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ANALYSES

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Gene Editing in Humans: Towards a Global and Inclusive Debate for Responsible Research

Itziar de Lecuona[a], María Casado[a], Gemma Marfany[b], Manuel Lopez Baroni[a], and Mar Escarrabill[a,*]

[a]*Bioethics and Law Observatory, University of Barcelona, Barcelona, Spain;* [b]*Faculty of Biology, University of Barcelona, Barcelona, Spain*

In December 2016, the Opinion Group of the Bioethics and Law Observatory (OBD†) of the University of Barcelona launched a Declaration on Bioethics and Gene Editing in Humans analyzing the use of genome editing techniques and their social, ethical, and legal implications through a multidisciplinary approach. It focuses on CRISPR/Cas9, a genome modification technique that enables researchers to edit specific sections of the DNA sequence of humans and other living beings. This technique has generated expectations and worries that deserve an interdisciplinary analysis and an informed social debate. The research work developed by the OBD presents a set of recommendations addressed to different stakeholders and aims at being a tool to learn more about CRISPR/Cas9 while finding an appropriate ethical and legal framework for this new technology. This article gathers and compares reports that have been published in Europe and the USA since the OBD Declaration. It aims at being a tool to foster a global and interdisciplinary discussion of this new genome editing technology.

INTRODUCTION

Biotechnology development advances rapidly and nowadays we are able to build scientific tools that years ago seemed like science fiction. This is the case of genome modification, which permits us to structurally alter the genetic background of humans and other living beings in order to decide on the characteristics of their descendants. Gene editing in humans, including the CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/Cas9) technique, already forms part of the molecular tools available to researchers and has increased its use among the scientific community over recent years.

Gene editing in humans has generated expectations, fears and many questions that deserve an interdisciplinary analysis and an informed social debate. There is a wide range of bioethical, political, and scientific positions which range from demanding a moratorium that would

*To whom all correspondence should be addressed: Mar Escarabill, Avgda. Diagonal 684, Facultat de Dret, 08034 Barcelona, Tel: (+34) 93 403 45 46, Email: marescarrabill@ub.edu.

†Abbreviations: CRISPR/Cas9, Clustered Regularly Interspaced Short Palindromic Repeats/Cas9; DNA, Deoxyribonucleic acid; RNA, Ribonucleic acid; PAM, Protospacer adjacent motif; OBD, Bioethics and Law Observatory; EASAC, European Academies' Science Advisory Council; ACMG, American College of Medical Genetics and Genomics; HFEA, British Human Fertilisation and Embryology Authority.

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paralyze this kind of research [1] to authorizing certain uses of gene editing in humans [2,3], passing through a gradualist paradigm [4]. Thus, it is necessary to clarify concepts, identify problems, and promote exchange between all stakeholders involved, such as universities, society, and science and technology systems, in order to articulate an optimal ethical and legal framework.

In this context, in December 2016, the Opinion Group of the Bioethics and Law Observatory (OBD) of the University of Barcelona (consisting of lawyers, biologists, philosophers, and physicians among other disciplines) launched its "Declaration on Bioethics and Gene Editing in Humans," which analyses the use of genome editing techniques in human beings and its social implications through an ethical and legal approach. It also presents elements of reflection and makes proposals for specific actions based on current knowledge.

The ethical, social, and legal concerns of the CRISPR/Cas9 technique (CRISPR from this point) have also been analyzed by other institutions such as the Nuffield Council of Bioethics [5], the Hinxton Group [6] and the UNESCO International Bioethics Committee [7]. This article aims at comparing and analyzing the documents that have been launched since the publication of the Declaration on Bioethics and Gene Editing in Humans developed by the Bioethics and Law Observatory. It analyses the document launched by the OBD and gathers the points of view that present the documents launched in 2017 by European and American scientific institutions regarding genome modifications.

In particular, this article gathers and compares the views of two European institutions (European Academies Science Advisory Council (EASAC) and The Company of Biologists) and two American institutions (The American College of Medical Genetics and Genomics (ACMG) and the National Academies of Science, Engineering, and Medicine).

