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SCIENTIFIC, ETHICAL AND LEGAL ISSUES OF GERMLINE GENE EDITING: LIGHT AND SHADOW IN THE DECLARATION OF THE SPANISH BIOETHICS COMMITTEE

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Abstract: The applicability of the CRISPR-Cas9 tool to the cure of several flaws in human embryos has raised up the number of worldwide basic and preclinical trials. By the end of 2018, the birth of the first genetically edited twins in China was known, intending to prevent them from catching HIV, since one of their parents had already suffered it. This led to social alarm, as the gestation process was carried out in disregard of medical standards and the assessments of ethics committees. The purpose of the present paper is to establish whether the intervention could be considered therapy, prevention – when trying to prevent an expected

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future pathology – or whether, in contrast, it would be, as has been widely defended, a clear case of enhancement, drawing the boundaries between all of them. To this end, the Declaration of the Spanish Bioethics Committee will be examined, highlighting some of their scientific, ethical and legal claims, and providing some comments that could call into question its original position.

Keywords: *CRISPR-Cas9, germline gene editing, human enhancement, gene therapy, Spanish Bioethics Committee*

1. INTRODUCTION

The desire to provide the descendants with the *best* possible genetic *qualities* to face the life's difficulties has been repeated in the history of human reproduction, to the point of considering the choice of lives with greater propensity to *welfare* a moral obligation – according to the principle of procreative beneficence – (Savulescu & Kahane, 2009). However, *good life* or the *best life* are commonly undefined and subjective goals: e.g., would it be coherent to extend this health imperative to cognitive (Yong, 2013[1]) or even social (Persson & Savulescu, 2019) capacities? Consensus has not been reached and this answer is still unclear.

That is the reason why a meeting point should be encouraged, starting with the cure of human illnesses (Sandel, 2004: 6):

> "To appreciate children as gifts or blessings is not, of course, to be passive in the face of illness or disease. Medical intervention to cure or prevent illness (...) does not desecrate nature but honours it".

In any case, there are researchers that report about the risk of making designer babies and returning to eugenics (Cavaliere, 2018: 7) – although it is underlined that the features of new eugenics differ from the tradi-

[1] Since August 2012, China has had projects aimed at using gene editing to improve intelligence. In this sense, a United States company announced in November 2018 a new test, based on the polygenic risk score, to rule out embryos susceptible of mental disability through Preimplantation Genetic Diagnosis. Accessed May 13th, 2021, https://www.newscientist.com/article/mg24032041-900-exclusive-a-new-test-can-predict-ivf-embryos-risk-of-having-a-low-iq/

tional in that the former one is aimed by technical knowledge, medicalisation and non-coercion (Bourne, Douglas & Savulescu, 2012: 42-43) –.

Among the measures of assisted human reproduction, the Preimplantation Genetic Diagnosis (PDG) or *In Vitro Fertilization* stands out, which consists, in the case of genetic disease of the embryo, in the screening and selection of the healthy ones, discarding those defective, and proceeding to the transfer and implantation of the first ones in the uterus. Hence, PGD is frequently defended by scientists (Evitt, Mascharak & Altman, 2015: 26) in terms of safety over reprogenetic emerging techniques – Zinc-Finger Nucleases, Transcription Activator-Like Effector-Based and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas9), being the most outstanding –; nonetheless, and in contrast to gene editing, PGD is an invasive procedure which is not useful in cases where couples have the same recessive genetic disorders and they want to maintain their genetic relationship with the child (Koplin, Gyngell & Savulescu, 2019: 49-50):

> "In the short term, GGE may allow couples to have a genetically related child without passing on genetic disease, including circumstances where it is not possible to select an unaffected embryo using a preimplantation genetic diagnosis. This includes cases where individuals are homozygotes for dominant conditions like Huntington's disease, or when dominant de novo disease-causing mutations develop in sperm or egg cells."

Besides, the ethical and religious argument about the moral status of the embryo, whether it should be discarded and not repaired (Caplan, 2019: 2) should be born in mind:

> "Screening embryos is useful, but it does not eliminate disease forever. And offering Preimplantation genetic testing (PGD) and embryo disposal is not an option that all parents find either morally or economically acceptable."

