering or modifying genes in the gametes or embryos in order to ensure that a healthy child or one with specifically tailored characteristics can be born.

China's first reaction stressed He's success and its pride in the great accomplishment of Chinese science, but the general climate had changed by 26 November, as a group of 122 Chinese scientists and ethicists published a joint statement through a Chinese application, calling the experiment 'crazy' and asking for serious penalties to be applied against him.

They also emphasized that it is forbidden to conduct such an experiment on human beings. Subsequently, many other Chinese scientists condemned the experiment. On 26 November, the Chinese government opened an investigation and referred to the violation of several regulations, but it has not been made at all clear which laws were broken by He's work. On 29 November, the Vice-Minister of Science and Technology issued an order to suspend any work at He's laboratory. After He left the summit on gene editing, he went to an unknown destination and all kinds of rumors spread about his whereabouts.

Previously, He worked as a researcher both at Rice University and Stanford University, so he maintained extensive international scientific relationships.

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29 Nuffield Council on Bioethics, *Genome Editing and Human Reproduction: Social and Ethical Issues* (17 July 2018), available online at: <https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction> (accessed 30 March 2021).

That is why, after announcing the birth of the gene-edited babies, investigations were also carried out at Stanford, during which they found that three of their academic staff were involved. It is interesting that the study report on gene editing was credited to several authors. Among other issues, the responsibility of Michael Deems, who is a researcher at Rice in genetic engineering as well as synthetic biology and one of the authors of the original study on editing CCR5, also arises. The paper was written by several co-authors who may also be held accountable.

There are a number of professional and ethical concerns regarding the intervention. For example, He disabled a completely healthy gene in order to reduce the risk of a disease that the children did not even have and that could have been prevented by antiviral drugs and safe sex. Even if the experiment was successful, disabling CCR5 does not guarantee full immunity to HIV infection, because some strains may enter healthy cells through another protein.

According to Kiran Musunuru, many scientific objections may be raised against He's experiment.<sup>30</sup> The most pervasive one is the mosaicism in the twins, which means that the gene editing did not lead to consistent outcomes in the cells and the interventions carried out influence the various cells of the children. in different ways. Moreover, only half of Lulu's CCR5 genes were edited; it appears that the other cells are all intact.

The Chinese gene-edited baby case was in front of the People's Court of Nanshan District, Shenzhen, Guangdong Province and the judgement was held on 30 December 2019.

The court found that Jian-kui He and others committed a crime of "illegal medical practice," sentenced to a fixed-term imprisonment of 3 years to probation, and a fine of RMB 3 million. Although the reference to *illegal practice* usually means that medical activity was conducted without license, it is not entirely clear what was the basis of the criminal proceeding in the Chinese law. Nevertheless, in December 2020 China modified its criminal code to include a ban on *changing the human genome*. In the new amendment<sup>31</sup> "Illegal medical practices" were added to Article 336, which includes "the implantation of genetically edited or cloned human embryos into human or animal bodies, or

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30 The view from inside the 'medical scandal' of China's gene-edited babies. In a Q&A, geneticist Kiran Musunuru describes his unintentional connection to the scientist behind the scandal and the book that came out of the experience, see <https://penntoday.upenn.edu/news/Penn-geneticist-offers-perspective-from-inside-medical-scandal-chinas-gene-edited-babies> (accessed 30 March 2021).

31 Amendments to the Criminal Law of the People's Republic of China (11) (Adopted at the 24th meeting of the Standing Committee of the 13th National People's Congress on 26 December 2020), in this revision Act (article 39), a new article 336-1 were added.

the implantation of genetically edited or cloned animal embryos into human bodies.” This amendment entered into force on 1 March 2021. This new law has no retroactive effect but clearly indicates that China would like include international standards of genome ethics in the future.<sup>32</sup>

## 6 What Are the Legal Aspects of Gene Editing?

Legal and ethical reactions to the latest transformation technologies have changed since the foundation of the Human Genome Project. First of all, reactions are no longer delayed, but mostly happen in parallel or, in the case of cloning, even anticipating the scientific possibilities. This is necessary because cloning or gene editing has created opportunities that cannot be corrected if implemented prematurely. The possibility of human cloning, for example, impelled legislators to introduce regulations banning cloning as early as in 1997, although the technology and successful implementation were far from being available then. The second important difference is that society today participates much more actively in shaping expectations, hopes and rejections of biotechnology, and several works of art, movies and literary pieces provided utopian or dystopian visions and predictions, some of which have already become reality. As all of this affects our thinking, law and ethics try to provide answers, and in many cases, they anticipate the changes in biotechnology. In the case of gene editing, it was Jennifer Doudna who drew the public's attention to the widespread social implications of gene editing.<sup>33</sup> Therefore, one can say she is a good example for a responsible scientist of the 21st Century. Earlier, it was not appropriate for scientists to share their doubts with the public. Instead, they were expected to behave as if they were successful and infallible.