CRISPR TECHNIQUE OF GENE EDITING IN HUMANS

Genome editing involves inducing a directed and specific modification in the DNA sequence of humans or other living beings. CRISPR is a gene editing technique that has exploded in popularity in the last few years. This tool has ancient roots, as it is an adaptation of the techniques used by bacteria to protect their cells from bacteriophages [8,9]. This archaic adaptive immune system present in some microbes is able to cleave the nucleic sequences of an invading virus [10]. Nowadays it can be used to cleave the genetic material of any organism and modify it [11]. CRISPR can be applied by using a piece of RNA called guide RNA (gRNA) that guides a Cas9 nuclease to a specific position of the DNA sequence [12]. Cas9 will not be able to recognize the position without the function of the protospacer adjacent motif (PAM) – a very short nucleic acid sequence that binds target DNA. Once they have arrived in the specific position, Cas9 nucleases can induce precise cleavage at genomic loci in humans. This cleavage is recognized by the cell's DNA repair machinery and, while the damage is being repaired, corrections of the DNA sequences or addition of new hereditary material can be induced in this position [13].

CRISPR has a wide range of characteristics that give this technique a potential and interest unknown until now. In particular, four peculiarities deserve to be mentioned: Specificity, efficiency, accessibility, and versatility (Table 1. Peculiarities of CRISPR) [14]. These characteristics make it a useful tool for developing precise genetic modifications in different cells, tissues, and organisms, including mammal and even human embryos, and it has rapidly become affordable for all science laboratories worldwide. In fact, data on the number of publications based on studies using this technique indicate an exponential growth in its use since 2012 [15]. Moreover, many start-ups that will commercially exploit this technology have been created.

A WIDE RANGE OF PERSPECTIVES REGARDING CRISPR

There is no global point of view regarding this tool that makes it possible to modify the genome of humans and other living beings. Not all countries and cultures share the same perspective regarding restrictions on the technology, but somatic cell gene therapy in humans is already being used in some countries [14].

While the EU has undertaken a bioethical debate about this technique (particulary the UK), in April 2015 Chinese researchers announced that they had applied CRISPR to non-viable human embryos. In particular, they reported that the CRISPR system was able to cleave endogenous genes efficiently in human tripronuclear zygotes [16]. Recently, another research group from China has demonstrated that CRISPR is also effective as a gene-editing tool in available human embryos. However, they have highlighted the limitations that their results revealed and the need for further research [17].

In September 2015, a team of British researchers asked for authorization to apply CRISPR in embryos left over from *in vitro* fertilization that had been donated by their progenitors, with the aim of studying human preimplantation embryo development. In February 2016, the British Human Fertilization and Embryology Authority (HFEA) gave its authorization, the first in the world for this type of research activity. This authorization allows research with healthy embryos, both newly

Table 1. Characteristics of CRISPR.

Specificity	CRISPR can induce genetic modifications at very specific points of the genome, whereas other transgenesis techniques have null or low precision. Specificity confers a high level of effectiveness on the genetic modification achieved and a very low incidence of undesired secondary effects.
Efficiency	This gene editing technique is easily produced and has a high final percentage of genetically modified sequences in a specific location.
Accessibility	CRISPR is considered relatively simple to apply. It just requires a minimum knowledge of genetic manipulation techniques and a modest investment in infrastructure. In addition, the molecular tools required are accessible in public repositories more cheaply than requirements for other gene editing techniques.
Versatility	A wide range of variants of the molecular bases used in this technology have rapidly emerged due to the deep knowledge of this kind of base. This great variety makes it possible to exercise greater control over technique and to obtain an even greater range of molecular modifications that adapt to the needs of the researcher.

formed and up to 7 days old. Moreover, it makes clear that the embryos must be destroyed after the experimental process because it is strictly prohibited to transfer these genetically modified embryos to a woman or to use them for any other purpose. In contrast, the United States and China seem to have a more permissive legislative process regarding advances in biotechnology. The first protocol for gene therapy through CRISPR was approved in the United States in 2016 [18]; in China, the first Phase I clinical trial of gene therapy against lung cancer in humans is imminent. At the moment, gene therapy only considers the modification of the human genome in *ex vivo* somatic cells, which will then be reintroduced into the patient's body. However, less than one year has passed between the publication of the gene editing of triploid human embryos developed in China and the introduction of this technology to cure serious cancers in patients that do not respond to chemotherapy and without the possibility of donors [14].

Due to the various applications of gene editing applied to human beings, it is impossible to give an overview of current international or national regulation. However, it is important to remark that the Council of Europe's Convention on Human Rights and Biomedicine (which is open for signature by all states) establishes in its article 13 "Interventions on the human genome" that "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants" [19].