This is exactly where CRISPR/Cas9 comes into play, which consists of directing the RNA guide to add, delete, modify or substitute the DNA sequence, using the Cas9 enzyme. After the cut, the cells proceed to regenerating the altered tissues quickly – although in a random way –: this is what is called "genetic scissors."

This process can occur both in the human somatic line, in other words, in the person's own cells – in which its effects will be extinguished with death – and in the germinal line, the latter being able to pass down ge-

netic changes through the progeny, thus constituting the main focus of a wide-ranging debate.

In terms of its advantages, it is considered more effective, easy and cheaper than other genome editing technologies (Cavaliere, 2019: 1), although its disadvantages are the lack of security and knowledge about the functioning of repair systems (Montoliu, 2018), and the foreseeable proliferation of black markets – since it is not necessary to have large infrastructures or staff –. Either way, given the revolutionary nature of the technique, it is likely that these handicaps will be progressively overcome looking forward to their forthcoming application (Anzalone, Randolph, Davis *et al*., 2019[2]).

2. THE BIOTECHNOLOGICAL RACE: GENETICALLY MODIFIED HUMAN BEINGS

As an example of the evolution of CRISPR/Cas9, since its applicability in 2013, a large number of experiments have been staged in what seems to be the reproduction of a new scramble between two world giants: China and the United States of America (USA).

To mention some milestones, in 2015 scientists from Sun Yat-sen University (Guangzhou, China) carried out cell modification of defective and non-viable human embryos in order to correct beta-thalassemia (Liang *et al*., 2015). This first trial had its second part by both Chinese and British research groups in 2016, which tried to edit embryo genes in order to make them resistant to the Human Immunodeficiency Virus (HIV; Kang *et al*., 2016) and to investigate – without reproductive purposes – some key genes in embryonic development (Callaway, 2016). Since them, there have been further studies in the European Union (EU), USA and even recently in the Russian Federation (Cyranoski, 2019c).

Nevertheless, the event that shocked the world was the one carried out by the Asian giant and announced by its author, He Jiankiu, at the Second International Summit on Human Genome Editing, claiming the birth of the first genetically edited human beings – dubbed Lulu and Nana – (Marchione, 2018) in the face of the risk of contracting HIV – of

[2] This is what David Liu and co-workers have found with prime editing, an alternative and super-precise new CRISPR tool that might reduce off-target effects, making gene therapies safer for people.

which their father was a carrier – and confirming a second pregnancy at term in 2019 (Regalado, 2019b).

Even though Jiankiu has already been sentenced to three years in prison, fined three million yuan and disqualificated for life from participating in reproductive medicine by the Shenzhen Court as a result of illegal medical practices, which happened gives rise to a battery of questions with no easy answer: What is considered to be a disease and where to place the limit of its severity? Is HIV, nowadays, deadly? Is this intervention – as has been declared – a clear case of enhancement? Could it be compatible with human dignity and personal identity or, on the contrary, could it breach the right to equality and become discriminatory? Was the use of CRISPR-Cas9 necessary, or were there safer alternatives? Can science ensure that those sisters will never suffer unexpected mutations and, if so, with which scope and consequences? Why is there no mandatory international rule if careless use could alter the genes of future children?

3. CLARIFYING THE CONCEPT OF SERIOUS DISEASE AND HIV

First of all, it must be specified that the normal functioning – understood as not pathological – of health is the starting point, and there are different definitions of disease[3]. It is more complex to specify what is a severe illness, because of the subjective position of each person. That is why currently there is no closed list on diseases that could be part of it, although there are some proposals, such as that by George Q. Daley; it includes at least, in order of devastating monogenic diseases, Huntington's, Tay-Sachs, cystic fibrosis and sickle-cell anaemia (Cyranoski, 2018a). This catalogue collides with the opinion of Julian Savulescu and Peter Singer, who consider Tay-Sachs as the first candidate (Savulescu & Singer, 2019: 221-222):

> "It is not clear whether Daley is endorsing these as first-in-human trials. Huntington's disease is very different to Tay–Sachs disease. Babies with Tay–

[3] For these purposes, the World Health Organization definition may serve as an international reference: "An alteration or deviation of the physiological state of one or various parts of the body. Generally by known causes, manifested through symptoms and characteristic signs. The evolution of which is more or less predictable." In a similar way, the Royal Academy of the Spanish Language expresses itself at a national level: "More or less serious alteration of health." Accessed May 13th, 2021, https://dle.rae.es/enfermedad?m=form

> Sachs disease die in the first few years of life; people with Huntington's disease have around 40 good years. Hence Tay–Sachs disease is a better candidate for early trials, as babies with that condition have less to lose."

