ARTÍCULO DE REFLEXIÓN

Reflections about the Molecular Tool That Could Change the Course of Human History: Genome Editing

Reflexiones sobre la herramienta molecular que podría cambiar el curso de la historia humana: la edición genómica

Reflexões sobre as ferramentas moleculares que poderiam mudar o rumo da história humana: a edição de genoma

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Abstract

Genetic editing has many applications in almost all areas of society, but may also lead to unpredictable consequences. Genome editing to modify the human germline is at the center of global discussion. Owing to the increasing number of unanswered scientific, ethical, and policy questions, the scientific community agrees that it would be inappropriate to genetically modify embryos. A serious and open debate is necessary to decide whether such research should be suspended or encouraged. Here we show some bold arguments in favor of deleting deleterious genes from the human genome and the risks liberal eugenism poses.

Keywords (Source: DeCS): Eugenics; designer babies; gene therapy; mutation; therapeutics; genetic engineering.

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Resumen

La edición genética tiene muchas aplicaciones en casi todos los ámbitos de la sociedad, pero también puede tener consecuencias impredecibles. La edición del genoma de la línea germinal humana es el centro de una discusión mundial. Debido al creciente número de cuestionamientos científicos, éticos y políticos, muchos sin una respuesta concreta, el consenso de la comunidad científica manifiesta que sería inapropiado modificar genéticamente embriones humanos. Se considera necesario un debate serio y abierto para decidir si se debe suspender o fomentar la investigación en este sentido. En el presente documento, se exponen algunos argumentos audaces a favor de la eliminación de los genes nocivos del genoma humano y los riesgos que supone el eugenismo liberal.
Palabras clave (Fuente: DeCS): eugenesia; bebé de diseño; terapia genética; mutación; terapéutica; ingeniería genética.

Resumo

A edição de genoma tem muitas aplicações em todos os âmbitos da sociedade, no entanto pode ter consequências imprevisíveis. A edição do genoma da linha germinal humana é o centro de uma discussão mundial. Devido ao número crescente de questionamentos científicos, éticos e políticos, muitos sem resposta concreta, o consenso da comunidade científica manifesta que não seria apropriado modificar geneticamente embriões humanos. Consideramos que é necessário um debate sério e aberto para decidir se é necessário suspender ou fomentar a pesquisa nesse sentido. Aqui mencionamos alguns argumentos audazes a favor da eliminação de genes nocivos do genoma humano e os riscos decorrentes do eugenismo liberal.
Palavras-chave (Fonte: DeCS): Eugenia; bebês design; terapia gênica; mutação; terapêutica; engenharia genética.

INTRODUCTION

In the same way that we can delete, copy and paste letters, phrases, or passages of text in text editing, genetic editing has the potential to rewrite the genome of any living organism (1). This tool will be very useful in all sectors of society soon, including the molecular improvement of the *Homo sapiens*.

In 2019 a Chinese scientist announced gene editing in twin sisters. Jiankui crossed the limits of ethics and science to create a pair of AIDS-immune twins for the first time in history. According to the scientist[2], the CCR5 genes necessary for the virus to penetrate the lymphocytes were edited to prevent the AIDS virus from attacking. This study sparked debates about ethical conditions in the medical intervention field that would be morally permitted. However, positive characteristics such as increased intelligence, physical traits, or social skills could be incorporated into children before birth.

Nevertheless, genetic therapy is a practice that receives the most support among the scientific community and public opinion. The advances in this technology will also make possible to treat almost all human diseases. Researchers have shown that it is possible to induce high precision mutation, including modifying regions as small as a base in the DNA (2). These studies are very encouraging for the patient's clinical treatment with accurate mutation.

The main discussion is embryo editing, a precision eugenics tool. There are arguments for and against this practice from all social sectors. Opinion studies reveal that the treatment of diseases before birth is morally more accepted by society than the editing of embryos to predestine physical or mental qualities in our children. This appears to be the product of cultural prejudice and misinformation about gene editing. Influential bioethical organizations such as the Nuffield Council suggested that there would be no reason to declare any application of gene editing in human embryos as immoral, as long as the technique guarantees moral and social well-being (3). Others claim that we have a scientific moral obligation to eliminate specific deleterious genes from the human genome (4). We encourage this position whenever practiced out of love for the individual, family, and social environment.

