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Genome editing in humans, a topic only for academics from industrialized countries?*

La edición del genoma en humanos, ¿un tema sólo para académicos de países industrializados?

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Resumen / Abstract: Los límites de edición de genes y los usos aceptables son objeto de fuertes debates en los campos científico y académico. Es importante cómo se conceptualiza esta técnica y cómo se presentan los pros y los contras. En este artículo queremos analizar cómo los actores globales y locales deben ser considerados e incluidos en el debate ético global sobre la edición de genes. Compararemos diferentes enfoques entre un país europeo (España) y dos países latinoamericanos (Argentina y Chile). Nos centraremos sólo en estos países en particular como estudios de caso y ejemplos de sociedades que muestran diferentes experiencias hacia las tecnologías reproductivas y la medicina regenerativa que están estrechamente relacionadas con la edición del genoma. Por último, examinaremos si la inclusión o no de los países en vías de desarrollo en el diálogo mundial sobre la edición de genes entraña algún peligro o problema y argumentaremos que no sólo se necesita una estrategia de arriba hacia abajo, sino de abajo hacia arriba que incluya a los países en vías de desarrollo.

Gene editing limits' and acceptable uses are subject of strong debates in the scientific and academic fields. How this technique is conceptualized and how pros and cons are presented is important. In this article we want to analyze how global and local players should be considered and included in the global ethics debate concerning gene editing. We will compare different approaches between a European country (Spain) and two Latin American countries (Argentina and Chile). We will focus only in these particular countries as case studies and examples of societies displaying different experiences towards reproductive technologies and regenerative medicine which are closely related to genome editing. Finally, we will examine if the inclusion or not of developing countries to the global dialogue on gene editing entails any dangers or problems and we will argue that not only a top-down strategy is needed but a bottom-up one including developing countries.

Palabras clave / Keywords:
Edición genética / Participación del público / Interés público / Países en vías de desarrollo / Uso indebido de la tecnología.

Genome editing / Public engagement / Public interest / Developing countries / Technology misuse.

1. Introduction

With the appearance of CRISPR/Cas9 technology strong debates re-arose regarding what are the appropriate limits or scope of use of gene editing. These debates are not new as there was a first wave of discussions in the 90' and the beginning of the new millennium: John HARRIS[1], Dan WIKLER[2], Peter SINGER[3], the lively public discussion between Peter SLOTERDIJK and Jürgen HABERMAS[4] among others. Although the tool proposed to attain impact over future generations was not the genome editing strategies but embryo or gamete selection, the aim of the proposal was perceived as essentially the same: to control the characteristics of new borns and, by extension, of the future of humanity.

Recently, a moratorium has been proposed[5] suggesting to stop the use of genome editing techniques in human germ line and embryos. However, stopping this technique does not seem to be plausible. Not only because there is not a wide consensus accepting this proposal[6] or to which extent it should be applied, but also because genome editing techniques have been worldwide spread and they are currently actively used by many labs (although not many of them in human germ line modifications).

In this scenario, a set of national and international initiatives discussing the legal and ethical aspects of genome editing appeared. They represent different positions regarding what are the limits and risks of this technique when applied to human germ line: THE HINXTON GROUP[7], IBC UNESCO[8], THE

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[1] HARRIS, J., *Wonderwoman and Superman. The Ethics of Human Biotechnology*, Oxford University Press, Oxford, United Kingdom, 1992.

[2] WIKLER D., "Can we Learn from Eugenics?", *Journal of Medical Ethics*, No. 2, Vol. 25, 1999, pp. 183-194.

[3] SINGER P., "Shopping at the Genetic Supermarket", *Los desafios éticos de la genètica humana,* LUNA F. / RIVERA LÓPEZ, E. (Eds.) Fondo de Cultura Económica, México, 2005, pp.131-146.

[4] SLOTERDIJK, P., *Normas para el Parque Humano*, Ediciones Siruela, Madrid, España, 2000.

[5] LANDER E. / BAYLIS F. / ZHANG F., *et ál.,* "Adopt a moratorium on heritable genome editing", *Nature*, No. 567, 2019, pp. 165-168.

[6] SCHAEFER G.O., *A case against a moratorium on germline gene editing*. Retrieved July 16, 2019, from: https://theconversation.com/a-case-against-a-moratorium-on-germline-gene-editing-113827. CHARO, A. "Rogues and Regulation of Germline Editing", *NEJM*, No. 10, Vol. 380, 2019, pp. 976-980.

[7] HINXTON GROUP, 2015. Retrieved July 16, 2019, from: http://www.hinxtongroup.org/Hinxton2015_Statement.pdf

[8] IBC UNESCO, *UNESCO panel of experts calls for ban on "editing" of human DNA to avoid unethical tampering with hereditary traits*, 2015. Retrieved July 16, 2019,

WELCOME TRUST[9], THE ACADEMY OF MEDICAL SCIENCES UK[10,11,12], LEOPOLDINA[13], THE US NATIONAL ACADEMIES OF SCIENCES, ENGINEERING AND MEDICINE[14],THE NUFFIELD COUNCIL ON BIOETHICS[15], THE EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES[16], THE OBSERVATORIO DE BIOÉTICA Y DERECHO[17], THE GERMAN ETHICS COMMITTEE[18], THE EUROPEAN ACADEMIES' SCIENCE ADVISORY COUNCIL[19] and a few others[20].

