The ethical impact of new genetic editing technologies

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Abstract

The discovery of the CRISPR/CAS 9 genetic engineering technique opens up important new horizons for scientific research. The ethical, legal and social problems that can be applied to humans are immense, and justify a broad social debate. The present study looks at the most significant issues that might be included in such a debate.

Keywords: Bioethics. moral Principles. Decision making.

Resumen

El impacto ético de las nuevas tecnologías de edición genética

El descubrimiento de la técnica CRISPR/CAS 9 de edición genética abre importantes horizontes para la investigación científica. Los problemas éticos, jurídicos y sociales que pueden importar su aplicación a humanos son inmensos, lo que justifica un amplio debate social. El trabajo indaga sobre los temas más significativos que podría incluir tal debate.

Palabras clave: Bioética. Principios morales. Toma de decisiones.

Resumo

O impacto ético das novas tecnologias de edição genética

O descobrimento da técnica CRISPR/CAS 9 de edição genética abre importantes horizontes para a pesquisa científica. Os problemas éticos, jurídicos e sociais que podem surgir com a aplicação em humanos são enormes, o que justifica um debate social amplo. O trabalho indaga sobre os temas mais significativos que poderiam ser incluídos em tal debate.

Palavras-chave: Bioética. Princípios morais. Tomada de decisões.

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Declara não haver conflito de interesse.

The scientific world has been transformed by advances in *human genetic* editing technology. According to Lacadena [1], this term refers to a type of engineering in which Deoxyribonucleic Acid (DNA) is inserted, deleted or replaced in the genome of an organism using nuclease type enzymes called "molecular scissors". Nucleases cause double-strand breaks at precise locations in the genome, and double DNA breaks can be repaired by non-homologous end-joining mechanisms or by homologically directed repair, resulting in controlled mutations.

In the 1970s Paul Berg, Herbert Boyer, and Stanley Cohen laid the foundations for recombinant DNA (insertion into the genome of genes belonging to another living organism) [2]. The methods used at the time had major limitations in that they were imprecise and difficult to apply. However, the idea of the recombination of genes to integrate a modified genome remained.

The issue of imprecision was overcome in the 1990s when proteins were designed that could cut the DNA at specific points. This was a breakthrough in techniques based on the random insertion of DNA. As a result, a series of trials were carried out that brought the process closer to its anticipated goal, with the works of Francisco J. Martínez Mojica from 1993 to 2005, and those of a Japanese interdisciplinary group in 1987, of particular importance [3].

As a culmination of this process, a key work by J. Doudna, E. Charpentier et al. was published in 2012 which dealt with the technique called CRISPR/CAS 9 (clustered regularly interspaced short palindromic repeats, alluding to the sequence of recognition that uses bacteria to identify the viruses that have infected them), which described the first "cut" in a test tube, sensing that it could be transferred to eukaryotic cells to be used for genetic editing [4]. Since then research in the field has increased, confirming that CRISPR/CAS 9 is a technique of unusually broad scope, which has already been successfully tested on plants [5], animals [6] and human embryos [1].

Discussing the extent of this impact, J. Lunshoft [7] points out that in less than three years CRISPR/CAS 9 has become a crucial tool for biologists, and warns that it is too late to argue that its use should be stopped. Its multiple and varied applications, in humans as well as in plants, animals and microorganisms, require ethical and legal evaluation – two areas which do not always agree.

The themes under debate

The publication of the work of the teams directed by Doudna and Charpentier stimulated various articles in specialized publications in which a certain degree of concern was expressed about the effects that the discovered technique could unleash. The situation is unique. Although the questions and fears revealed had been exposed beforehand, in the past they referred to a distant, hypothetical future, whereas today they concern a future that is considered close.

It may be that the fear of the uncontrolled application of genetic engineering techniques has generated a reaction founded in ignorance of the current reality. John Harris, demonstrating great power of synthesis, said this of the new phase: *we are on the verge of a new revolution with an amazing power. The reevaluation of molecular biology will give us unprecedented scope. It will allow us to manufacture new forms of life on request, life forms of all kinds. The decision that we are making is not whether to use this power or not, but how and to what extent* [8]. In the present case - in our opinion - three human applications of the new technique are proposed: in germinal gene therapy; in somatic cells; and in "improvement" interventions. We will now examine these.

Germinal gene therapy

This is the most questioned intervention relating to the effects that the alteration of the genome can cause in the hereditary line, either by the addition or the deletion of genes.