The minority seems to favor the molecular improvement of physical or psychological attributes. The arguments are generally valid but provisional. Eugenic programs for characteristics of zero adaptive value could have negative consequences for the adaptive capacity of our species in the long term. Here we critically analyze the position taken by some international institutions and preeminent scientists and opinions on the potential of gene editing for the molecular improvement of the human being.

GERMLINE GENE EDITING SHOULD BE CONSIDERED A MORAL OBLIGATION

What is done out of love always takes place beyond good and evil

Friedrich Nietzsche

Genetic intervention could entail risks and unknown consequences (5). We agree that particular technical challenges must be overcome to improve the degree of

2 See https://www.youtube.com/channel/UCn_Elifynj3LrubPKHXecwQ

Why not consider gene editing as a potential tool to "avoid serious genetic disease"?

uncertainty in gene editing. For example, it is impossible to control undesirable mutations that off-target effects can cause. However, the technique is being perfected with surprising speed. Several strategies to eliminate off-target modifications have been published recently (6–9). Some scientists claim that they can modify the genome with precision as high as one nucleotide (10–12). This year, they published the map of the first human chromosome sequenced from telomere to telomere, revealing genomic areas that were previously unknown (13). This gigantic advance could contribute to preventing and detecting off-target effects. A group of scientists is studying the possibility of editing stem cells that produce sperm or ovules before using these gametes in vitro fertilization (14). These studies will provide significant advances in the technique's efficacy before any gamete is even considered to create an embryo (14). We are confident that in the future, this technology would be safe enough to use in baby design to the delight of the people who would accept gene editing in their germlines.

Ethical implications will undoubtedly take much longer to resolve. There is extensive debate on whether editing babies' genomes is morally correct. The conclusions usually lean towards rejection, and in some cases, historical background have motivated increasing ethical concern in eugenic thinking. Based on possible eugenic effects, arguments arise against genome modification in the germline (15).

Eugenics practices have been present in the history of man since the beginning of humanity. In Sparta, for example, robust women were encouraged to bear strong children, while children born weak or with imperfections were killed (16). Terrifying cases were recorded in the late 1930s when negative eugenics was adopted as a governmental practice in Nazi Germany. Richard and Lina Kretschmar petitioned Hitler to assassinate their son Gerhard Kretschmar, who was born with deformed limbs. Hitler approved his death and extended a racial cleansing program for other underprivileged children. Several countries adopted sterilization policies as negative eugenics measures in the mid-twentieth century. In the early 1990s, Preimplantation Genetic Diagnosis (PGD) was subtly masked as a new eugenics practice. Embryos that fail genetic testing are discarded prior to implantation to select healthy embryos. Several public opinion studies indicate that around 75 % of respondents approve PGD as a tool to "avoid serious genetic disease" (17). We will not enter into a deep ethical discussion about PGD, knowing that it is considered a medical procedure and has been established in many IVF clinics. We intend to answer the following question: Why not consider gene editing as a potential tool to "avoid serious genetic disease"?

Bioethicists often debate whether there is an ethical distinction between modifying and selecting human embryos. Joshua Shaw (18) raises questions about whether a significant moral difference can be drawn between the two techniques

> Arguments which distinguish modification from selection can be understood in two ways. One is to read them as presenting a No Harm, No Foul argument. Another is to read them as presenting

> a Harming versus Letting Be argument. Neither succeeds, however, either in establishing a meaningful moral distinction between modification and selection, or in showing that the second is morally permissible in contradistinction to the first. (18)

On the other hand, Christoph Rehmann-Sutter (19) draws a line between modification and genetic selection, arguing that the latter would be ethically permissible compared to the former:

> The future children who would result from treatment by human germline gene editing may rather have an interest in not having been treated since it makes the intergenerational relationships more complicated and burdensome. The question is genetic editing justified, or even an obligation? (19)

Before answering Christoph Rehmann-Sutter's question, we would like the reader to consider the following statement:

A couple decides to have children and go to a doctor for a genetic diagnosis. After conducting some tests, the doctor discovers that both parents are homozygous carriers of harmful mutations in the BRCA1 and BRCA2 genes. These are responsible for almost half of families with cancer and up to 90% of families with breast and ovary cancer (20). After the emotional load of the news, the couple asks the doctor if there is any preventive treatment for their children. The doctor answers that the government approves a specific genetic intervention with the same probability of causing side effects as any other medical treatment and that it is in their hands to decide if genetic editing is justified or an obligation.