As mentioned earlier, the aim of the programme was to tackle HIV, a retrovirus that attacks the immune system of the affected person, causing the transmission of Acquired Immunodeficiency Syndrome. On the one hand, this disease can be residual or lead to a hypothetical public health crisis. It cannot be ignored that China has a dizzying increase of HIV in its population, which, linked to stigmatisation and socio-labour discrimination, could explain the efforts of that country for its eradication. On the other hand, this situation contrasts with its low mortality rate in the EU. In addition, inactivation of the CCR5 gene may immunise against HIV, but it increases vulnerability to other more serious infections, such as flu virus or West Nile fever. Along with the above, HIV may have a gateway other than the modified one, acquired through the CXCR4 gene. As if all of the above were not enough, the mutation of two copies of CCR5 may be associated with a 21% increase in mortality before the age of 76 (Maier, Akbari, Wei *et al*., 2020).

4. THE GREY ZONE BETWEEN GENE THERAPY AND HUMAN ENHANCEMENT

Although quite some academics have made valuable contributions to establishing the differences between therapy (Morán González, 2012: 2) and enhancement (European Parliament, 2009: 17), the boundaries of these categories are blurry at best, and controversy exists about including one or the other, or even combining characteristic notes of both (Navas Navarro & Camacho Clavijo, 2018: 9[4]).

Moving on to the study case, there is no consensus on its acceptability. In this way, geneticist George Church defended the research because there was no cure for HIV, which puts public health at risk (Cohen, 2018). Others, such as Julian Savulescu, opposed it because the embryos were healthy and had no known diseases (Savulescu, 2018).

[4] This is the case of "mixed technology" or "therapeutic enhancement", which combines repairing components and, at the same time, expansion of non-natural capacities or abilities.

With regard to its classification, it should be noted that most of the committees – to cite a few, the Council of Europe Committee on Bioethics (Council of Europe, 2018), ARRIGE Steering Committee (ARRIGE, 2018) and the Spanish Bioethics Committee (SBC, 2019) – categorically described it as an assumption of human enhancement. However, therapy and enhancement are often slippery concepts between which prevention appears. Moreover, the intervention could be equated to the purpose sought by a vaccine, since the disease had not yet manifested – which certainly makes its consideration as treatment unfeasible – and was intended to prevent the emergence of a future disease, but may also constitute the optimization of immune resistance against that of third parties. In this way, it could not only be justified as prevention but, even more, as a hybrid between prevention and enhancement (Morán González, 2012: 8):

> "A method that generally improves the functioning of a person's immune system could, on the contrary, be included in both categories, because it prevents the appearance of certain diseases and constitutes a general enhancement in the resistance of the human body."

4.1. ANALYSIS OF THE STATEMENT OF THE SPANISH BIOETHICS COMMITTEE

The Statement of the SBC is, by its content, of particular interest. Although, in fact, some of their considerations are admissible, there is no broad consensus on others. Hereunder we are spelling out the scientific, ethical and legal legitimacy to support it and their potential weaknesses.

4.1.1. Scientific current state of the art

To begin with, the experiment immediately triggered widespread condemn over the scientific community. The SBC devotes several paragraphs to this, and the second one is as follows:

> "(...) the current state of such techniques (...) does not meet the safety level required for their clinical use on humans, owing to the possibility of, among other things, altering similar genome sequences which fall outside the designated target area."

It is an evidence that the lack of security is, certainly, one of the objections of greater importance, because the therapies in the human body – *in vivo* – can accidentally provoke secondary effects, off-target effects or mosaicism (Harper, 2018) in the patient and in their future offspring. So it is not possible to guarantee that any of this will happen with Lulu and Nana, which will most likely force them to remain monitored not only until they reach the legal age – something that Jiankiu has already undertaken to do - but throughout their entire life, questioning their right to privacy and the free development of their personality. The SBC goes on to say, in point fourth:

> "(...) in that other alternatives are at present available for the therapeutic approach to and prevention of HIV transmission."