Opinions and declarations against any modification of the human genome or any extreme forms of care that might produce such alterations have arisen since the first investigations into the subject, even though at that time no practical techniques for such editing existed. In this context I would highlight:

- The Group of Advisers to the European Commission on the Ethical Implications of. Biotechnology, in Opinion No 4 dated 12 February 1994, warned that in the state of scientific knowledge "human germline therapy was not acceptable from an ethical point of view" "(point 2.7) [9].
- The Council for International Organizations of Medical Sciences (CIOMS), in the 1990 *Inuyama Declaration*, advised that prior to initiating germline gene therapy it would be necessary to ensure its perfect safety, considering that the modifications made to germ cells can affect offspring [10].

In 1982, the Council for Responsible Genetics issued a statement on the manipulation of the human germline. It stated: *there is no universally accepted ideal of biological perfection. To make intentional changes in the genes that people will pass on to their descendants would require that we, as a society, agree on how to classify "good" and "bad"*

genes. We do not have the necessary criteria, nor are there mechanisms for establishing such measures. Any formulation of such criteria would inevitably reflect particular current social biases. The definition of the standards and the technological means for implementing them would largely be determined by economically and socially privileged groups [11].

The April 24, 2003 Statement of the International Bioethics Committee (IBC) of the United Nations Educational, Scientific and Cultural Organization (UNESCO) on pre-implantation diagnosis and germline interventions points out that *the correction of a specific genetic abnormality in germ cells or early stage embryos (germ-line intervention) has not yet been carried out in medical practice. Because of the many technical problems and uncertainties about possible harmful effects on future generations, germ-line intervention has been strongly discouraged or legally banned* [12].

Subsequently, in the light of the progress made, in July 2017 the same organization produced a document entitled "the Report of the International Bioethics Committee (IBC) on Updating Its Reflection on the Human Genome and Human Rights," which states: *recent advances have opened the door to genetic screening, genetic testing for hereditary diseases, gene therapy, the use of embryonic stem cells in medical research and the possibility of cloning and genetic editing, both for medical and non-medical purposes,* adding that *UNESCO considers that the human genome must be protected and that the advances in science must be considered in the light of ethical norms and human rights* [13].

In relation to the theme that expressly interests us: *at the same time, this development seems to require particular precautions and raises serious concerns, especially if the editing of the human genome should be applied to the germline and therefore introduce heritable modifications, which would be transmitted to future generations. As a result, it recommended a moratorium be applied to this specific procedure* [13].

From the transcribed opinions it is possible to identify that the majority of opinions argue in favor of the impossibility of gene therapy, based on concepts ranging from the preservation of the unmanipulated genome to the protection of future generations. Taking a less categorical position, some predicted the possibility of germline therapies, but warned that extreme care must be taken. Other than the above, germline gene therapy has led to further discussions that remain a long way from reaching a conclusion, such as pre-implantation diagnosis and interventions in human embryos.

The main arguments supporting the opposition to germline gene therapy are as follows:

- ***The risks to the individuals***

The precautionary principle has often been used to prohibit the application of genetic engineering techniques. The precautionary principle - as it is known - is based on the existence of a scientific uncertainty about the effects of the application of a given technique. For some, the invocation of such a risk is sufficient reason to reject the procedure.

We would argue that is not enough to simply invoke a risk. It is also necessary to determine as accurately as possible the consequences that may arise from the application of the technique and choose accordingly whether to reject it or not, whether to carry out further scientific research, or whether to establish a moratorium during which further investigations could be carried out into the risks in question [14].

Of course, the application of any technique involves risks. Negative effects in the medium and long term are inevitable. As Schramm teaches, the zero-risk society does not exist, as we know that complex societies like ours are societies based on structural risk.

If the relevant steps established by science have been followed, the application of the technique cannot be viewed from an ethical viewpoint. A contrary position would lead to every new technique being rejected, which wuld be objectionable [15].

- ***The belief in the sacredness of the genome***

According to those who adopt this argument, the human genome is inviolable and cannot be tampered with.

At the beginning of human genome sequencing the fear of undue deviations led to the genome being consecrated as "a common heritage of mankind". UNESCO specifies this in Article 1 of the *Universal Declaration on the Human Genome and Human Rights* adding in article 11 that practices that are contrary to human dignity shall not be permitted; and in article 12 that benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual. This is the relevant limit: respect for dignity and human rights. Does genetic manipulation violate this? [16].