It seems that the most reasonable answer would be for the couple to accept medical treatment, and here we will cite some arguments:

- Arguments in favor of the future human being (the embryo). The embryo could be considered a potential human being, and in that case, it has the right to exist and enjoy the highest degree of health that can be achieved (21). Indeed, the future patient (the embryo) will not be able to listen to the risks and consequences of the treatment, much less will be able to authorize medical intervention. However, it may be possible to accept the consent of those linked to them for family or legal reasons, considering that he is intellectually and emotionally unable to understand the scope of medical treatment (as is currently done when the patient is a minor).
- Arguments in favor of the family. The couple who decides to have a child will have the moral obligation to seek, making use of all available information, the best possible treatment or, at least, not the worst treatment that maximizes the quality and the possible lifetime for their future child (similar to the principle of "procreative benefit" proposed by Savulescu, 22). Considering this principle, the eradication of diseases as severe as cancer in the embryo is not only justified, but also becomes a moral obligation because no theory would deny that chronic pain caused by disease would reduce the well-being and happiness of the future child (the embryo) and their family.
- Arguments in favor of the company. Delivering a baby without genetic treatment will increase the rate of mutations in the male gene pool, which may pose a risk to future generations. These disease-predisposed individuals will eventually undergo invasive clini-

> cal treatments, spending much more of their time and money on medical treatments and therapeutic products. Like cancer, several types of diseases are worthy of being eliminated from the human genome, which would allow future generations to enjoy better health than we currently have. Scientists argue that eliminating mutations from our genome is not only something merely permissible but should be considered a "moral imperative" (23).

Disease treatments using genome editing were endorsed positively by highly influential bioethics institutions such as the Nuffield Bioethics Council of the United Kingdom, with arguments such as the following:

> Complex diseases, where there is a significant risk of later morbidity or mortality requiring intrusive or invasive treatment, or where later treatment would or might be ineffective. (3)

Furthermore, the Nuffield Bioethics Council does not restrict itself to accepting germinal genome editing technologies as clinical use. It also opens the possibility of asking ourselves what other positive value results we could achieve through embryo editing. The report suggests a wide range of applications offered by germinal genetic treatment, including the possibility of enhancing physical or cognitive abilities (3).

PART OF THE POPULATION IS MORALLY READY FOR BABY DESIGN

Nothing vast enters the life of mortals without a curse

Sophocles

According to some studies, the reduced support for human genome editing is a consequence of common mistakes made by even some of the most prominent biomedicals in thinking about the ethics of human enhancement.

Improvement practices in our species exist from immemorial times, although the techniques have changed throughout history. Practices such as the "screening" of embryos using the PGD technique and the subsequent "selection" of presumably healthy embryos are frequently used in genetic improvement programs of any other organism. Therefore, classifying embryo editing as the "emergence of a new era of eugenics" (or similar) is perhaps not the most appropriate. We could consider embryo editing as an additional tool to human genetic improvement programs, currently approved in many countries as PGD . We could even distinguish PGD as a damaging eugenics practice because it discards embryos with abnormalities.

In contrast, embryo editing could be more included in the type of positive eugenics, which recognizes the improvement of the human species as the only limit. Some critics consider the first morally permissible in contrast to the second (23). However, the two techniques could not be independent because at least one PGD step would be necessary (23).

Genetic modification could aid selection processes. The selection of embryos for complex polygenic characteristics may need to produce and discard large numbers of embryos in search of the desired genetic combination (if possible). Genetic editing, for its part, promises to treat multiple genes that influence a specific trait with greater efficiency. It has been suggested that, if embryo editing was highly efficient

We could consider embryo editing as an additional tool to human genetic improvement programs, currently approved in many countries as PGD.

and safe, it could even increase the efficiency of in vitro fertilization and PGD processes (24), including the selection of monogenic characteristics when the proportion of embryos is low (when both parents are heterozygous dominant) (25).

On the other hand, we would like to discuss arguments commonly used by detractors to embryo editing. Some bioethicists claim that a distinction should be made between genetic modification and selection because they consider the former more intrusive than the latter (18). Dramatic concerns move around interpersonal relationships of modified individuals with their parents or society (19). In this sense, questions arise: What would be the implications of embryo editing in the parent-child relationship? Will society discriminate against improved individuals? There is certainly no absolute answer to these questions due to the complexity of human behavior. We could predict public opinion attitudes using mathematical models built by Dalege (26). Eventually, positive and negative situations will occur. However, we can recognize the population's attitudes to the genetic effects caused by the lifestyle we lead.