Indeed, there are clinical treatments in laboratories that, while not healing HIV, do allow its containment efficiently. Without being exhaustive, we can mention PGD, sperm washing, antiretroviral therapy and the use of condoms for intercourse. As if this were not enough, one of the twins could only have modified one of the two copies of the CCR5 gene, so she would not be protected against HIV, with which her right to life, physical integrity and health would have been jeopardised. Therefore, as long as the scientific progress is this, ethical and legal arguments take a back seat.

4.1.2. Ethical arguments and guiding principles

To carry on, the moral reasons exhibited by the SBC to explain its disapproval to Germline Gene Editing (GGE) should be mentioned. The SBC goes further into the irresponsibility committed, recalling, in its third point, that genome editing should be carried out:

> "(...) in all cases subject to rigorous scientific evaluation by experts, both beforehand (see, research committees and the like) and afterwards with respect to the results (see, for example, peer review)."

It should be reported that Jiankiu disclosed publicly his experiment at the Hong Kong Conference, and revealed his publication in a scientific journal without, of course, having been submitted to any previous evalu-

ation, thus crossing the bottom line of the standards of good practice. All this seems to be driven by the search for fame and notoriety of its author. Along with the above, there are suspicions about the alleged financing of the Chinese government, as well as about the knowledge of the project by some colleagues who, presumably, would have been aware of his intentions, covering them up. In any event, Jiankiu stated that the sisters had not undergone any unexpected mutation which, in the absence of information and evidence, not only could not be guaranteed, but could have affected their brains (Regalado, 2019a). It appears that neither the requirements of informed consent or genetic counselling have been satisfied (Emaldi Cirión, 2001). Furthermore, the signatories seemed to lack sufficient knowledge in biology to understand the trial, and in the documents, in addition to the use of technical language, the words "gene editing" were avoided. To continue, SBC argues that:

> "(...) is totally unacceptable and inadmissible. This is demanded, not only by the essential values of dignity and equality of human beings, (...)."

Thus, human dignity, established in the Universal Declaration of Human Rights and the Spanish Constitution, is often invoked against heritable GGE. Despite its undeniable validity, human dignity's contents are not defined descriptively – although it could be understood as the respect for humans' autonomy, and as an end or subject in itself, rather than a mere object, in the face of new technologies (Segers & Mertes, 2020: 34) –. That is why some researchers (Raposo, 2019: 250-251) believe that dignity is a vague argument, since it is an indeterminate concept or speculative card where *dignity talk* ends with all kind of debate (Kirchhoffer, 2017: 376).

In addition, the question arises as to whether, precisely, it would be non-intervention that could breach the dignity of the children; otherwise, the interest of the society would prevail over the individual, in a sense opposed to what is provided for in the Oviedo Convention (ECHRB), while it would also not serve the best interests of the child. In fact, responsibility could not only be demanded for gene editing actions, but also for the consequences that, for life or health, could result from an eventual non-action or omission (Chan, 2020: 114-115).

With regard to the right to personal identity, its violation does not seem to be entirely clear when it the only purpose was to change the healthy embryos expression for their own good (de Miguel Beriain, 2019b:

1258). Alternatively, would it be preferable for their identity to be "HIV Lulu and Nana" rather than "HIV-free Lulu and Nana"? An affirmative answer would seem to be in favour of the sanctity of the human genome, following the principles of playing God and slippery slope – which defend the wisdom of nature and the future risk of admitting techniques that could go beyond it –. Nevertheless, the fact that the human pool is not a static entity, but one in constant evolution, being able to undergo genetic, environmental or life disorders would be overlooked. Thus, there are authors (de Miguel Beriain, 2018:2) who maintain that the respect for dignity should entail the following:

> "(...) to use gene editing to remove any natural, random mutations (...) we would have a moral obligation to use genetic editing techniques to reserve the changes brought about by nature."

The same cannot be said for the right to non-discrimination (Hercher, 2018), as it entails a more feasible risk. This would be the case in a world such as GATTACA with the creation of a new lineage, which would divide humankind into enhanced and natural – i.e. not improved – humans (de Miguel Beriain & Armaza Armaza, 2018: 192-193):

> "With this, its use would eventually lead to a scenario in which the human species would be divided into two different groups: human beings and those who would hold the additional category of improved, (...)."