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from: https://en.unesco.org/news/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits?language=en

[9] WELLCOME TRUST, *Genome editing in human cells – initial joint statement*, 2015. Retrieved July 16, 2019, from: https://wellcome.ac.uk/sites/default/files/wtp059707.pdf

[10] THE ACADEMY OF MEDICAL SCIENCES, *Human genome-editing research should proceed, say leading UK science bodies,* 2015. Retrieved July 16, 2019, from: http://www.acmedsci.ac.uk/more/news/human-genome-editing-research-should-proceed-say-leading-uk-science-bodies/

[11] THE ACADEMY OF MEDICAL SCIENCES, *The Academy of Medical Sciences' response to the Nuffield Council on Bioethics Genome Editing Call for Evidence*, 2016. Retrieved July 16, 2019, from: https://acmedsci.ac.uk/file-download/38579-56bc88dc0dea4.pdf

[12] THE ACADEMY OF MEDICAL SCIENCES, *Response to the House of Commons Science and Technology Committee inquiry into genomics and genome-editing*, 2017. Retrieved July 16, 2019, from: https://acmedsci.ac.uk/file-download/83063056

[13] LEOPOLDINA, *The opportunities and limits of genome editing*, 2015. Retrieved July 16, 2019, from: http://www.leopoldina.org/uploads/tx_leopublication/2015_3Akad_Stellungnahme_Genome_Editing.pdf

[14] NATIONAL ACADEMIES OF SCIENCES, ENGINEERING AND MEDICINE, *On Human Gene Editing: International Summit Statement,* 2015. Retrieved July 16, 2019, from: http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a

[15] NUFFIELD COUNCIL ON BIOETHICS, *Genome editing. An ethical review. Short-guide*, 2016. Retrieved July 16, 2019, from: http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-an-ethical-review-short-guide.pdf

[16] EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES, 2016, available at: https://ec.europa.eu/research/ege/pdf/gene_editing_ege_statement.pdf

[17] SANTALÓ, J. / CASADO, M., *Document on bioethics and gene editing in humans*. Observatorio de Bioética y Derecho, Edicions UB, Barcelona, 2016. Retrieved July 22, 2019, from: http://www.bioeticayderecho.ub.edu/es/documento-sobre-bioetica-y-edicion-genomica-en-humanos

[18] Available at: https://www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/englisch/opinion-intervening-in-the-human-germline-summary.pdf

[19] EASAC, 2017. Retrieved July 16, 2019, from: https://easac.eu/publications/details/genome-editing-scientific-opportunities-public-interests-and-policy-options-in-the-eu/

[20] DE LECUONA, I. / CASADO, M. / MARFANY, G. *et ál.,* "Gene Editing in Humans: Towards a Global and Inclusive Debate for Responsible Research", *The Yale journal of biology and medicine,* No. 4, Vol. 90, 2017, pp. 673-681.

If we focus on the origin of these different statements and, therefore, which societies' opinions they represent, we could conclude that the leading opinions of these debate seem to proceed mainly from the USA, UK and Europe (mainly France and Germany). To counteract this apparent unbalance, similarly international initiatives have been set up to discuss and propose different positioning such as The International Summit on Human Gene Editing held in Washington D.C[op.cit.note 14], the ARRIGE initiative held in Paris[21] or the WHO panel of experts that recently started their work[22]. The latter one will report in 2020.[23]

However, in spite of the variety of fora engaged in this discussion, they mostly share a crucial characteristic: most representatives are from industrialized countries and, for instance, Latin American region is scarcely represented.

An example of this situation is the recently created initiative of a new "International commission on the clinical use of heritable human genome editing" launched by the U.S. National Academy of Medicine, the U.S. National Academy of Sciences, and the Royal Society of the U.K.[24] Among the 18 members of the commission, 4 are from the UK, 5 from the USA, 2 from China and the other 7 from different countries around the world with only three representatives from developing countries (Malaysia, India and South Africa). A better initiative is the WHO Expert Advisory Committee on Developing global standards for governance and oversight of Human Genome editing. Among the 18 member, 7 are from developing countries and 11 from developed countries. However only one member is from Latin America.[25]

In this article, our objective is to analyze how global and local players should be considered and included in the global ethics debate concerning gene editing. In the first part we will compare different approaches between a European country (Spain) and two Latin American countries (Argentina and Chile). We will focus only on these particular countries as case studies and examples of societies displaying different experiences towards reproductive

[21] ARRIGE Kick-off meeting. Retrieved July 22, 2019, from: https://arrige.org/meeting1.php

[22] WHO panel of experts on Human Genome editing. Retrieved July 22, 2019, from: https://www.who.int/ethics/topics/human-genome-editing/en/

[23] NATURE EDITORIAL, retrieved in November 2019. Available at: https://www.nature.com/articles/d41586-019-03525-0

[24] THE NATIONAL ACADEMIES OF SCIENCES ENGEENERING MEDICINE, *International commission on the clinical use of heritable human genome editing,* 2019. Retrieved July 16, 2019, from: http://www.nationalacademies.org/gene-editing/international-commission/index.htm?_ga=2.145952625.476755953.1559119783-174920231.1558680314

[25] There is only one person from Panama.

technologies and regenerative medicine which are closely related to genome editing in gametes and embryos.

