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Human Genetic Editing: Analysis of Some Ethical Challenges

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Abstract: Scientific advances suggest that, in the near future, the possibility of editing the genes of a new individual, either by acting on germ cells or in preimplantation embryos, will be within the reach of the entire population, a possibility that raises important ethical concerns. At the end of 2018, the international scientific community expressed its concern about the experiments carried out by Dr. He Jiankui who, through the CRISPR-Cas 9 technique, genetically modified human embryos for reproductive purposes, achieving the birth of at least two girls. In this article, we will make an ethical analysis of Dr. Jiankui's experiment following Emanuel's criteria; according to this view, this experiment did not comply with any of the ethical standards commonly used by research ethics committees when evaluating a protocol. We will then review the ethical controversies related to the use of human gene editing in germ cells (sperms and eggs) and preimplantation embryos for reproductive purposes. Considering that these changes are heritable for future generations, and that the technique is still in an experimental stage, we will argue in favor of a moratorium on its use for these purposes. When gene editing is used without reproductive purposes but solely for research, we will justify why we consider it necessary to distinguish the application of this technique in germ cells from research in human embryos, a distinction that may be questioned depending on whether the human embryo is considered as a living organism of the human species. Likewise, we will briefly discuss the differences that exist between the use of genetic editing techniques to cure or prevent diseases, and that used to produce improvements or "enhancement" of the human race, since the latter has several moral objections. We will end by providing a brief analysis of regulatory aspects in Chile and internationally, as some of the applications of these techniques raise ethical issues that have highlighted the need for strong supervision in this area.

Key words: gene editing; CRISPR-Cas system; ethics; genetic enhancement; research

1. Introduction

Science fiction literature and movies, from *Frankenstein* to *Gattaca*, have given us a glimpse of what could be a society in which human beings are "created" artificially, rather than being the product of the generative process of the species. As shown in the film *Gattaca* [1], in the near future, parents will be able to condition the genetic material of their future children, creating beings endowed with all their capacities expressed to the maximum. The film raises an ethical issue that is still relevant today: "do parents have the right or are they entitled to intervene genetically in their children to perfect them? The new genetic engineering technologies make it possible to modify human genes with the aim of correcting genetic defects and, eventually, also to achieve the expression of traits considered more suitable to face today's world; of special ethical consideration is when these techniques are performed on germ cells (eggs and sperm and their

precursors) and on preimplantation embryos, since the consequences of these interventions affect future generations. In this sense, in this article, we will consider that gene editing of germ cells and preimplantation embryos have similar ethical objections, without this meaning in any way that the moral status of these cells is equivalent. For reasons of space, we will leave out of this paper the specific moral considerations regarding the human embryo, which have been addressed by other authors [2].

There are several medical uses of human genomic editing. It can be used for diagnosis, therapy and prevention of genetic disorders; for the treatment of infertility or to produce resistance to certain diseases and also to understand physiological phenomena [3]. More controversial uses are related to the possibility of improving human traits, such as physical appearance, altering muscular abilities, increasing longevity or intelligence, or acquiring resistance to contaminants or to the effect of radiation. From a theoretical point of view, the technique can also be used to introduce in humans certain traits that are not characteristic of the species, such as the possibility of expressing a fluorescent protein, introducing improvements in the nutritional system, generating the capacity to degrade plastics or increasing tolerance to cold or drought, among other changes not related to disease therapy, but which could allow the survival of the species in an increasingly hostile world [3].

At present, after a preimplantation genetic diagnosis process, it is already possible to genetically select healthy embryos for transfer, thus discarding embryos with a high genetic disease load. The use of new technologies, such as CRISPR-Cas9 (Clustered Regulatory Interspaced Short Palindromic Repeats and Cas for CRISPR associated system), is a novel gene editing technique that allows deleting, adding or changing genes, which can be carried out both at the level of germ cells and preimplantation embryos - having consequences in future generations - and also at the fetal level, or in somatic cells of those already born [3].

At the end of 2018, the international scientific community became aware of the experiments carried out by the Chinese scientist Dr. He Jiankui who, by means of the CRISPR-Cas9 technique, managed to genetically modify human embryos for reproductive purposes. Jiankui chose fertile couples, in which the male parent was HIV+, and subjected them to a process of in vitro fertilization, and then genetically modified the embryos, managing to deactivate the CCR5 gene, which is one of the genes used by HIV to enter the cells. Through this modification, he hoped that the future girls, later known as Lulu and Nana, would be immune to the AIDS virus. This genetic modification has a clinical correlate, as HIV+ patients who received bone marrow transplantation from donors with a spontaneous mutation in both alleles of the CCR5 gene went into remission and were even able to discontinue therapy [4].