Gene editing raises numerous legal questions, such as: would it be possible to make a legal difference between specific versions of gene editing? Who decides on what is considered a disease or an anomaly, which diseases are worth being corrected, treated and improved and which ones can be? What kind of social implications will gene editing have when it becomes widely available?

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32 I am very grateful to Yao-Ming Hsu for his kind help with the clarification of the relevant Chinese law.

33 R. Sanders, 'CRISPR Inventor Calls for Pause in Editing Heritable Genes', *Berkeley News* (1 December 2015), available online at <https://news.berkeley.edu/2015/12/01/crispr-inventor-calls-for-pause-in-editing-heritable-genes/> (accessed 30 March 2021).

Some normative distinctions have been made already in the case of gene therapies, separating somatic and germline interventions. Somatic gene therapies involve modifying a patient's DNA to treat or cure a disease caused by a genetic mutation.

While somatic gene editing affects only the patient who is being treated (and only a part of his/her cells), germline editing affects every cell of the organism, including eggs and sperm, and this way the edited characteristics are passed on to the future generations. At the moment, it is difficult to foresee its possible consequences.

Human germline genome editing means deliberately changing the human genome (not only a single cell) that will become a characteristic of the child to be born. Human germline editing modifies the genome of a human embryo and it may affect every cell, which means it may have an impact not only on the person to be born, but also on his/her future descendants. Because of this, the clinical application of germline editing is banned in the United States, Europe, the United Kingdom, China and many other countries.

Somatic gene therapies are often used for treating patients who suffer from genetic diseases. Somatic gene therapies involve the placement of genetic material into a targeted part of the patient's existing cells. Somatic gene therapies are often used for treating patients who suffer from genetic diseases. Somatic gene therapies involve the placement of genetic material into a targeted part of the patient's existing cells.

Although Article 13 of the Oviedo Convention (1997) was not drafted to respond to the issues of gene editing — at that time nobody knew of this procedure — nevertheless, the distinction it makes is also applicable for gene editing.

According to the Article, “an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.”

The Committee on Bioethics of the Council of Europe reaffirmed this important distinction;<sup>34</sup> however, in the further future, it is questionable whether it is right to maintain the ban on germline gene editing, even when it will become completely accurate and safe. Must a serious genetic disease be treated generation by generation if it could be cured once and for all?

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34 “Ethics and Human Rights must guide any use of genome editing technologies in human beings,” Statement by the Council of Europe Committee on Bioethics, available online at <https://rm.coe.int/168049034a> (accessed 30 March 2021).

Among bans on interventions, it is important to mention Article 14 of the Oviedo Convention, which bans sex selection: “The use of techniques of medically assisted procreation shall not be allowed for the purpose of choosing a future child’s sex, except where serious hereditary sex-related disease is to be avoided.”

The other normative anchor is to examine that for what purpose could such an intervention serve. Although it is difficult to establish it legally, it is important to define the difference between a disease to cure and an anomaly. Who decides about what is considered a disease or an anomaly, and which conditions are worth correcting, treating and improving?

In the Eu legal framework different aspects of the human gene editing are addressed in different legal instruments.<sup>35</sup> The Eu frameworks clearly distinguishes between human and non-human application of biotechnology, between in vitro and in vivo applications, and between somatic and germline interventions. These normative anchors are based on safety or reversibility and irreversibility and overall, they aim to control the ethical boundaries of new inventions.

Furthermore, in general, patents can be considered as additional regulatory instruments beyond their commercial significance. Therefore, the Biotechnology Directive<sup>36</sup> provides limited scope for patentability, by allowing patents on products rather than methods in the medical field. This in turn facilitates the wide use of gene-editing methods of therapeutic, diagnostic, and surgical treatment on the human or animal body.

The ATMP Regulation<sup>37</sup> provides various incentives for the marketing of such products, not least the centralized marketing authorization procedure.