G. Hottois argues: *this sacralization of the genome comes from its assimilation to nature, and even more to the essence of man. This biological idealism is hardly intelligible from an empirical scientific-technical approach. From this perspective the human genome does not exist. There are genomes of individuals that are more or less related, but also diverse (polymorphism, the product of long evolution). The idea of a unique, ideal and stable*

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genome on the model of Platonic or Aristotelian idealism is an archaic metaphysical ghost [17].

- ***The risk of a "new eugenics"***

Prior to the work of the researchers Doudna and Charpentier, the danger of a "new eugenics" was envisaged by the application of hereditary techniques: genetic analysis, pre-implantation diagnosis, prenatal diagnosis, genetic screening and recombinant DNA engineering. All or some of these techniques – in Carlos Maria Romeo Casabona's judgment – may be the background of the resurgence of ideas of eugenics at the beginning of the millennium, known as neo-eugenics [18].

In a similar way, Iañez Pareja talks about the challenges of the "new eugenics" [19] while Soutullo [20] argues that many of the therapeutic interventions aimed at reducing the suffering of people and guaranteeing them a dignified and healthy life in which avoidable diseases cannot occur and which become socially acceptable because they do not have serious negative consequences can also be considered as a form of eugenics.

More recently and from a philosophical viewpoint J. Habermas, referring to genetic techniques prior to CRISPR/CAS 9 warned about the installation of a "liberal eugenics" [21]. Based on two advanced techniques at the time of giving his opinion - pre-implantation diagnosis and research with totipotent stem cells - Habermas understood that if "embryo-consumer" research and pre-implantation diagnosis trigger so many hostile reactions it is because they are perceived as the exemplification of an approaching liberal eugenics. Perhaps - in the light of the advances that we are facing today - his judgment would be more rigid.

I believe that several of the assessments made in the essay could help to strengthen the care taken during the manipulation of human genes, without giving up the benefits of scientific research aimed at the solution of problems which afflict humanity. As Victor Penchaszadeh says, *the benefits of genetics are the people, and distant from eugenic factors* [22].

So far, Habermas says*, controversies over research and genetic techniques have revolved essentially around the question of the moral status of 'pre-personal' human life; I now adopt a 'present-future' perspective from which it is possible that we retrospectively see practices that are today controversial as pioneers of a liberal eugenics regulated on the basis of supply and demand* [23].

Embryonic research and pre-implantation diagnosis inflame passions, especially since we associate them with the metaphor of "human creation." While it is possible that by using genetic engineering techniques situations can arise that border on what Habermas calls "liberal eugenics", I believe that generalization carries with it an unmotivated pessimism, as though we were dealing with the inaccessible problem of setting limits on the deviant use of such techniques, including human genome engineering with the CRISPR/CAS 9 technique. To speak of eugenics in this scenario is to go too far in the argument against the deviant use of techniques.

Beyond its etymological root, the use of the term "eugenics" has always been linked with the imposition of population policies for the "improvement of the race" from the top of the state power pyramid and not for the individual use of a given technique. The mere use of the term – associated with negative memories - leads to a visceral rejection. In this sense, Nikolas Rose argues that to avoid the term eugenics becoming a multipurpose rhetorical device, empty of analytical meaning, we must reserve it for biopolitical strategies that are properly defined according to the original meaning of the term [24].

When we refer to the individual use of genetic techniques we are moving in another direction. The aim pursued by parents who request a pre-implantation diagnosis is to avoid the birth of a child with a serious illness. This private "eugenics", linked to the freely consenting practice of prenatal diagnosis, has no relation to actual state eugenics.

Greater care is required in the use of the word precisely to avoid unwanted deviations. It is true that there are and potentially will exist situations in the future that can be difficult to define, and here we should handle ourselves with the necessary care. Habermas himself teaches us that we must draw and impose borders precisely where they are flexible [23].

The employment of the term liberal eugenics to prevent the use of new techniques in a field as delicate as genetics, refers us to the so-called "slippery slope" argument, which in summary argues that the exercise of prohibitive policies in research can be the starting point for situations that are not wanted or morally acceptable. John Harris, considering these ideas, reflects that there is no safe route.

For the author, if we stop making changes in humans, the result may simply be to ensure that the future is worse than it otherwise should be. If we err in the changes we make, the same thing can happen. We must try to learn to choose responsibly, but it makes no sense that doing nothing is necessarily a more responsible choice than doing something [25].