Our habits can affect the health of future generations. There is extensive evidence of spontaneous mutations and epigenetic modifications established in the germline (similar to gene editing) due to environmental effects influencing the health and well-being of our children (27). For example, nutritional changes in the pregnant mother affect the prevalence of type 2 diabetes, obesity, dyslipidemia, hypertension, hyperinsulinemia, metabolic syndrome, and vascular diseases, the effects of which can be transmitted to the embryo for more than one generation (28,29).

For decades, the World Health Organization has recommended diets fortified and supplemented with folic acid for women trying to get pregnant, mainly in the preconception period (30). It is widely accepted that folate deficiency causes embryonic malformations due to modifications in epigenetic marks, resulting in congenital diseases (30). Another classic example is that of babies of women subjected to severe food restrictions in the Second World War, who were diagnosed as low birth weight, and this phenomenon persisted for at least two generations (31). In the same way, various genetic disorders are caused by poor eating habits, lack of physical activity, obesity, the use of drugs, tobacco, or alcohol (27,28,30,32,33). As a result, parents are primarily responsible for the next generations' health, at least in their reproductive stage.

Considering these studies, prejudices about interpersonal relationships may take a back seat. As far as we know, no one has filed the first legal claim against her grandmother for eating poorly in her preconception period, nor have tobacco companies been sentenced for the potential risk their products have on the health and well-being of future generations. The most ironic thing is that scientists study how to eliminate certain

epimutations caused by our bad habits using embryo editing techniques (34). This should be a relief to the public willing to accept germline genetic treatment. The rejection of genome modification in these aspects seems to result from the paranoia generated by the media and misinformation.

Influential international organizations, such as the Nuffield Council, consider that the editing of embryos in the germline could be considered as morally permissible, even in the cases modestly called "human enhancement" (molecular improvement of the *H. sapiens*). We encourage the report points stating that, in the long term, there may be no moral reasons to ban embryo editing in a wide range of possibilities (3):

- Built-in genetic resistance or immunity to endemic disease
- Tolerance to adverse environmental conditions
- Supersenses or superabilities
- Other factors that are likely to improve the welfare

It should be highlighted that both the International Commission on the Clinical Use of Human Germline Genome Editing and The Nuffield Council on Bioethics concluded that the modification of human embryos could still cause unexpected consequences, and for now, they cannot be used efficiently and reliably (3,14).

Studies indicate that a large part of the population is dissatisfied with the idea of improving physical or cognitive characteristics. Sometimes it may not be clear the difference between bringing babies without serious illnesses into the world and editing them to be taller or more brilliant. Those in favor of embryo editing to prevent congenital diseases could argue that it is necessary to avoid the physical suffering of the future individual that, otherwise, could end with disturbances in their physiological functions. Those in favor of editing embryos for aesthetic purposes might say that they do it to avoid the mental suffering of the individual that could otherwise end up with imbalances in their psychological functions. Doctors consider that the suffering caused by a perceived defect may not be different for a patient than the pain caused by a physical disturbance (35).

Furthermore, the two situations seem to be protected by the right to an open future. Beauty, for example, is an indicator of morality in contemporary society. Social psychologists call it the "halo" effect to the social thought that the most attractive people are considered the most competent, confident, and socially skilled compared to the least attractive (36). More attractive individuals are more likely to be hired, promoted, considered more persuasive, have more dating and sexual experiences (35). Attractive people have so many social and economic advantages that we might assume that they are happier than other people (35). Thus, questions arise such as: Is not it the parents' duty to prioritize the children's right to happiness?

Beauty is an intersubjective notion. It only exists in humanity's collective imagination, but its impact can be gigantic like that of other critical intersubjective forces in history: laws, money, gods, nations (37). The reader may be shocked by this line of thinking. However, many will be spending considerable sums of money on cosmetic products and aesthetic treatments so that their children can show a white, clear, and perfect smile to society and thus have more possibilities to make friends and influence people. This social behavior has been

responsible for imposing the value of aesthetic quality in our thinking, the same herd thinking with which we judge people who care too much about being beautiful. However, to what extent can aesthetic suffering be considered a pathology worthy of being corrected before birth? This discussion is temporary; ethics evolve. For now, there are objective, solid reasons to reject embryo gene editing: It is not efficient, it is not reliable (3,14).