As we have seen the distinction between the therapy and enhancement is not so relevant for the law as for instance the distinction between somatic and germ line interventions. Furthermore, enhancement and performance enhancing have become accepted in many fields; it is enough to think about the improvement of vision through eye surgery, or the numerous — legal and illegal — means of performance improvement in sport.

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35 A. Mahalatchimy, ‘Genome Editing and the European Union’, in: J. Sandor (ed.), *Genome Editing and the Law Around the World*, World Association of Medical Law: Newsletter (January–March 2019) 1–5, available online at <http://wafml.memberlodge.org/resources/Documents/2019%20WAML%20Newsletters.pdf>.

36 Directive 98/44/EC on the Legal Protection of Biotechnological Inventions, OJ 1998 L 213/13.

37 Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products of 13 November 2007 and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ 2007 L 324/121.

Julian Savulescu and his colleagues believe that most of the leading athletes are born with a genetic advantage; consequently, they claim that genetically enhancing athletic performance is completely legitimate, as elite and competitive sport above a certain level is all about competition between genetic advantages anyway.<sup>38</sup> Obviously, diligence and a lot of training are essential but, according to Savulescu, in this case, genetic intervention in order to enhance performance can be justified.

## 7 Therapy or Enhancement?

During the application of new procedures, one of the most controversial topics is how to set the boundaries between therapy and enhancement. Russian biologist Denis Rebrikov, for example, offered his help in gene editing to allow deaf couples to give birth to children without a genetic mutation that impairs hearing. Rebrikov emphasized that he will implant gene-edited embryos only if he receives regulatory approval. The community with hearing disability, nevertheless, may regard this offer as an indication that their identity needs to be gene-edited. For them gene editing may be regarded not as a desirable therapy but rather a form of intervention that indicates their disability. On the other hand, those who advocate for enhancement of different capabilities in sport and other fields of life may welcome gene editing as a form of enhancement.

According to a survey on gene editing, conducted by the Pew Research Center in 2018, 54% of respondents thought that people will use gene editing in morally unacceptable ways. Furthermore, about seven-in-ten Americans (72%) were on the opinion that changing an unborn baby's genetic characteristics to treat a serious disease or condition that the baby would have at birth is an appropriate use of medical technology, while 27% of the respondents say this would be taking technology too far.<sup>39</sup>

It is even a more complex moral question what constitutes an editable genetic anomaly. For instance, there are autistic individuals in the upper spectrum with exceptional mathematical creativity. An artist might suffer from several mood disorders, but in some ways, this is what feeds their artistic creativity. It can be concluded that neurodiversity is also an important value.

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38 F. Baylis, *Altered Inheritance* Cambridge (Cambridge, MA: Harvard University Press, 2019), p. 58.

39 C. Funk and M. Hefferon, 'Public Views of Gene Editing for Babies Depend on How It Would Be Used', *Pew Research Center* (26 July 2018), available online at <https://www.pewresearch.org/science/2018/07/26/public-views-of-gene-editing-for-babies-depend-on-how-it-would-be-used/> (accessed 30 March 2021).

Genome research and gene editing raise numerous ethical, legal and social questions, many of which — including privacy issues, informed consent and the equitable representation of participants — are still unsolved. Furthermore, the availability and open distribution of genomic data is still uneven.

The World Medical Association developed the main ethical principles of medical research in 1961, which are known today as the Helsinki Declaration and which has been amended several times since then. Besides containing the most important principles of research, this document also includes a section on the comparison of risks, disadvantages and advantages, and expresses that the potential risks of a medical research project cannot outweigh the potential benefits.

In 2018 The Nuffield Council's 205-page-long report reflected on the social and ethical issues related to genome editing in a more venturesome way than any previously published ethical or legal statements.<sup>40</sup> To understand the novelty and ethical significance of this Report, it is important to state the ethical consensus that has defined the legal and ethical framework for interventions into human genes over the past two decades. For a long time, modification of the human gene was considered 'manipulation' and faced strong ethical and moral reservations. Although the relatively new technique of genome editing raises similar concerns as 'gene therapy', it modifies the human genome in a different way than the earlier 'gene therapy' or genetic modification procedures. Genetic modification inserts new, foreign genes or knocks out existing ones in the DNA artificially and as a result, the genetic material changes in a way that would not be possible through natural recombination or fertilization. Gene editing (or genome editing when more than one gene is edited), on the other hand, treats genes by repairing sections in the genetic structure of the DNA with the help of molecular scissors — and the outcome is 'natural' or naturally healthy without the disease.