In the second part, we will examine if the inclusion or not of some developing countries to the global dialogue on gene editing entails any dangers or problems. We will specifically focus on the developing countries (such as Argentina, Mexico, Chile, India, etc…) that are in between the poorest and less developed societies and those among the most scientifically and technologically advanced ones. These countries have some characteristics that make them particularly vulnerable to unscrupulous scientists. The reasons for this attraction are: they possess some scientific infrastructure, a less developed legal framework or a lack of efficient adherence to scientific and integrity rules and laws that leave a favorable playground for carrying on their activities otherwise forbidden or under a moratorium in their own countries.

Finally, we will argue for a double strategy. In addition to the top-down strategy already in place, we propose a bottom-up one including developing countries experiences.

2. Part I. Local interest: the case of Spain, Chile and Argentina

2.1. *Local media*

If we consider the lack of developing countries members in global fora, we can think of a first reasonable answer. The origin of this situation could be attributed to the mild interest gene editing technologies rise in these societies in general and in the mass media of different countries, in particular. This leads to a first question: how gene editing has been discussed by local media? To do so, we have chosen our own countries assuming that we can better evaluate the situation by being an interested part of this public opinion. Therefore, we[26] did a search from January 2015 to August 2018 of the news published in the main newspapers of Spain, Argentina and Chile by searching for two key words: “CRISPR” and “genome editing”. We have chosen this period of time because it represents the appearance of the new CRISPR/Cas9 technology in the mass media. Secondly, we assessed how sensationalist the approach each country was regarding this technique: if there were original and local approaches, how positively or negatively this technique has been depicted and if there were local positions regarding limits and scope of germ line use. We have analyzed the interest expressed by mass media as an indicator of the attention payed by the respective societies

[26] We based our work on the research done by each of the researchers of the countries involved. for Spain Dr. Josep SANTALÓ, for Chile Dr. Susan TURNER and for Argentina Dr. Florencia LUNA. We do not pretend to be exhaustive, but to depict how the situation was perceived by the media of our own countries.

in these issues and, thus, whether they are willingly or not part of the public agenda.

The interest of the Spanish public opinion for genome editing initiatives is unquestionable. Making a search on the 6 nationwide highest circulation newspapers[27] of the term “CRISPR” from January 2015 to July 2018, a total of 1043 entries have been found. Interestingly, when making the same search but using the term "genome editing", which must be considered a wider term containing the CRISPR/Cas9 concept itself, only 379 entries were found. This fact suggests that the interest of the public opinion and, therefore, the mass media for the genome edition is more probably due to the novelty of the CRISPR/Cas9 technique than to the realistic possibility of the use of genetic modifications on different species, including humans.

Another factor that could have contributed to this interest is the fact that CRISPR technology is based on the discovery in bacteria obtained in Spanish salt lakes by Dr. Francis Mojica[28] of a sort of "immunological system" that have evolved among bacteria to stop bacteriofagi development and horizontal gene transmission. The fact that CRISPR/Cas9 technology is ultimately based on a Spanish discovery should, undoubtedly, contribute to the interest for this novel technology in this country. The Informe Quiral can be considered for a thorough analysis and research of Spanish communication media and its relation to science. In[29] 2017 it devoted an issue to gene editing.

If we take a look at Latin America, we can see similarities and differences between Chile and Argentina. In the case of Chile, the three more important newspapers[30] published in the three years studied 25 news under “CRISPR” and 31 under “genome editing”. Most of them were reports extracted from the international press like the BBC or El Mundo (a Spanish newspaper) or from foreign scientific journals such as Science explaining achievements happened in the US, Europe or China. Here, headlines were grandiloquent and appealing to science fiction or warn against the dangers associated with this technique[31]. In general, the perspective adopted by these journalistic reports describes a revolutionary technique that lies well beyond the local reality.

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[27] ABC, El Mundo, El País, El Periódico, La Razón, La Vanguardia.

[28] MOJICA, FJ. / DÍEZ-VILLASEÑOR, C. / SORIA, E. / JUEZ, G., “Biological significance of a family of regularly spaced repeats in the genomes of Archaea, Bacteria and mitochondria”, *Molecular Microbiology*, No. 1, Vol. 36, 2000, pp. 244-246.

[29] FUNDACIÓ VILA CASAS, Universitat Pompeu Fabra, *Informe Quiral. La edición genética ante la sociedad,* 2017. Available online: https://www.fundaciovilacasas.com/download-publicacio.php?id=2006

[30] El Mercurio, La Tercera and El Mostrador.

[31] "La terapia genética podría hacer a alguien tan fuerte como Jessica Jones" (El Mercurio, 18 May 2018); “¿Hijos a la carta?: mitos y certezas tras la manipulación genética CRISPR/Cas9" (El Mostrador, 19 August 2017).