In this context, the bioethical and legal debate is particularly necessary in international forums, where scientists, experts in bioethics, and legal scholars can discuss and promote an ethical acceptable technology that solves social needs rather than individual interests. Due to the social impact of this technique and the wide range of points of view regarding this technology, in December 2016, the Bioethics and Law Observatory (OBD) of the University of Barcelona launched the Declaration on Bioethics and Gene Editing in Humans in order to guarantee a multidisciplinary, global, and flexible conception of gene editing in humans and analyze its ethical and legal framework.

THE DECLARATION ON BIOETHICS AND GENE EDITING IN HUMANS (OBD)

The Declaration on Bioethics and Gene Editing in Humans proposes a set of recommendations to different stakeholders. Firstly, it highlights the need for a framework based on respect for the precautionary principle. Within a gradualist position, the Opinion Group of the Bioethics and Law Observatory holds that genome editing techniques should proceed in phases. This means allowing the use of gene editing in basic research, approving therapeutic use in somatic cells, and assessing the possibility of approving germinal therapy for certain cases. In all cases, it should be applied for therapeutic purposes and not human enhancements. Sometimes the line between therapy and enhancement is not that obvious; thus, a clear definition of both concepts is necessary to better define the use of CRISPR.

The Declaration also suggests analyzing and revising current regulation at all levels, from the criminal code to assisted human reproduction law and the law on biomedical research. In this sense, an informed social debate is needed and decisions regarding the development of gene editing research and its application should be taken among different stakeholders. Thus, the research work emphasizes that technology should improve quality of life and, in this sense, decisions must be guided by the idea of the common good and not remain in the hands of financial powers. In contrast, patent policy and the current privatization process of

gene information are paradigmatic examples of practices that should not be followed. In this context, it is important to raise awareness about the possible existence of conflict of interests between scientists as researchers who look forward to an increase in global knowledge, and "entrepreneurs" who seek to maximize individual profits. Among its recommendations, the Declaration also says that it is necessary to have public policies to determine research priorities and ensure public participation and transparency in decision making accompanied by policies of open access to information.

In order to ensure the success of the recommendations proposed, there must be an effective system for evaluating and controlling research. Research ethics committees must review the integrity of research and innovation as well as its ethical, legal, and social implications [20]. The evaluation must be carried out by committees, whose members must have up-to-date training. Lastly, the report calls on the media and the public to get involved in an inclusive and informed social debate regarding genomic edition in humans. In order to achieve a non-discriminatory debate, it is necessary to promote an informed public discussion at different levels involving citizens, researchers, policy-makers, and commercial sectors as well as the media. Science communicators must promote a responsible communication of science avoiding alarmism or exaggerated expectations regarding results.

GLOBAL AND INCLUSIVE DEBATE

After the Declaration on Bioethics and Gene Editing in Humans developed by the Bioethics and Law Observatory was launched, European and American institutions also presented documents focused on the analysis of CRISPR. Like the OBD's declaration, they highlight strengths, limitations, ethical concerns, and recommendations that should be taken into account before applying CRISPR.

In March 2017, the European Academies Science Advisory Council (EASAC) launched a report called "Genome editing: scientific opportunities, public interests and policy options in the European Union." This document is a broad synthesis of genome editing and aims at fostering an informed social debate about this issue [21].

The report of the American College of Medical Genetics and Genomics (ACMG) "Genome editing in clinical genetics: points to consider" was published online on 26 January 2017. It focuses on the analysis of the CRISPR system and suggests a set of points for consideration regarding the potential clinical application of genome editing addressed specifically to medical geneticists and other healthcare providers [22]. The Company of Biologists summarized the CRISPR genome editing system, discussed its potential applications and limitations in human pre-implantation embryos and the ethical considerations that this technique involves in a spotlight article launched in 2017 called "Towards a CRISPR view of early human development: applications, limitations and ethical concerns of genome editing in human embryos" [23]. Finally, in 2017 the National Academies of Science, Engineering and Medicine launched the Document "Human Genome Editing: Science, Ethics, and Governance" [24]. It was prepared by an interdisciplinary group that included biologists, bioethicists, and social scientists, and incorporated perspectives from potentially affected patient and stakeholder communities. The main strengths, limitations, ethical concerns, and recommendations raised by each document are summarized in Table 2.

DIVERGENCES AND COMMON POINTS

It is noteworthy that not all the reports are addressed to the same stakeholders; the focus of each one is different, making it difficult to compare them. However, their main common points can be seen and the main divergences can be discussed. OBD, EASAC, ACMG, the Community of Biologists, and the National Academies of Science, Engineering and Medicine reveal that CRISPR can be a valuable contribution to basic research. Additionally, the Community of Biologists and the National Academies of Science, Engineering and Medicine also explain in more detail the benefits of the gained knowledge for clinical applications (*e.g.* the treatment of infertility and stem-cell-based regenerative medicine) although they point out that more investigation is needed. The Company of Biologists shows a less gradualist position than the others.