We are responsible for the future of the *H. sapiens* gene pool. Liberal eugenics programs have been proposed in favor of genetic improvement with minimal intervention from the state. Even the Nuffield Council mentions that apparently, there are no fundamental reasons to differentiate the use of embryo editing to prevent diseases from human improvement (3,4).

However, in the long term, eugenic programs could put the adaptive abilities of our species at risk. The dissemination of aesthetic medicine practices has influenced the morals and behavior of people, which many spread like a virus in society. For example, the disclosure of the hormonal treatment of Lionel Messi (Argentinian soccer player) influenced the wishes and behavior of parents of children with short stature. According to Dr. Schwarsztein:

> Ever since the therapy given to Messi became public knowledge, for many people the growth hormone has been transformed into the 'magic drug' that makes little children grow… many parents are demanding from their paediatricians the same treatment given to Leo Messi. (38)

Indeed, an additional 10 cm could not be decisive for Lionel Messi to achieve his dreams and become one of the best footballers of all time. What is worrisome is the bubble effect that this type of news can have on our beliefs and opinions. Liberal eugenics programs could put the genetic diversity of *H. sapiens* at risk if we speculate that it becomes possible to edit embryos for polygenic characteristics over the years.

Genetic improvement has benefited humanity for thousands of years. However, we simplify certain organisms so that some life forms can only be maintained through human intervention and today coexist with our species. Furthermore, the experience with PGD shows us that not only positive characteristics are demanded by the population. In 2008 it was announced that 3% of clinics used PGD to identify embryos with markers for deficiency, such as deafness or nanism (18). Shared love between families with the same culture could be a valid argument. The question is: Are we ready to edit embryos to put them in a less open future? International legislation should consider the genetic responsibility that we have with future generations. We are responsible for what will happen to the gene pool that we have acquired over millions of years. Governments have a great responsibility for molecular tools, which could well change the course of the evolutionary history of our species.

WHO WILL DECIDE THE FUTURE OF GENOME EDITING TECHNOLOGIES?

No man is good enough to govern another man without that other man's consent

Abraham Lincoln

Studies reveal that the population is mainly afraid of uncertainty about possible complications resulting from

INTERNATIONAL LAWS REGULATING GENE EDITING WILL BE NECESSARY IN A WORLD THAT IS EXTREMELY MULTICULTURAL.

intervention in patients' DNA (39). The current panorama shows the difficulty of specifying global policies. The focus of the debate seems to be on germline gene editing. Support for genetic editing is typically drastically reduced when it improves physical or cognitive characteristics. We must accept that once we unleash precision medicine, the door will be open for genetic enhancement purposes.

Furthermore, embryo editing in clinical treatments could accidentally cause human enhancement in several ways. For example, it has been shown that the overexpression of genes to prevent neurological diseases can improve the cognitive potential of mouses and even increase the life span by up to 30% (40). Before starting to write the political outlines, this type of pleiotropic effects must be considered from all spheres of society.

International laws regulating gene editing will be necessary in a world that is extremely multicultural. Sixty-four percent of Americans interviewed indicates that the government should be responsible for using genetic editing for clinical treatments (41). Moral values differ primarily about gene therapy and embryo editing. This is perhaps one of the main concerns when structuring legal and regulatory laws. Medical tourism and the emergence of clandestine clinics are some of the main challenges associated with the governance of gene editing (42). International institutions recommend that the public opinions of all sectors should be considered before creating laws and regulations (3,14). However, human genome editing has received 30% greater acceptance when people are well informed about scientific issues (4). Some even suggest not relying too much on public opinion because it may reflect cultural preconceptions (43). Society and institutions have a significant educational challenge to improve our knowledge of these new technologies. In this way, we can prevent our opinions from being influenced by the political weapon of disinformation.

The knowledge of genome editing correlates with the acceptance of gene editing (44). In contrast, high levels of religious orientation are associated with lower support levels for genetic editing (44). Global surveys show that the population is usually more doubtful when genetic intervention treats diseases (45,46). Although gene therapy could save lives, universal acceptance today is far from being a reality.