In this article, we will make an ethical analysis of Dr. Jiankui's controversial experiment following Emanuel's criteria; then we will review the ethical controversies related to the use of the gene editing technique in germ cells and preimplantation human embryos, especially when it is used for reproductive purposes, since, unlike what happens when the technique is applied to somatic cells, its consequences can affect future generations. We will also discuss the differences that exist between the use of gene editing techniques to cure or prevent diseases, and those used to produce improvements or "enhancement" of the human race.

We will conclude with a brief analysis of the regulatory aspects in Chile and internationally, since some of the applications of these techniques raise ethical issues that have highlighted the need for strong oversight in this area. For reasons of space and especially because it is not the focus of this work, we will leave out of this analysis those ethical problems associated with gene editing of germ cells of non-human animals and plant species, which can also affect the ecosystem.

2. Ethical Aspects of Dr. He Jiankui's Experiment

In 2000, Emanuel, Wendler and Grady proposed seven ethical criteria that are widely used in our country when deliberating on the eventual approval of a given research protocol. These requirements provide a systematic framework for determining whether a clinical investigation is ethical [5]. For these reasons, we consider it interesting to apply the Emanuel et al criteria to evaluate Dr. Jiankui's research proposal, which may help to better understand how the Emanuel criteria are used.

2.1 Social or scientific value

Social or scientific value refers to the possibility that the experiment will produce an improvement in the health or welfare of people or increase scientific knowledge. The rationale for this requirement is the responsible use of ever scarce resources and the avoidance of exploitation or exposing human beings to potential harm if there is no possible social or scientific benefit. In this case, the social value is doubtful, since there are other ways to protect people from becoming infected with HIV. At the same time, the embryos had no defect to repair, so the technique, still in the research stage, was not used to cure a serious disease and exposed healthy embryos to unreasonable risks.

2.2 Scientific validity

The research must use the scientific method to produce reliable results. At the time of reporting the birth of the two genetically modified girls, there was no access to the protocol itself and doubts were generated regarding the genetic modifications made, without convincing elements being provided regarding the success of the technique in these two girls (for example, if all their cells expressed the desired mutation or if there were unwanted mutations). Nor was it made known how many couples underwent this technique, how many in vitro embryos were produced, intervened, discarded or transferred; without these essential aspects, it is not possible to know the scientific validity of this protocol.

2.3 Fair selection of subjects

The selection of research subjects should protect those most vulnerable or at risk of stigmatization. In this case, Jiankui chose vulnerable families, fearful of being stigmatized because of the parent's HIV status and who did not require any intervention to father children, since they were not infertile. Even more serious is that those who will bear the burden of the intervention for life will be the future children subjected to the technique during their embryonic period, without there being a clinical condition whose severity justifies performing this procedure, even at the experimental stage, for reproductive purposes.

2.4 Favorable risk-benefit balance

Every effort should be made to decrease the risks and increase the potential benefits; the risks to the subject should be proportional to the benefits to the subject and society. In his experiments, Jiankui subjected women to invasive procedures (ovarian stimulation and assisted fertilization), without clinical cause. At the same time, the technique was still in the experimental stage, which meant destruction of embryos and potential disproportionate risks for the offspring of presenting mutations not sought elsewhere. Being homozygous for this deletion of the CCR5 gene, it exposed them to eventual diseases; for example, this same gene is believed to be important in fighting other infections, such as West Nile virus [6]. On the other hand, this gene is known to play an important role in neuroplasticity, learning, and memory. In mouse models, it has been seen that a decrease in the function of the CCR5 gene accelerates learning-dependent neuronal plasticity, so it is believed that this mutation can produce improvements in brain function [7], an aspect that generates new ethical controversies. As has been mentioned by other authors, after the use of CRISPR-Cas9, extensive deletions have been observed that could produce disastrous results if it is intended to be applied in the clinic [8].

2.5 Independent review

It is considered a fundamental aspect that the research has the proper ethical approval, contributing to public faith in the research and minimizing the influence of potential conflicts of interest. In this case, the Southern University of Science and Technology, the university where Jiankui worked, issued a public statement condemning these experiments and also pointed out that they had been conducted without any ethical oversight, in violation of internal codes of conduct. After these experiments became known, the university disaffiliated him [6].