There is a global point of view that suggests that a better understanding of CRISPR is needed before its clinical application. The common limitations raised in all documents are the possibility of mosaicism (the presence of two or more populations of cells with different genotypes in one individual. It can occur when the cells divide before the genome editing takes place), off-target effects, and unknown long-term consequences. Moreover, the National Academies of Science, Engineering and Medicine highlight the effects on the human gene pool. Some genes that cause serious genetic diseases have been subject to positive selection to maintain the disease-causing allele in the population because it produces some protection against infectious disease when present in one copy. If this gene is modified this protection will be lost. Apart from the technical limitations that CRISPR presents itself, the Community of Biologists mentions the restrictions in the analysis of the results (the time window for the analysis after gene editing in human embryos

Table 2. Main points of view of each document.

	Strengths	Limitations	Ethical Concerns	Recommendations
OBD	-CRISPR can contribute to basic research due to its specificity, efficiency, accessibility, and versatility	-Mosaicism -The possibility (although very low) of off-target effects -Unknown long-term consequences	-Conflict of interests between scientific activity and entrepreneurial purposes -Unknown environmental effects -Impact on future generations -The line between therapeutic and non-therapeutic purposes is not always clear	-Allowing the use of gene-editing in basic research; approving therapeutic use in somatic cells and assessing the possibility of approving germinal therapy for certain cases -Analyzing the risks and benefits of gene editing techniques in animals and plants, carefully evaluating their impact on the environment - Revising current regulations, updating them for the possible use of gene-editing techniques under certain requirements and with due guarantees. In this sense, an informed social debate is needed -Decisions regarding the development of gene editing research and its applications should be taken among different stakeholders -Ethics committees must evaluate the scientific and methodological implications of the research, as well as its ethical, legal, and social implications -The role of media is particularly important. They must be careful in transmitting techno-scientific information
EASAC	-CRISPR has a great potential in a wide range of sectors (*e.g.* human and animal health, food and agriculture, microbiology, biotechnology and bioeconomy)	-There is a need for a better understanding of the potential benefits and risks of gene-editing techniques	-Gene-editing in humans applied to enhancing may accentuate concerns about equality and proportionality -The right of individuals to decide as long as nobody else is harmed	-Investigate the risks and potential benefits of genome modification more extensively -Enhance global justice in order to tackle social inequalities that genome modification could cause -It is necessary to promote public engagement and the involvement of different stakeholders while discussing about genome modification -Legal and ethical issues need to be explored more in depth before its application. If, during the research process, early human embryos or germline cells undergo genome editing these modified cells should never be used to establish pregnancy

ACMG	-The research applications of genome editing technologies could be of great value in developing disease models and studying disease mechanisms	-The risk of off-target effects of genome editing may have unpredictable consequences for the embryo and future generations -The consequences of editing a pathogenic variant may have unknown epigenetic effects	-The potential for rapid advance of this technique, and the pressure to apply it clinically, should not be underestimated -The line between therapeutic and non-therapeutic purposes is not always clear	-Human embryo editing is premature and should be subject to vigorous ethical debate among different stakeholders. Additionally, further refinement of technological issues is needed -Clinical application of genome editing technology will require medical and genetic review -The decision as to which specific genetic variants should be subject to genome editing needs further discussion
The Company of Biologists	-Simplicity, high efficiency, and versatility -Useful for basic research -The gained knowledge could be of importance for the treatment of infertility and stem cell-based and regenerative medicine, among others	-The faster cell divisions (*e.g.* in the pre-implantation embryo), the higher risk of mosaicism [25]. However, Reyes and Lanner highlight that CRISPR achieves lower rates of mosaicism in embryos than other methods -Off-target effects may induce mutations in other genes -Availability of human embryos -The time window for the analysis after gene editing in human embryos is restricted to first week of development	-The document refutes any ethical concern based on the publications of Kang et al, 2016 [26] and Liang et al. 2015 [16]. In short, the Company of Biologists reports that there are already regulations to avoid any potential misuse of CRISPR technology	-Investigate strategies more in depth to reduce the risk of off-target effects