CONCLUSIONS

Part of the population favors the use of gene therapy for clinical purposes. Support in this context is essential to stimulate the development of this technique by the public and private sectors. Somatic cell gene editing offers enormous potential for biological and therapeutic applications. The center of the discussion arises when it comes to inducing changes in the germline in human embryos. The main arguments against genetic manipulation arise from religious, social, and scientific perspectives. The time has come to start a reasoned reflection on the pros and cons of genetic manipulation. There are certainly risks and dangers associated with a gene-editing technique, which are nevertheless being overcome with fantastic speed. It will take a more significant effort to resolve ethical and social implications and must be widely

discussed to prevent discrimination and stigmatization. Institutions and academics seem to be reaching a consensus that the use of gene editing to treat congenital diseases is morally permissible. We agreed with some scientists that it should be a moral imperative to modify DNA sequences that cause severe diseases to eradicate chronic diseases.

On the other hand, liberal eugenics is supported by a small group of academics that accept gene editing to improve physical and cognitive characteristics. If this is possible one day, our main concern will be our future generations' responsibility. The gene pool of *H. sapiens* was acquired over thousands of generations, and it could be a bit naive to modify it for selfish whims.

Influential organizations suggest that regulatory measures must come from inclusive debates. Education will play a fundamental role in political decisions if we want to have the objective opinion of the public. Our first thoughts are that genetic editing must be regarded as a common good for everyone. However, the world is unequal, which furthers us from the democratization of gene editing. Current eugenics programs (in vitro fertilization and PGD) are only available to a small population group. Foremost minds have a heavy intellectual burden to achieve international consensus on political decisions based on love for the individual, the family, this society, and future generations. Love eugenic should include the essential elements described by Erich Fromm: care, responsibility, respect and knowledge (47).

References

1. Pinello L, Canver MC, Hoban MD, Orkin SH, Kohn DB, Bauer DE, et al. Analyzing CRISPR genome-editing experiments with CRISPR. Nature Biotech. 2016;34:695–7. DOI: https://doi.org/10.1038/nbt.3583

2. Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature. 2016;533(7603):420–4. DOI: https://doi.org/10.1038/nature17946

3. The Nuffield Council on Bioethics. Genome editing and human reproduction. Social and ethical issues; 2018. DOI: https://doi.org/10.1515/jwiet-2019-0012

4. Gyngell C, Bowman-Smart H, Savulescu J. Moral reasons to edit the human genome: Picking up from the Nuffield report. J Med Ethics. 2019;45(8):514–23. DOI: https://doi.org/10.1136/medethics-2018-105084

5. Gaskell G, Bard I, Allansdottir A, Vieira da Cunha R, Eduard P, Hampel J, et al. Public views on gene editing and its uses. Nature Biotech. 2017;35:1021-1023. DOI: https://doi.org/10.1038/nbt.3958

6. Hajiahmadi Z, Movahedi A, Wei H, Li D, Orooji Y, Ruan H, et al. Strategies to increase on-target and reduce off-target effects of the CRISPR/Cas9 system in plants. Int J Mol Sci. 2019;20(15):3719. DOI: https://doi.org/10.3390/ijms20153719

7. Li D, Zhou H, Zeng X. Battling CRISPR-Cas9 off-target genome editing. Cell Biol Toxicol. 2019;35:403–6. DOI: https://doi.org/10.1007/s10565-019-09485-5

8. Coelho MA, De Braekeleer E, Firth M, Bista M, Lukasiak S, Cuomo ME, et al. CRISPR GUARD protects off-target sites from Cas9 nuclease activity using short guide RNAs. Nat Commun. 2020;11(1):1–12. DOI: https://doi.org/10.1038/s41467-020-17952-5

9. Naeem M, Majeed S, Hoque MZ, Ahmad I. Latest developed strategies to minimize the off-target effects in CRISPR-Cas mediated genome editing. Cells. 2020;9(7):1608. DOI: https://doi.org/10.3390/cells9071608

10. Shevidi S, Uchida A, Schudrowitz N, Wessel GM, Yajima M. Single nucleotide editing without DNA cleavage using CRISPR/ Cas9-deaminase in the sea urchin embryo. Dev Dyn. 2017;246(12):1036–46. DOI: https://doi.org/10.1002/dvdy.24586

11. Chen C-L, Rodiger J, Chung V, Viswanatha R, Mohr SE, Hu Y, et al. SNP-CRISPR: a web tool for SNP-Specific genome editing. G3-Genes Genom Genet. 2020;10(2):489–94. DOI: https://doi.org/10.1534/g3.119.400904