In the case of Argentina, we reviewed the three most popular newspapers.[32] They published 78 news with the term "CRISPR" and 99 under "gene editing". It tripled news found in Chile but it was far below the entries found in Spain. Interestingly, in the case of Argentina, besides the sensationalists headlines and the international press pointing to different scientific achievements and worries that were also present; there was a rather positive view regarding the use of this technology. There was specific local news regarding its application: for example, in animals (in polo horses)[33], applied to the agro-industry (crops and other food product as potatoes)[34] as well as new possibilities related to biotechnologies[35]. This can be explained because Argentina is fundamentally an agro-food producer. In addition, in the past decade a Ministry of Science and Productive Innovation was created[36] in tune with a tradition of good scientists and three scientific Nobel Prize winners. Thus, there is some scientific optimism reflected in the Argentinian press regarding local discoveries and possibilities in these areas. Yet, as in the other countries studied (Chile and Spain) there does not seem to be much development on the local ethics debate regarding germ line applications in humans (this may also be because research on embryos is rather taboo and –as we will see it is banned in the last version of the Civil and Commercial Code- hence it appears to be not an issue to speak to the press). Note that in 2018 Argentina engaged, for the first time, in a public discussion on the non-penalization of abortion, so the country is still discussing the moral status of embryos among other issues. In the case of Chile, abortion is also a hot issue[37].Thus, even if there were some possible local applications, debates regarding germ line and research with human embryos may seem a distant topic of interest for the public opinions of both countries and for Latin American public in general.

2.2. *Other players?*

If we want to know how informed the public is focusing only on the media might not be enough. Are there other players? Are there some initiatives fostering public engagement?

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[32] El Clarín, La Nación and page 12.

[33] "Argentina hace historia con el primer caballo de polo de diseño" (Clarin, 30 November 2017).

[34] "Manipulan genéticamente la papa para que no se ponga negra" (Clarin, 6 May 2018); "Una firma de Rosario desarrolla cultivos resistentes a herbicidas con edición génica"(Nación, 5 July 2018); "El INTA logró modificar el gen que hace que la papa se ponga negra" (Nación 4 May 2018).

[35] "La biotecnología Argentina apunta al exterior"(Nación 16 January 2018).

[36] This year (August 2018) given the last economic crisis it has been downgraded to a Secretary but it still has the main function of promoting science.

[37] Chile had one of the most restrictive laws: not allowing abortion in any case. Only in september 2017, a law has been passed that legalized abortion in three narrow grounds.

In spite of the public attention in Spain, scarce initiatives have been launched to incorporate public opinion and lay persons into the discussion about the responsible use of such a new technology beyond scientists and few bioethicists and lawyers.

In this sense, to our knowledge, only debates in scientific, academic or bioethical related meetings have been held[38,39,40]. Perhaps the sole event that included lay persons as participants was a Conference-coffee on "Genomic medicine: Tailoring the treatments of the future", organized by the Centre for Genomic Regulation (CRG) of Barcelona (Barcelona, 11/21/2017) where an active participation of the public on the ethical aspects of gene editing took place, although the number of participants was limited to a couple of dozens, with no formal conclusions afterwards elaborated. However, due to the scandal of Dr. He-Jiankui (who claimed having edited two baby girls to make them immune to HIV)[41] the *Comité de Bioética de España* made a statement[42] (January 2019) adopting a position related to this question. In any case, no multidisciplinary meetings such as the ARRIGE (Association for Responsible Research and Innovation on Gene Editing) initiative launched in Paris (Paris, 3/23/2018), nor initiatives such as those developed by the Nuffield Council or the Welcome Trust in the UK performing large scale queries among the general population about gene editing technologies have been held in Spain to our knowledge.

In fact, UK represents a quite singular situation among other countries or societies because it has a long tradition of large-scale consultations of the public opinion on science and scientists in general. Thus, UK has been periodically publishing surveys on public attitudes to science since 2000

[38] The role of CRISPR in personalized medicine: Legal and Ethical Problems. (2017). Retrieved July 16, 2019, from: https://www.encuentrosconlaciencia.es/?p=3052

[39] X Meeting of the Red de Comités de Ética de Universidades y Organismos Públicos de Investigación. (2017). Aspectos éticos de la edición genómica: Modelos animales y terapia génica en humanos. Retrieved July 16, 2019, from: http://www.ub.edu/rceue/archivos/XEncuentro_Programa.pdf

[40] Aplicaciones de edición genética en la investigación y terapia sobre enfermedades raras. Fundación Ramón Areces, 2018. Retrieved July 16, 2019, from: https://www.ciberes.org/agenda/simposio-internacional-aplicaciones-de-la-edicion-genetica-en-la-investigacion-y-terapia-sobre-enfermedades-raras

[41] JIANKUI, He, *Human Embryo Editing Session. Second International Summit on Human Genome Editing,* Hong Kong, 27-29 November 2018. Retrieved July 22, 2019, from: https://www.nap.edu/read/25343/chapter/1

[42] COMITÉ DE BIOÉTICA DE ESPAÑA, 2019. Retrieved July 22, 2019, from: http://assets.comitedebioetica.es/files/documentacion/es/CBE%20Declaracion%20sobre%20edicion%20genomi

conjointly run by the country administration and the WELLCOME TRUST[43] but, besides that, other non-profitable institutions also run public queries on more specific topics such as reproductive technologies and genome editing by running public on line questionnaires[44] or other initiatives such as a workshop to discuss the possibilities and limitations of public dialogue for genome editing policy and regulation[45] where biomedical researchers, policy makers and engagement specialists met together to define the need for public engagement and timing for discussion on this topic.