The National Academies of Science, Engineering and Medicine	-Preventing transmission of inherited genetic diseases -Basic laboratory research to advance understanding of human cells and tissues and mammalian reproduction -Improvements in genome editing are increasing the efficiency and accuracy of the technique while also decreasing the risk of off-target effects	-Mosaicism -Off-target effects -Effect on the human gene pool -Unknown long-term consequences	-Germline editing is highly contentious precisely because of the impact on future generations -The line between therapeutic and non-therapeutic purposes is not always clear. It needs to be clarified -Possible benefits that accrue primarily to individuals against possible harm at a social level *(e.g.* accentuate inequality)	-The Principles for the Governance of Human Genome Editing must be: a) promoting well-being, b) due care, c) responsible science, d) respect for persons, e) distributive justice, f) transnational cooperation -Policy in germline editing will require a careful balancing of cultural norms, the well-being of children, parental autonomy, and regulatory systems to prevent inappropriate applications -Permitting clinical research trials only for compelling purposes of treating or preventing serious disease or disability and within a robust and effective regulatory framework -Government bodies should promote transparency and encourage public discussion and policy debate -Use existing regulatory processes to oversee human genome-editing laboratory research such as safety for laboratory workers and the environment, donor consent, and privacy and reviewed protocols by institutional review boards -Do not proceed at this time with human genome editing for enhancement purposes

is restricted to the first week of development) and the limitations in the availability of human embryos.

ACMG, OBD, EASAC, and the National Academies of Science, Engineering and Medicine suggest that there should be an informed social debate regarding the application of CRISPR involving the general public, scientists, commercial sectors, and policy-makers. This would both avoid discriminatory decisions and foster public research policy based on respect for human rights. In this sense, the role of the media is key to promote responsible science communication. Moreover, ethics committees must serve to evaluate the scientific and methodological implications of the research, as well as its ethical, legal, and social implications.

The misuse of this technology, the impact on future generations, the unclear definition of therapeutic and enhancement purposes, and the possible accentuation of social inequalities that CRISPR could produce are the main ethical concerns that these four institutions highlight. The Company of Biologists refutes the possibility of future misuse of this technology since it considers that there are already regulations that can avoid any potential misuse. In contrast, ACMG, OBD, and EASAC suggest exploring the current regional, national, and international regulations in more detail. OBD proposes allowing the use of gene-editing in basic research, approving therapeutic use in somatic cells and assessing the possibility of approving germinal therapy for certain cases. The National Academies of Science, Engineering and Medicine propose using existing regulatory processes to oversee human-genome-editing laboratory research and permitting clinical research trials only for compelling purposes of treating or preventing serious disease within a robust regulatory framework while taking cultural norms into consideration. Like OBD, they recommend not to proceed with human genome editing for enhancement purposes.

Finally, OBD also recommends avoiding any kind of conflict of interests between scientific activity and entrepreneurial activity that could emerge.

CONCLUSIONS

As this report says, gene editing in humans is an issue that generates expectations and worries in many scientific institutions. The Bioethics and Law Observatory was one of the first institutions to launch a Declaration that aims at analyzing CRISPR from an interdisciplinary point of view and promoting ethically acceptable research and an informed social debate. As this article reports, after the publication of the Declaration on Bioethics and Gene Editing in Humans, other scientific institutions have analyzed this technique and have raised their ethical concerns.

The research of the Bioethics and Law Observatory reveals that a global discussion regarding genome modification is needed for two main reasons. Firstly, there is increasing interest in the biological development of CRISPR and its social impact. Secondly, there is a shared view that CRISPR has both benefits and limitations and, therefore, further research is needed before its application. However, there is a wide range of opinions regarding the ethical and legal framework in which this research should be done and in which cases this technique should be applied.

OBD aims at opening a global discussion among different stakeholders such as universities, society, and science and technology systems on the application of gene editing in human beings. Moreover, we aim at moving one step further and propose some modifications to the Council of Europe's Convention on Human Rights and Biomedicine. It was made precisely because of the fears of cloning and the possibilities of biotechnology and genetic engineering in the late 1990s, and it should be updated. It is necessary to face the current challenges that CRISPR poses in our century.

We think that a moratorium is completely useless in a very competitive scientific world with heterogeneous regulations and cultural environments. The example of China made us realize that the worst option is to ban. We need to start thinking both nationally and internationally about how to regulate this new technique that has changed the way we understand most of the things that we were discussing in the past century from a bioethical and legal perspective: for example, the nature of an embryo or the embryonic stem cells and their uses.

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