12. Wang Y, Wang M, Zheng T, Hou Y, Zhang P, Tang T, et al. Specificity profiling of CRISPR system reveals greatly enhanced off-target gene editing. Sci Rep. 2020;10(1):1–8. DOI: https://doi.org/10.1038/s41598-020-58627-x

13. Miga KH, Koren S, Rhie A, Vollger MR, Gershman A, Bzikadze A, et al. Telomere-to-telomere assembly of a complete human X chromosome. Nature. 2020;585(7823):79–84. DOI: https://doi.org/10.1038/s41586-020-2547-7

14. Cohen J. Commission charts narrow path for editing human embryos. Science. 2020; DOI: https://doi.org/10.1126/science.abe6341

15. Ranisch R. Germline genome editing versus preimplantation genetic diagnosis: Is there a case in favour of germline interventions? Bioethics. 2020;34(1):60–9. DOI: https://doi.org/10.1111/bioe.12635

16. Mai LD, Saporiti AEL. Negative and positive eugenics: meanings and contradictions. Rev Latino-Am Enfermagem. 2006;14(2):251–9. DOI: https://doi.org/10.1590/S0104-11692006000200015

17. Arzheimer K. Secular citizens, pious MPs: why German attitudes about genetic testing are much more permissive than German laws. Polit Res Exch. 2020;2(1):1765693. DOI: https://doi.org/10.1080/2474736X.2020.1765693

18. Shaw J. Selecting for disabilities: selection versus modification. New Bioeth. 2018;24(1):44–56. DOI: https://doi.org/10.1080/20502877.2018.1441671

19. Rehmann-Sutter C. Why human germline editing is more problematic than selecting between embryos: Ethically Considering Intergenerational Relationships. New Bioeth. 2018;24(1):9–25. DOI: https://doi.org/10.1080/20502877.2018.1441669

20. Campeau PM, Foulkes WD, Tischkowitz MD. Hereditary breast cancer: New genetic developments, new therapeutic avenues. 2008;124:31–42. DOI: https://doi.org/10.1007/s00439-008-0529-1

21. Naciones Unidas. La Declaración Universal de Derechos Humanos. Available from: https://www.un.org/es/universal-declaration-human-rights/index.html

22. Savulescu J. Procreative beneficence: Why we should select the best children. In: Bioethics. Blackwell Publishing Ltd; 2001. p. 413–26. DOI: https://doi.org/10.1111/1467-8519.00251

23. Andorno R, Baylis F, Darnovsky M, Dickenson D, Haker H, Hasson K, et al. Geneva statement on heritable human genome editing: The Need for Course Correction. Trends Biotechnol.2020;38(4):351–4. DOI: https://doi.org/10.1016/j.tibtech.2019.12.022

24. Lander ES, Baylis F, Zhang F, Charpentier E, Berg P, Bourgain C, et al. Adopt a moratorium on heritable genome editing. Nature. 2019;567(7747):165–8. DOI: https://doi.org/10.1038/d41586-019-00726-5

25. National Academy of Medicine, National Academy of Sciences, the RS. Heritable human genome editing. Washington, D.C.: National Academies Press; 2020. p. 224. DOI: https://doi.org/10.17226/25665

26. Dalege J, Borsboom D, van Harreveld F, van der Maas HLJ. The attitudinal entropy framework as a general theory of individual attitudes. Psychol Inq. 2018;29(4):175–93. DOI: https://doi.org/10.1080/1047840X.2018.1537246

27. Xavier MJ, Roman SD, Aitken RJ, Nixon B. Transgenerational inheritance: How impacts to the epigenetic and genetic information of parents affect offspring health. Hum Reprod Update. 2019;25(5):519–41. DOI: https://doi.org/10.1093/humupd/dmz017

28. Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD, Hanson MA. Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. Pediatr Res; 2007;61:5-10. DOI: https://doi.org/10.1203/pdr.0b013e318045bedb

29. Ramírez-Alarcón K, Sánchez-Agurto Á, Lamperti L, Martorell M. Epigenetics, maternal diet and metabolic programming. Open Biol J. 2019 Oct 18;7(1):45–51. DOI: https://doi.org/10.2174/1874196701907010045

30. Pentecost M, Meloni M. "It's Never Too Early": Preconception Care and Postgenomic Models of Life. Front Sociol. 2020;5:21. DOI: https://doi.org/10.3389/fsoc.2020.00021

31. Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. Early Hum Dev. 2006;82(8):485–91. DOI: https://doi.org/10.1016/j.earlhumdev.2006.07.001

32. Kuniyoshi KM, Hang B, Rehan VK. Early-life tobacco smoke/nicotine exposure and offspring health. In: Early-life Environmental Exposure and Disease. Singapore: Springer Singapore; 2020. p. 23–50. DOI: https://doi.org/10.1007/978-981-15-3797-4_2

33. Yankai X. Early-life Environmental Exposure and Disease. Xia Y, editor. Singapore: Springer Singapore; 2020. DOI: https://doi.org/10.1007/978-981-15-3797-4

34. Goubert D, Beckman WF, Verschure PJ, Rots MG. Epigenetic editing: towards realization of the curable genome concept. Converg Sci Phys Oncol. 2017;3(1):013006. DOI: https://doi.org/10.1088/2057-1739/aa5cc0

35. Datta Gupta N, Etcoff NL, Jaeger MM. Beauty in Mind: The Effects of physical attractiveness on psychological well-being and distress. J Happiness Stud. 2016;17(3):1313–25. DOI: https://doi.org/10.1111/maq.12025

36. Aquino YSJ. Is ugliness a pathology? An ethical critique of the therapeuticalization of cosmetic surgery. Bioethics. 2020;34(4):431–41. DOI: https://doi.org/10.1111/bioe.12721

37. Harari YN. Sapiens: Uma breve história da humanidade. L&PM. 2015. Available from: https://www.amazon.com.br/Sapiens-Uma-breve-história-humanidade-ebook/dp/B00UZLPCGQ

38. Caioli L. Messi: the inside story of the boy who became a legend. Thriplow: Corinthian; 2012. Available from: https://www.ebay.com/itm/Messi-The-Inside-Story-of-the-Boy-Who-Became-a-Legend-ExLibrary-/312484387280

39. Persaud A, Desine S, Blizinsky K, Bonham VL. A CRISPR focus on attitudes and beliefs toward somatic genome editing from stakeholders within the sickle cell disease community. Genet Med. 2018 Aug 1;21(8):1726-1734 DOI: https://doi.org/10.1038/s41436-018-0409-6

40. Juengst ET, Henderson GE, Walker RL, Conley JM, MacKay D, Meagher KM, et al. Is Enhancement the Price of Prevention in Human Gene Editing? Cris J. 2018;1(6):351–4. DOI: https://doi.org/10.1089/crispr.2018.0040

41. Blendon RJ, Gorski MT, Benson JM. The public and the Gene-editing revolution. N Engl J Med. 2016;1(6):1406–11. DOI: https://doi.org/10.1089/crispr.2018.0040l

42. Rosemann A, Balen A, Nerlich B, Hauskeller C, Sleeboom-Faulkner M, Hartley S, et al. Heritable genome editing in a global context: national and international policy challenges. Hastings Cent Rep. 2019;49(3):30–42. DOI: https://doi.org/10.1002/hast.1006

43. Halpern J, O'Hara SE, Doxzen KW, Witkowsky LB, Owen AL. Societal and ethical impacts of germline genome editing: how can we secure human rights? Cris J. 2019;2(5):293–8. DOI: https://doi.org/10.1089/crispr.2019.0042

44. Scheufele DA, Xenos MA, Howell EL, Rose KM, Brossard D, Hardy BW. U.S. attitudes on human genome editing. Science. 2017;357(6351):553–4. DOI: https://doi.org/10.1126/science.aan3708

45. Shew AM, Nalley LL, Snell HA, Nayga RM, Dixon BL. CRISPR versus GMOs: public acceptance and valuation. Glob Food Sec. 2018;19:71–80. DOI: https://doi.org/10.1016/j.gfs.2018.10.005

46. McCaughey T, Sanfilippo PG, Gooden GEC, Budden DM, Fan L, Fenwick E, et al. A global social media survey of attitudes to human genome editing. Cell Stem Cell. 2016 May 5;18(5):569–72. DOI: https://doi.org/10.1016/j.stem.2016.04.011

47. Erich F. The art of Loving. The centennial edition A&C Black. 2000. 128 p. Available from: https://www.amazon.com/Erich-Fromm-Art-Loving-Inquiry/dp/B002278W40