The Argentine Ministry of Science and the Chilean CONICYT have had some initiatives to communicate science. For example, in both countries there is a "Coffee and science" cycle of lectures currently carried on with scientists and the public. There is also a national program ("Explora"[46]) in Chile, while there is a television channel in Argentina (TecTV). These activities are designed as vehicles for bringing science closer to the people, but CRISPR/Cas9 has not been one of the topics discussed during the time studied until mid 2019. Yet it is worth mentioning that in November 2016 there was a first meeting organized in Buenos Aires by the French scientific organization INSERM and Welcome Trust, though it was not intended to the broad public but to researchers of the region.[47]And in December 2018 there was a public symposium on gene editing convened by different governmental organizations.[48] This meeting was open to the general public and 452 participants attended onsite and nearly 200 persons viewed it by streaming.[49]

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[43] OFFICE OF SCIENCE AND TECHNOLOGY AND THE TRUSTEE OF THE WELLCOME TRUST, 2000. Science and the Public. A Review of Science Communication and Public Attitudes to Science in Britain. The Wellcome Trust.

[44] NUFFIELD COUNCIL ON BIOETHICS, *Genome editing and human reproduction*, 2018. Retrieved July 16, 2019, from http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL-website.pdf

[45] NUFFIELD COUNCIL ON BIOETHICS, *Why? When? Who? Report of workshop on genome editing and public dialogue now published,* 2016. Available at: http://nuffieldbioethics.org/news/2016/why-when-who-report-of-workshop-on-genome

[46] Programa Nacional de Divulgación y Valoración de la Ciencia y la Tecnología. Chile.

[47] It was a close meeting of less than 20 people. Global Forum on Bioethics in Research. 2019. Background paper: Genome editing for human benefit: ethics, engagement and governance. Meeting in Singapore, 12-13 November. Inserm, 2016. Fostering global responsible research with CRISPR-Cas9: Latin America workshop, Argentina, https://www.inserm.fr/en/research-inserm/ethics/inserm-ethics-committee-cei/ethics-committee-workshops/fostering-global-responsible-research-with-crispr-cas9 [Last accessed: 27 November 2019].

[48] Ministry of Science and Technology development; Ministry of Health and Ministry of Agro-industry of Argentina.

[49] GLOBAL FORUM ON BIOETHICS IN RESEARCH, *Conference given by Sebastián Barbosa "An unprecedented outreach event in Argentina to raise awareness about gene editing: A communication challenge to engage the general public,* 2019.

Therefore, there is interest and some initiatives to communicate science, but it does not seem to have given breath to the strong debate of these technologies for people of these countries.

We should also point out the scarce quantity of books for the general public in Spanish where basic concepts of gene editing are explained.[50] While in English there are several publications[51] in Spanish -as far as we know- there is only one book that explains in simple words gene editing and CRISPR Cas system.[52] [53]

However, besides the UK; very few initiatives have sought the general opinion of the society around the world. A wide survey was launched by some Australian investigators in 2016 reaching a considerable success in terms of number of responders (over 12.000) but again an important bias appeared in their origin, since more than 51% of responders were from USA, UK, Japan or China alone. Moreover, there was also an overrepresentation of scientists and bioethicists among them[54]. In addition, here is a more recent survey done with 1004 Australians on public attitudes toward gene editing of germlines[55] and in the US the Pew Research Center survey gauged, in broad terms, what the public thinks about the potential use of gene editing to enhance people´s health.[56] [57]

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[50] We thank an anonymous referee for this point.

[51] KOZUBEK, J., *Modern Prometheus. Editing the Human Genome with Crispr-Cas9*, Cambridge University Press. Cambridge, 2018; DOUDNA, J.A. / STERNBERG, S. H. *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution*. Houghton Mifflin Harcourt. Boston, 2017; BAYLIS, F., *Altered inheritance: CRISPR and the ethics of Human genome editing*. Harvard University Press. Massachusetts, 2019; PARRINGTON, J., *Redesigning life: hoy genome editing will transform the world*, Oxford University Press, Oxford, United Kingdom, 2016.

[52] MONTOLIÚ,L., *Editando genes: recorta, pega y colorea: Las maravillosas herramientas CRISPR*. Next Door Publishers S.L. Navarra. Available at: https://www.amazon.es/Editando-genes-recorta-maravillosas-herramientas/dp/8494924516#reader_B07MTG1C3K

[53] There are obviously other books in Spanish such as LUNA, F. / RIVERA LÓPEZ, E., *Ética y Genética. Los problemas morales de la genética humana. Catálogos, among others, but they are written for a more knowledgeable or academic audience,* 2004.

[54] MCCAUGHEY, T. / SANFILIPPO, P. / GOODEN, G. *et ál*., "A Global Social Media Survey of Attitudes to Human Genome Editing", *Cell Stem Cell*, Vol. 18, 2016, pp. 569-572.

[55] CRITCHLEY C. / NICOL, D. / BRUCE, G. *et ál*, "Predicting Public Attitudes Toward Gene Editing of Germlines: The Impact of Moral and Hereditary Concern in Human and Animal Applications", *Frontiers in Genetics*, Vol. 9, 2019, pp. 1-14.