The editorial committee of the book published by the Academies of Science and Medicine of the United States this year defined a set of criteria under which genetic germline editing should be allowed [26]. They are:

- Absence of reasonable alternatives;
- Restrictions to prevent serious illness;

- Restrictions to edit genes that have convincingly been shown to cause or strongly predispose the individual to serious illness;
- Restrictions to convert those genes into versions that are dominant in the population and that are associated with health, without categorical evidence of adverse effects;
- Availability of clinical information on risks and possible health benefits of these procedures;
- Continuous monitoring during the respective testing of the effects of the procedure on the health and safety of the participants;
- Continuous monitoring of health and social benefits and risks, with broad and continuous public participation;
- Reliable monitoring mechanisms to prevent uses other than the prevention of serious diseases.

These represent a handful of comparable criteria which, based on the need for further scientific research, point to the use of the technique by limiting it to situations in which it can contribute to eradicate the negative effects of serious pathologies where there are no reasonable doubts, avoiding entering into dogmatic positions that do not favor the solution of problems for which at this moment there is no acceptable manner of resolving the problems of the patient or their future offspring.

Somatic gene cell therapy

Somatic gene therapy consists of correcting or improving a pathological state by transferring genetic material into an organ or tissue, excluding the germ cells. It is called somatic as it deals with differentiated cells (of the fetus, of the child, of the adult) [27]. When genetic engineering emerged, some supported the idea of performing this therapy without sufficient technical support. The failures in this task revealed the difficulties of creating a safe and effective way to introduce genes into the tissue in question.

Subsequently a paper published at the time of the CRISPR technique in 2014 expressed some optimism, recalling that in 2012 Europe had authorized the first treatment of a rare condition and that by the end of 2013 the National Institutes of Health (NIH) in the USA decided to eliminate certain legal challenges which it considered unnecessary [28]. In any case, the publication emphasized that "much work remained to be done".

Considering that the effects of germline gene therapy are only revealed through experimentation or treatment, the ethical objections against it are considerably diminished. The prevalence here is limited to the protection of the health and physical integrity of the subject. The possibility of CRISPR treatment for diseases such as cancer or schizophrenia has already begun to be explored, although the fact that it is so easy to modify genomes with this method raises ethical concerns [29].

In the recommendations contained in the text elaborated by the American Academies to which we have referred, the following ethical limits are established for its use:

- Use existing regulatory processes on human gene therapy to conduct research and applications on somatic human genome editing;
- Limit clinical or therapeutic trials to disease prevention or disability treatment;
- Evaluate safety and effectiveness in the context of the risk and benefit of intended use;
- Demand a broad favorable public opinion before extending its use.

"Improvement" interventions and genetic editing

In previous sections - somatic gene therapy and germline gene therapy - the prevailing concept, which allowed its acceptance or rejection, was focused on the idea of disease. When we move away from this focus, with all the reservations required, we enter a difficult area.

In an essay on disease Giovanni Berlinguer, an illustrious Italian thinker, asks – "what is normal?" Answering the question seems quite simple, but normal is difficult to evaluate in physical terms and even more so in biological systems. Today the biological sciences that study living beings increasingly emphasize individuality, thus returning to the concept of normality and eliminating the rigidity that dominated the last century. For disease, the distinction between normal and abnormal and between abnormal and pathological is still complicated, especially in the specific field of diagnosis [30].

While these considerations seem incontestable, it should be noted that there are cases in which disease as a normal concept can be clearly distinguishable (e.g. monogenic diseases), while in other cases the distinction depends on social construction. If gene therapy is ultimately accepted - whether in somatic cells or the germline – a regulation could be imposed that helps to refine criteria. Questionable situations requiring a greater level of precision would continue, but in spite of the difficulties that this task may entail, it should not be considered an insurmountable obstacle.

At this point in the discussion we should question the concept of the "improvement" of the human being. Undoubtedly, such improvement brings us closer to the debate about the normal and the pathological. However, in Romeo Casabona's opinion the elements of the confrontation are

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very different, because they deal with moving from the "normal" to therapeutically treated perfection, or more precisely towards improvement or strengthening. Making this distinction is a task that cannot be ignored, but at the same time it represents a goal that may be unattainable [18].