2.6 Informed consent

Participants or their representatives must be fully informed of the purposes and procedures of the research, so that they can make an informed decision as to whether or not to participate. Although in this case, there was an informed consent signed by the parents, the information provided was misleading in stating that this technique could result in the babies obtaining a genotype similar to that of northern Europeans, which could confer immunity to HIV. In turn, the call was for participation in a project to develop a new HIV vaccine. Additionally, it is known that Jiankui and his team funded the infertility treatment, but were apparently told that they would have to return the money (approximately US$ 42,000) if they abandoned the study, which constitutes undue pressure [6]. The consent form also failed to adequately explain the potential risks of this genetic change in the embryos and to inform about future consequences, including transgenerational effects, and also shielded the team from potential liability for future risks. Consequently, it fails to meet the minimum ethical requirements for valid consent [9].

2.7 Respect for the potential participants and for those already enrolled

The company should have a policy that guarantees their right to opt out of participation, protects their privacy and confidentiality, and is concerned about their wellbeing. In this case, the consequences of genetic modification may extend to future generations; babies should be permanently monitored, but no funds were provided for this. In addition, the experiments included the production of numerous human embryos that were subsequently discarded. For the above reasons, Dr. Jiankui's experiment did not take into account any of the commonly accepted ethical requirements for human research.

3. Ethical Issues of Gene Editing of Germ Cells and Preimplantation Embryos

For reproductive purposes: The main problem with gene editing of germ cells (sperm and oocytes) and preimplantation human embryos for reproductive purposes is that it affects future generations in a way that is not yet fully controlled. Therefore, we do not know the consequences of these heritable genetic alterations and how this could change the very future of humanity. In addition, there are problems with the technique itself, as it is not yet safe enough to guarantee that mutations will not occur elsewhere.

It has been considered that two minimum conditions must exist for this technique to be ethically acceptable. On the one hand, the technique should be safe and effective, so that the risk-benefit balance for children born with this genetic modification is always favorable. In addition, there should be a broad social consensus on the appropriateness of its use for these purposes [10]. For these reasons, there is international consensus that for the time being the technique should not be used for reproductive purposes, but only for research purposes (see below).

A relevant question from an ethical point of view is whether parents or society have an obligation to repair genetically defective embryos, as opposed to selecting, through preimplantation genetic testing, healthy embryos. As Rehmann-Sutter states in her article, because of the consequences of this repair on future generations and our responsibility towards them, it is therefore not entirely clear that this "obligation" to repair can be defended [11], just as there is an ethical obligation to try to cure a disease in an individual already born, at least until the technique is safe and the consequences on future generations have a favorable risk/benefit balance. In this sense, it has been pointed out that since gene editing of germ cells

and embryos has consequences for other individuals for several generations, the reproductive autonomy of the parents should be restricted [12]. It should be noted that the genetic selection of embryos itself is also a matter of intense ethical deliberation. For some, selecting embryos by deliberately discarding other embryos because of their disease burden, because of their sex, or because being healthy they would not be part of their culture (in the case of deaf-mute couples who prefer embryos that have the gene for deafness), would always be morally wrong. This is what has been called the restrictive view, since children, present or future, are always "unique", possessing an intrinsic dignity, so that embryos should not be subject to any selection [13].

The moderate view is that genetic selection would be permissible, depending on the wishes of the parents; if the future life of that child is deemed difficult because of the genetic condition they have, it is up to the parents to decide whether or not to give that child the opportunity to live, but they have no duty to prevent that child from being born. The permissive view, on the other hand, points out that there is an obligation to carry out genetic selection in order to avoid bringing children into the world with chromosomal changes that are likely to make it more difficult for them to live a full life [13]. It is very likely that these different views can also be contemplated when analyzing the ethical scope of repairing an embryo whose genetic alteration suggests that it will not have a valuable future; some will consider that its "disease" should be "cured" and others that it is better to select the healthy embryo. However, an absolute and permanent restriction on the genetic editing of human embryos, when it is aimed at repairing a lethal condition, could be seen as an unacceptable intrusion into the reproductive autonomy of individuals, especially if the technical problems have been solved and also if the scope that these techniques will have on future generations is better known. Also, as we will see later, it is not the same thing to "cure" an embryo of a serious genetic condition that would prevent it from living and developing, as it is to introduce "improvements" so that future parents can satisfy their ideal child.