[56] Available at: https://www.pewresearch.org/science/2016/07/26/u-s-public-opinion-on-the-future-use-of-gene-editing/ [Last accessed: November 2019].

[57] We thank an anonymous referee for this point.

2.3. *Differential approaches*

If we want to further analyse the lack of interest of some developing countries, we can ask why is there a lack of debate and not enough communication regarding gene editing or CRISPR/Cas9 technique? In the case of Latin American' countries there might be more urgent problems to be discussed: from economic crisis to other ethical debates such as abortion that might be perceived as more pressing. This can explain why lay people are not so interested in these topics and also that there are very few "country initiatives" to inform, educate, or think about these technologies. However, we should be careful regarding this attitude. Ignoring these new techniques or lacking a social debate is not completely harmless. An argument endorsing no commitment to public engagement in these countries suggest that only well scientifically developed countries should perform this sort of debate as they are leading the technological drive and their scientists are more involved and concerned than those of other regions.

On the contrary, we think this is not the right approach. In a 1996 article, Luna and Salles[58] distinguished between what was denominated "sexy problems" and "boring problems" in bioethics. While "sexy problems" attracted the media and spoke about the power of science and technologies (it referred to the genome project, assisted reproduction); "boring problems" concerned the fragility and vulnerability of relations (allocation of scarce resources, patient-physician relationship, etc) were much less addressed by mass media. The point made was that these problems did not have frontiers and even if the "sexy" ones started in the industrialized countries (as they develop the new technology), they nonetheless impact rapidly in developing countries. Therefore, thinking some problems as more pertinent for some countries than others should be avoided.

This situation is not exclusive for some Latin American countries but might be spread among most of developing countries. For instance, an anthropologist at Panjab University, Kewal Krishan (cited in Ledford[59]), states that there has been little discussion of heritable gene editing in India. Or in African cultures, where the pressure for having children is so intense that other debates, such as gene editing, are left apart (Andoh, cited in Ledford[op.cit.note 45]).

In addition, a consequence of this lack of discussion is that in societies that do not have any opinion most probably no law will be passed to regulate the practice and use of these new technologies. Or if they are laws, these may not be applicable or amended if safe and relevant medical uses are

[58] LUNA F. / SALLES A.L.F., "Desvelando la Bioética", *Perspectivas bioéticas*, No. 1, Vol. 1, 1996, pp. 10-22.

[59] LEDFORD, H., "CRISPR babies. When will the world be ready?", *Nature*, Vol. 570, 2019, pp. 293-296.

found. For example, in the case of Argentina, the Comercial and Civil Code (article 57) passed on 2015 forbids any practice designed to produce a genetic alteration to the embryo that can be transmitted to their descendants[60]. So the lack of societal debate and engagement may not allow re thinking existing laws. In the case of Chile law 20.120 (2006) regulates scientific investigation involving human beings and the human genome and prohibits cloning. It establishes the respect human beings deserve from conception and explicitly prohibits the manipulation of embryos.[61]

The Spanish situation, instead, seems to be better because, even if there are no major efforts to communicate with lay people or to work in public engagement; Spain -as a member of the European Union- has a strict legal framework that may be enforced. Spain, as an industrialized country, could be considered as an example of a society situated in an intermediate position between most technologically and scientifically advanced societies (at least referring to the genome editing in humans' issue) and less developed countries. This characteristic might have an influence on the public opinion on genome editing in humans. It's legal framework is integrated into the European background. This is not trivial, as we will point out in the next section. This intermediate situation does provide to Spain a solid legal frame to discourage abuse situations exerted by local and foreign scientists and practitioners.

3. Part II: Developing countries

3.1. *Some problems and previous experiences*

The existence of a legal framework with a strong accountability system or the knowledge that there are clear and enforceable limits "organizes" society. And though there may always be abuses or frauds, there is also the perception that if these abuses are known they will not be accepted and will receive some kind of sanction. This seems the case of industrialized countries where the social and scientific environment are accountable and watchful and where unethical behaviours are more difficult to hide or disguise as unquestionable scientific advances. We can thus place the Spanish case within this environment. However, this does not apply to societies that do not have any opinion and, frequently, no law. And even in the case of Argentina that there is a prohibition, this is a partial one and other gene editing techniques could be done. In this environment, local scientists with the help of foreign scientists (or just by themselves) can perceive these technologies as an opportunity to gain scientific respect as well as economical income without considering the ethical problems or risks involved. This explanation

[60] *Código Civil y Comercial de la Nación*, 2015. Buenos Aires: Honorable Cámara de Diputados de la Nación.

[61] Available at: https://www.leychile.cl/Navegar?idNorma=253478.

considers these practices in their better light. Yet in a more obscure interpretation, it can just be an abuse by researchers or practitioners of the loopholes present in the system and the law.

In fact, this has already happened in the use of a related technology such as mitochondrial donation. Its clinical use was, at the moment, under an active discussion in the USA and the UK. It was first done in Mexico (2016) by north American clinicians and scientists that had developed the technology in the USA[62] but were not authorized to do it there. Shortly after the birth of this baby in Mexico the HFEA authorized the technique in the UK (March 2017) but the FDA suggested that the technique should not be marketed in the USA (August 2017).