Human beings can improve their physical state, their abilities or their capacities through practices or treatments that may or may not involve the medical sphere (sports, food, mental training, etc.). Nothing suggests this is bad, because the right to feel better or to correct disabilities is indisputable. The subject that interests us in this collaboration is whether such improvements can be obtained through genetic manipulation, if feasible in the current state of science.

Here - in my opinion - we reach the limit of what is morally permissible. Genetic manipulation has a moral basis if used to prevent or cure pathologies, whilst not forgetting the difficulties that may exist when defining them; but not to satisfy the desires or whims of men, even if it were scientifically or technically possible. In this sense Javier Gafo pointed out that a major ethical objection arises from the fact that this is not a therapeutic intervention on a sick person. The desire for improvement entails the danger of not valuing the person in themselves, but because of characteristics that they have and that have been selected by a third person [31].

I admit that this is not a universally shared position. Thus, John Harris and J. Savulescu, among others, consider that the goal of improvement, far from being selfish and unethical, must be guided by the deep aspirations that have always marked bioethics: the aspiration to improve ourselves and improve the world in which we live. The pursuit of beneficence, the good life or even, perhaps, the better life [32].

The objective determination of improvement from a social context tells us nothing about its moral merits or demerits. In reality - as Lema Añon refers to it - the objectivity of improvement is defined by instrumental rationality with respect to an objectively existing purpose or scale of values, but tells us nothing about the value of that scale in ethical terms [33].

Improvement, even if it is improvement in objective terms, is not necessarily at the same time positive in moral terms [33]. It should always be remembered that therapy is a universal requirement and is based on the ethical principle of non-maleficence, while improving interventions are not universal and hence the source of discrimination and inequalities [33].

Other than the above, improvement interventions in the human genome in the current state of knowledge constitute a fantasy that have much more to do with literature than the men of science. The multiplicity of genetic factors converging in the determination of a human ability or aptitude, coupled with the necessary intervention of environmental (taken in a broad sense) and social factors, means it is not yet a problem to be addressed. Nevertheless, the simple possibility of a future in which this could exist sets alarm bells ringing.

Norman Daniels argues that it is possible to reasonably establish the distinction between therapeutic treatment and improvement, although complex cases will remain. At the same time, he warns not to expect any such distinction to represent a complete guide to defining health services that should be included in the right to health nor a simple criteria for defining the limit between what is or is not morally admissible in cases in which the determined future probabilities of genetic improvement are available [33]. The relevance of the topic in different planes explains why it must be included on the agenda of a necessary social debate.

Final considerations

The possibility of altering the composition of the human genome was first identified through the aforementioned works by Correa, Bergel and Kors [2] in the 1970s, with inevitable ethical and legal consequences.

Hans Jonas, in an original publication dating from 1985, wondered if are we perhaps on the threshold of a technology that is based on biological knowledge and provides us with a capacity for manipulation of which man himself is the subject. With the advent of molecular biology and its understanding of genetic programming, this has become a theoretical and a moral possibility, through the metaphysical neutralization of the human being. But this neutralization, which undoubtedly allows us to do what we want, at the same time denies us the guidance to know what we want [34].

Today, the discovery of the technique discussed in this work has forced us to emerge from the imagined hypotheses of the future to face, in the not very distant future, the applications of a technology that allows us to modify the human genome without great difficulty, either by the addition or deletion of genes. This makes it possible to consider the avoidance of hereditary diseases, but also fantasies about children with altered characteristics or qualities based on the whims of their parents.

Where will the dividing lines be drawn, and who will draw them? How can deviations that seem to clash with elementary ethical principles be avoided? We are discussing a future that is dangerously close to the present, forcing us to be cautious and establish principles and rules of general social acceptance.

In this sense we agree that *public education and engagement are crucial in the process of assessing and applying societal values to the risks and benefits of genome editing technologies and the ethical dimensions they involve. For somatic genome editing, the committee concludes that transparent and inclusive public policy debates should precede any consideration of whether to authorize clinical trials for indications that go beyond treatment or prevention of disease and disability (e.g. for enhancement). With respect to heritable germline editing, in addition to the strict criteria and stringent oversight discussed above, broad participation and input by the public, along with ongoing reassessment of both health and societal benefits and risks*[26]. This highly illustrative conclusion of the volume published by the aforementioned Academies of Science and Medicine of the United States demonstrates the fundamental importance of guaranteeing public education to reinforce social commitment to the application of genome editing technologies.

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