By 2019 almost all relevant international organizations and professional societies issued a statement or a declaration on genome editing. In 2019, UNESCO's International Bioethics Committee organized a round table discussion with the aim to deal with the subject of gene editing as well.<sup>41</sup>

In September 2020, the American National Academy of Medicine and the Royal Society of Great Britain published a report entitled *Heritable Human Genome Editing* (HHGE).<sup>42</sup>

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40 Nuffield Council on Bioethics *supra* note 29.

41 UNESCO, *Roundtable on the Impact of Genome Editing on Our Health and Environment* (2 December 2019), available online at <https://en.unesco.org/events/roundtable-impact-genome-editing-our-health-and-environment> (accessed 30 March 2021).

42 National Academy of Medicine, National Academy of Sciences, and the Royal Society, *Heritable Human Genome Editing* (Washington, DC: The National Academies Press,

The HHGE Report does not recommend a moratorium on research. Instead, it clearly delineates six categories of potential clinical applications of HHGE and indicates that only two of those could be considered today. HHGE may be applied initially for only the most severe monogenic diseases and in a limited number of situations. I think in the future, the sharp distinction between the somatic and germ line editing should be revisited.

In 2021 WHO published a useful guidance on the regulation of genome editing technology published.<sup>43</sup> This document applies a very clear structure and language, and it recognizes the broader social consequences of this technology, its impact on human rights, and on the sustainable development. It differentiates between somatic and germline technologies.

While gene editing is often discussed in its potential use for enhancement the therapeutic applications are much closer to the realization. For instance, Zolgensma, a recent gene therapy medicinal product that has obtained a marketing authorization valid throughout the EU from 18 May 2020, is a genetically modified vector infused into a vein to treat spinal muscular atrophy for patients with inherited mutations affecting specific genes.<sup>44</sup>

## 8 How Does Gene Editing Rewrite the Structure of Ethical Debates?

Gene editing changes not only the legal reactions but also significantly alter the usual camps in ethical debates. To put it simply, there are two very contrasting perspectives in ethical debates: there are those who argue for the sanctity of life, which cannot be altered, and the others who support the individual's decision and autonomy.

The fact that, through gene editing, those embryos that would not otherwise have gained a chance of life can also be implanted encourages pro-life advocates to support gene editing, because this way may give a chance of life to embryos and fetuses with serious diseases. However, this goes against the usual combination of protecting life and refusing interventions. A challenging intervention might save potential lives.

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2020), available online at: <https://www.nap.edu/catalog/25665/heritable-human-genome-editing> (accessed 30 March 2021).

43 WHO, *Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing* (14 July 2021), available online at <https://www.who.int/news/item/12-07-2021-who-issues-new-recommendations-on-human-genome-editing-for-the-advancement-of-public-health>.

44 Spinal muscular atrophy is a serious condition of the nerves that causes muscle wasting and weakness. EMA, Zolgensma, European Public Assessment Report (2020), EMA/200482/2020.

The concept of autonomy is also difficult to define in the context of gene editing procedures. Whose autonomy are we talking about? The autonomy of the pregnant woman, the unborn child, the parents? It is important to highlight that one's genes are not one's fate, and personality is not determined by any single gene. The interests and viewpoints of families affected by genetic diseases have to be respected. Extreme interventions like germline gene editing may be justified only in exceptional and justified cases to fight serious diseases.

Consequently, gene editing also rewrites the structure of ethical debates. It affects the concept and cases of discrimination and the field of assisted reproductive procedures. It revolutionizes the concept of medical treatment. It may raise or reduce those inequalities based on health conditions. It may lead to numerous new rights in the field of genetics. Good gene editing practice can only be achieved through the close cooperation of natural and social sciences.

## 9 Conclusions

With the technical possibility of genome editing, we have reached a new era of altering human beings and even altering human inheritance. Genome editing constitutes new responsibilities in many fields. Science and society have never been so much dependent on each other. We may look optimistically into our future with mRNA-based vaccines in our arms and may rightly hope to tackle other dreadful diseases by using genetic knowledge. But we must also learn from the past episodes of eugenics and the instances of fraud and failure that have been the result of merciless scientific competition, unfettered commercial interest, or simply individual pride. As human rights lawyers we need to engage in regular communication with scientists in the field of biotechnology, as these emerging technologies are going to shape humanness in the future, and they may influence the rights of children and adults, and affect our perceptions of disability, discrimination and privacy.

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