Another threatening consequence of this lack of opinion in countries scientifically less concerned with is the possibility gene editing becomes another of the so called "miracle technologies". To avoid this the central idea would be to properly inform the public opinion about the real possibilities and achievements this new technology can reasonably offer. This could help keeping out unscrupulous scientists aiming to earn fame and money by offering results beyond real possibilities of the technology or, even worse, supplying clearly dangerous practices. This situation has already appeared for instance in stem cell technologies and has produced the clash of interests among authorities, national health services and patients. For example, in Argentina, the Regenerative Medicine Commission[63] has been trying to fight abuses and fraud with stem cell technologies that were offered as "treatment" while they were not proven. There were known centres and researchers offering these "miraculous treatments" but given the loopholes of the law it was very difficult to stop them.[64] There was also an organized system to raise funds to pay trips to China and other centres exploiting the good will of people as well as abusing the hope and desperation of families of very ill patients (frequently children).

For developing countries or countries without a strong legal system and a "real enforcement" of it, this is a challenge and not a minor issue. The risk of this lack of interest and of leaving this discussion only to scientifically leading countries is that these developing countries could experience a sort of

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[62] ZHANG J. / LIU, H. / LUO, S. / LU, Z. / CHÁVEZ-BADIOLA, A. / LIU, Z. / YANG, M. / MERHI, Z. / SILBER, S.J. / MUNNÉ, S. / KONSTANTINIDIS, M. / WELLS, D. / TANG, J.J. / HUANG T., "Live birth derived from oocyte spindle transfer to prevent mitochondrial disease", *Reproductive Biomedicine Online*, Vol. 34, 2017, pp. 361-368.

[63] Regenerative Medicine Commission at the Ministry of Science and Technological Innovation.

[64] Argentina has a federative government system. Only few national laws apply to the whole territory, and many other laws concerning research and health system regulation differ from Province to Province.

"scientific imposition or externalization" meaning that technologies that are not welcomed in scientifically leading societies are finally done and applied in developing countries because they have not had such debate (as was the mitochondrial donation case in Mexico) or because the society is less prepared and easily falls prey of abuses (as stem cell use in Argentina). This is specially the case for some developing countries that have certain scientific or clinical infrastructure. In these countries there is a sort of coexistence of a "Third" and a "First" world at the same time. Argentina, Mexico, Brazil, Peru, Chile have to fight against serious public health problems (malnutrition, neglected diseases, etc.) similar to the most poor developing countries; but at the same time they also share some achievements industrialized countries have. They have sophisticated equipments in private clinics and public hospitals, well trained researchers or physicians, etc. Thus they present a complex situation and they face several challenges.[65] Difficulties that face these developing countries are not sufficiently considered in the international general debates run until now.

3.2. *Back to gene editing technologies*

Even if developing countries show no interest in these topics, the need for a wide discussion and reflection in the society is of utmost importance[66]. A very dangerous scenario is the one in which no social discussion about de convenience of using or not genome editing technologies takes place. Or where there is no information about real possibilities of such techniques. And though at a first glance scientific topics such as gene editing seem irrelevant or luxurious issues to work on; awareness of the technology, its development and possible impact not only can be useful and needed for scientifically developed societies, but also for developing ones.

If we look to possible scenarios regarding the implementation of these technologies we can envision two main options. The first possibility implies a global agreement in which a well-defined position is attained: for instance, the acceptance of basic research while delaying the application of genome edition (especially heritable genome edition) until a clearer understanding of the risks (and also the benefits) this technology may entail. This can be in the line of WHO's interim recommendations.[67] Being realistic, this situation is the less probable. Such a wide consensus is almost impossible because

[65] For example, assisted reproduction is publicized as providing top treatments in excellent clinics for an international clientele.

[66] SANTALÓ-PEDRO, J., "Edición genómica. La hora de la reflexión", *Revista de Bioética y Derecho*, No. 40,2017, pp. 157-165.

[67] See NATURE, *op. cit* 23

of many reasons. Among them, which international organism, society or organization will promote this consensus?[68] Under who's mandate? Which mechanism of legitimation should follow to such a decision? Who will be in charge of supervising the adherence and observance of it? Clearly, the threats and obstacles of this possibility are overwhelming.

The second possibility, a consensus at a national scale is more realistic. This scenario could solve most of the questions previously posed but, at the same time, it will open new difficulties and threats to overcome.

The first one is the risk of countries proposing a wide variety of decisions, aiming different objectives and ways to achieve them[69]. Such disparity of decisions would most probably entail the appearance of diverse legislations in different countries that would allow to dodge the constrains appearing in a state by simply moving the research to a more permissive one.

The second risk is the disinterest for these topics from societies more preoccupied for other more pressing bioethical problems. Disinterest for a topic inevitably leads to a lack of opinion and, as already pointed out, to a probable lack of legislation, or outdated legislation. This situation could imply a sort of "scientific *laissez faire*" as a way to escape control under a false appearance of progress. The example of Mexico and mitochondrial donation technique is, again, a good example of this. This process could probably end up by a sort of an imposition of the technology spreading from some regions towards other nations but without the necessary guarantees and protections.