For non-reproductive purposes: If gene editing of germ cells and embryos does not have reproductive purposes, the ethical considerations are similar to any other research on this type of cells. We must point out that it is necessary to differentiate between research on gametes and research on embryos, since embryos are new organisms of the human species that need to be protected. For example, if there are embryos discarded in assisted reproduction processes because they have genetic alterations incompatible with extrauterine life, they could be used in research aimed at repairing this condition, rather than simply discarding them or leaving them cryopreserved indefinitely. In the opinion of this author, it would not be admissible to produce human embryos expressly for their use in research or to be destroyed to obtain stem cells. In turn, research on gametes (oocytes and spermatozoa) must consider the risk/benefit balance and an adequate informed consent process, whether they are used for experiments related to gene editing or for other scientific purposes.

4. Ethical Problems of Somatic Cell Gene Editing

Currently, there are several preclinical studies and also human trials using the technique of somatic cell gene editing, either at the fetal level or in people already born, to try to solve serious health conditions. There are two ways to repair defective genes. One is "ex vivo", whereby cells, for example lymphocytes, are removed, genetically modified and then transfused. The other way of therapy is "in vivo", in which the vector that produces the genetic change is injected into the organism and the hope is that it will eventually find the right sites to produce the gene editing, with no guarantee that unintended changes will not occur elsewhere. Examples of the first situation have been studies with modified lymphocytes to treat some types of leukemia; in vivo studies have already been performed to treat certain types of blindness, including that produced by ocular angiogenesis [14]. In these cases, DNA modification is restricted to the subject receiving the intervention, with no risk to future generations.

The use of this technique, even in the experimental stage, should be governed by the same ethical considerations as any other innovative therapy. There should be a favorable risk-benefit balance, an adequate informed consent process and fairness in the selection of subjects. At this stage, it appears advisable to restrict it to serious health conditions, in which no other type of therapy is possible, until there is more evidence regarding its safety.

Similar ethical conditions should be taken into account when gene editing is performed at the fetal level. Progress has already been made in studies in a mouse model to treat a hereditary type of tyrosinemia through the use of gene editing with CRISPR by injecting the vector into the vitelline vein. Its use at the fetal level has comparative advantages, due to the immunological immaturity and greater efficiency due to the lower fetal weight, and may be useful for those diseases without therapy and with great morbidity [15].

5. Ethical Problems Related to "Genetic Improvement"

There is much discussion regarding the use of gene editing techniques in order to achieve "improvements" in the human species. Some consider that it would be mandatory to be able to provide children with the best possible start in life. Others, on the other hand, consider that its use for breeding purposes contributes to increase existing inequalities and, in addition, limits the freedom of individuals born after genetic programming.

An example of a position in favor of genetic intervention for breeding purposes is that held by Julian Savulescu, in what he has called the "principle of procreative beneficence" [16]. Savulescu points out that parents committed to the welfare of their children have a moral duty to use all scientific advances (including genetic enhancements) to provide them with the best opportunities to achieve a better life [16, 17]. He postulates that these interventions do not harm the individual, but rather improve him or her, although he does not address the effect of genetic changes on future generations.

Michael Sandel considers that genetic intervention to perfect the species means intervening on a "gift that has been given to us", so that its use for the purpose of improvement would not be ethically acceptable [18]; he thus considers that the only valid intervention on children is that which seeks to cure them of some disease, since we are the depositaries of talents and capacities that are not entirely our own. For these reasons, children should be accepted as they are, since they are not the property of their parents [18].

Jürgen Habermas is also against the use of genomic editing to improve the species, since it could affect the autonomy of the new individual [19] and considers that genetic manipulation is linked to the identity and self-understanding of the species. Therefore, knowledge of one's own hereditary factors may be restrictive for the choice of an individual's way of life, thus undermining symmetrical relationships between free and equal human beings; moreover, the promise of achieving greater autonomy of individuals is also not such, since parents, by opting for this "genetic enhancement" for their children, impose expectations on them that the latter may not want to realize [19].

In addition, the use of genetic techniques to achieve "improvements" in the human species may increase the already existing inequalities in society, since only the most advantaged individuals would be able to finance them. A potential problem arises if these techniques are made available as state policies, to increase the war power of a nation, which would be absolutely unacceptable. Finally, we must point out that their use on germ lines and embryos necessarily implies that their effects will have consequences on future generations. At this stage in the development of the technique, when there are still undesirable changes in the genes to be repaired or modified, it is understandable that there should be a worldwide moratorium on its use for reproductive purposes (see below). A summary of the main uses of this technique and recommendations is given in Table 1 [20].