Another consequence of the lack of awareness and interest of society is the possibility of accepting these technologies as if they were good and validated while they are still the product of adventurers trying to win wealth or some kind of recognition without taking care of the persons they involve as it was the case with stem cell research in Argentina. In the gene editing area a good example of this process is the recently appearing news claiming the birth of two baby girls genetically edited to be immune to HIV virus (He Jiankui[op. cit. note 37]). In this case, while the scientific and bioethical community was still discussing about the convenience of accepting therapeutic use of heritable human gene editing, a Chinese cowboy manages to dodge any control. Moreover, very recently a Russian scientist expressed his will to repeat the experiment with more human embryos[70] while recent news inform that he already has a queue of 6 couples aiming to treat their embryos to

[68] See NATURE, *op. cit* 23

[69] CHARO, A., "Rogues and Regulation of Germline Editing", *NEJM*, No. 10, Vol. 380, 2019, pp. 976-980.

[70] NATURE, *Russian biologist plans more CRISPR-edited babies*, 2019. Retrieved July 16, 2019, from: https://www.nature.com/articles/d41586-019-01770-x

avoid congenital deafness. Luckily Russian authorities have recently declared that this is a "premature intervention" and it will not be approved.[71] Yet these cases show the threat posed by the current situation: unscrupulous persons trying to take advantage of vulnerability of parents willing to accept a "pseudoscientist" promising an unproven miracle therapy for their children. In front of them, societies and international initiatives can only respond by making statements and expressing good wills (WHO, ARRIGE, Genome Writers Guild, the Japanese Society for Genome Editing joint statement[72]).

In addition, if we can take seriously into account past experiences and challenges of developing countries, this may enrich international commissions debate regarding how to regulate or what kinds of safeguards may be implemented (how feasible they are, etc…)[73]. Thus, a bottom-up dialogue including past experiences of developing countries may be fertile and useful. Moreover, as the possibility of a global agreement respected by all countries does not seem probable and a consensus at a national scale is more realistic; these national agreements may need strong public engagement in order to inform society, alert about possible misuses as well as welcome needed and scientifically and ethically well-designed research. And even if there were an international consensus, public engagement and information to countries will be also needed. If this is the case, we think some developing countries must be seriously included in this debate as they may be the targets for moving unscrupulous research and externalizing it to these countries. In addition, taking part on these fora may be helpful for developing countries themselves as they can be more alert and aware of such possibilities and begin designing strategies to avoid misuses of the technologies in their countries.

We want to stress the need for reflection, awareness and public engagement on the bioethical problems related to genome editing at a regional and local level. This strategy may be a mean of avoiding the uncontrolled spreading of this technology through a process of *faits accomplies* without the due guarantees. The recently statement proposed by some investigators and stake holders suggesting to introduce a moratorium to the use of heritable genome editing in humans to rethink the current legislation in force in some

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[71] See Retrieved 22 November 2019: https://www.statnews.com/2019/10/16/russia-health-ministry-calls-human-embryo-editing-premature/ https://www.sciencemag.org/news/2019/10/embattled-russian-scientist-sharpens-plans-create-gene-edited-babies

[72] ARRIGE, *Genome Writers Guild, the Japanese Society for Genome Editing joint statement*, 2019. Retrieved July 16, 2019, from: http://jsgedit.jp/wp-content/uploads/2019/06/common_statement_Arrige_GWG_JSGE.pdf

[73] BARONI, M. J. L. / NADAL, G. M. / DE LECUONA, I. / BIDASOLO, M. C. / PALÀ, M. B. / ROYES, A. / SANTALÓ, J. / CASADO, M., "La edición genómica aplicada a seres humanos: aspectos éticos, jurídicos y sociales". *Revista de derecho y genoma humano: genética, biotecnología y medicina avanzada,* Vol. 46, 2017, pp. 317-340.

countries (Lander et al.,[op.cit.note 5]) -though interesting and well intended- can be easily boycotted by unscrupulous scientist simply by changing the site of their labs to more permissive or uninformed societies, promising them huge investments in terms of money and scientific prestige. Developing countries with some scientific infrastructure (as in Latin-American are Argentina, Mexico, Brazil, Chile, etc) are perfect targets to carry on these strategies. One of the ways to try to avoid this real threat is, under our point of view, to spread the discussion about gene editing towards as many societies and countries as possible and by integrating to this discussion the whole society. In summary, for us, the strategy should be going from local to global, from bottom-up, as well as from global to local.

4. Conclusions

We seem to face at least two challenges: a) to raise global awareness of ethical problems in gene editing technologies through education and information to society (with the extra burden that, at a first glance, many citizens and governments of some countries do not perceive these issues as even relevant); b) to seriously work with developing countries and to acknowledge and consider the kind of problems they face or may be exposed to face.

Developing countries, from a bottom-top strategy, can inform global fora or commissions about fraudulent possibilities, loopholes and the means used (they can bring in their experience on possible threats and work with them towards adequate answers). And because of their engagement in these international fora, they may be also helped and be more committed to these problems before these practices disembark in their countries. This may also benefit their work at a local level to generate public awareness regarding these techniques. We should remember that developing countries can be the target and final destiny for unscrupulous scientists. While developing countries may face the above-mentioned challenges, other countries such as Spain appear to be protected by the legal system already in place and the one that the EU may adopt. In that sense, they are on a safer side.

Last but not least, the risk of not incorporating the opinions of developing countries are that, finally, the decision may be left to some economical or intellectual elites that decide according to interests or criteria not completely shared by the rest of global world.