Table 1. Recommendations regarding the use of gene editing techniques

Use	Recommendation
Basic research	Use existing regulations for oversight of human gene editing research.
Genomic editing of somatic cells	Use existing regulation for oversight of human somatic cell gene editing research. Limit clinical trials to treat or prevent disease or disability. Evaluate efficacy and safety in the context of expected risks and benefits. Do not extend its uses until there is broad social support.
Germline genomic editing (heritable)	Allow clinical research only to treat or prevent serious disease or disability and only if there is a trained oversight system in place to limit its uses to certain well-defined criteria.
Genetic improvement	For now, human genome editing should not be used for purposes that are not related to curing or preventing diseases. Promote broad public discussion on whether or not to allow somatic genome editing for uses other than curing or preventing disease or disability.

Adapted from: National Academies of Sciences, Engineering, and Medicine; National Academy of Medicine; National Academy of Sciences; Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations. Human Genome Editing: Science, Ethics, and Governance. Chapter 8. Washington (DC): National Academies Press (US); 2017.20

6. Regulatory Aspects

In Chile, there is no specific legislation prohibiting the genetic editing of human embryos or germ cells, but the current Law on Scientific Research (Law 20.120), states in its Art. 1° that the "genetic diversity and identity" of human beings must be protected, prohibiting any eugenic practice and any "form of arbitrary discrimination based on the genetic patrimony of persons". It also prohibits the cloning of human beings, "whatever the purpose and whatever the technique used" [21]. In turn, it only allows gene therapy in somatic cells, provided that it is "for the treatment of diseases or to prevent their appearance" and protects, to a certain extent, the integrity of human embryos, by stating that "in no case may human embryos be destroyed to obtain the stem cells that give rise to such tissues and organs". However, it makes no reference to the possibility of destroying embryos for purposes other than obtaining stem cells. Our interpretation is that this law does not prohibit the use of genetic editing techniques of somatic or fetal cells, as long as its objective is preventive or therapeutic; however, it could not be used at the level of germ cells or embryos.

It may be advantageous if a future research law could be harmonized with the current Law on Voluntary Interruption of Pregnancy (VIP), which allows the destruction of non-viable embryos, by incorporating the incompatibility of an embryo or fetus with extrauterine life as a ground for requesting an abortion. Therefore, if the current VIP law allows the destruction of non-viable embryos or fetuses, a future research law should not prohibit, a priori, research on human embryos that are going to be discarded because they have a genetic alteration that is considered lethal. In this sense, a preimplantation embryo carrying a genetic alteration incompatible with life could benefit from advances in gene therapy that could modify this alteration, bringing it closer to the possibility of having "a valuable future".

At the international level, several experts have called for a moratorium on gene editing of germ cells and embryos for reproductive purposes, at least until there is reasonable safety with the technique [22]. Likewise, it seems prudent that before the technique is used for "improvement" purposes, there should be a broad social discussion on what should be the agreements for its "ethical" use, especially when attempting to intervene in the genes of germ cells and embryos. It may well be that after this broad discussion has taken place, society as a whole will decide that this is a line that should not be crossed. In this sense, it would be imprudent and unethical for the scientific community to exclude social actors from this necessary discussion [23], as it would require a well-informed citizenry regarding the scientific, ethical, social, and legal aspects of utilizing these new techniques. It is interesting to note that a recent study, which evaluated existing legislation on

the subject worldwide, showed that most countries (75 out of 96) prohibit human gene editing in germ cells and embryos for reproductive purposes [24].

7. Conclusion

It is evident that, as with any new technology, there is a tension between the need to promote rapid innovation and the necessary caution that requires seeking greater efficacy and safety before using the technique at the clinical level. In this sense, human gene editing requires special considerations, as pointed out in the World Health Organization document [3]. The technique can be used in search of a good, such as curing or preventing serious diseases, or it can be used to introduce "improvements" to the human race, which could contribute to increasing existing inequalities. As mentioned above, its use in germ cells and preimplantation embryos is of special concern, since the consequences of these genetic changes will affect future generations. In this regard, we believe that as suggested by the National Institutes of Health (NIH) document, the entire society, not just the scientific community, should be involved in this important discussion [23]. In the words of the World Health Organization, 'In a diverse world, countries and regions will consider their cultural, historical, and religious aspects and choose different regulatory approaches on this issue.' Therefore, it is necessary to correctly determine the values and principles that guide these decisions [3].

Declaration

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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