At the same time, it is possible that, owing to its high cost, gene editing were not available to the public as a whole, which would undermine the right to health of the least well off. In any way, this is already the case with the distribution of some medicines, as well as with public research, without ending their commercialization or justifying their suspension; otherwise, the fundamental right to scientific and technical production and creation would be breached. Even in the fiction of its universalization, it would be taken for granted that all citizens would want this technology when, among others, ideological or religious arguments can be used to reject it. There is also the question of enhancement in the field of health: would it not be praiseworthy to improve the withdrawal of diseases? (Braun & Meacham, 2019: 2):

> "It would be foolhardy and irresponsible to claim that the deletion of the CCR5 gene undermines moral and social equality, (...)."

Together with the above, there are goods that are absolute, since an improvement of this does not imply in principle a damage to third parties, as is the case with human health. The same does not happen, on the contrary, with other goods such as intelligence or beauty, which are positional insofar as the increase of those qualities in a person can mean a comparative decrease of the rest (de Miguel Beriain, 2019a: 49):

> "(...) In the case of pure positional goods, such as intelligence, this is perfectly relevant. Indeed, one can feel bad if one understand that there are other humans more intelligent than oneself. In the case of health, however, this does not happen, or should not happen. Only very mean people are relieved to contemplate another human being with more serious health problems than their own. Most of us usually focus on our own health exclusively. (...)."

In some cases, enhancement could rather be a necessary and simultaneous stage of healing. The SBC states the following in point five:

> "There is clear international consensus in bioethics circles in currently rejecting the use of germinal gene therapy for safety and ethical reasons, (...)."

Although GGE has sectors – particularly those headed by the bioconservative movement – that totally disagree, it should be noted that more and more voices are bit by bit changing and softening this message. As an example, Japan has published a project to authorize the edition of genes in human embryos (Cyranoski, 2018b), and some scholars already guess the short-term application of germline gene editing (Daley, 2018):

> "Just because the first steps into a new technology are missteps, it doesn't mean we shouldn't step back, restart, and think about a plausible and responsible pathway for clinical translation."

Moreover, the evolution of this idea in several reports of international organizations is striking. In this sense, the National Academy of Sciences, Engineering, and Medicine (NASEM) suggested in 2017 that (NASEM, 2017):

> "Clinical trials for genome editing of the human germline – adding, removing, or replacing DNA base pairs in gametes or early embryos – could be permitted in the future, but only for serious conditions under stringent oversight (...)."

A year later, the Nuffield Council on Bioethics (NCB) reached the same conclusion, considering it a moral imperative in certain cases (NBC, 2018: 154):

> "We can, indeed, envisage circumstances in which heritable genome editing interventions should be permitted."

More recently, the Second International Summit on Human Genome Editing found that GGE could be acceptable if a number of requirements were met (NASEM, 2018):

> "(...) germline genome editing could become acceptable in the future if these risks are addressed and if a number of additional criteria are met. These criteria include strict independent oversight, a compelling medical need, an absence of reasonable alternatives, a plan for long-term follow-up, and attention to societal effects."

Consequently, the Organizing Committee concluded that (NASEM, 2018):

> "Progress over the last three years and the discussions at the current summit, however, suggest that it is time to define a rigorous, responsible translational pathway toward such trials."

This makes visible a future landscape in which it could be applicable, if the tool was safe and the therapeutic benefits outweighed the harms – or at least there were no logical alternatives – without damaging third parties.

Lastly, the SBC expressly includes some guiding principles. Thus, in point fourth and six, respectively:

> "(...) is totally unacceptable and inadmissible (...) also by the principles of precaution and proportionality, (...)".

> "The Spanish Bioethics Committee wishes to call (...) to ensure that the use of these techniques is made subject to respect for (...) the principles of responsibility, precaution and safety."

Once the existence of real risks has been verified, it seems advisable to pay attention to the precautionary principle, which acts as a limit to the

freedom of research, recommending caution and moving forward step by step, at least until a higher level of knowledge and technical control is achieved (Romeo Casabona & de Miguel Beriain, 2010: 191):

> "(...) the precautionary principle is not applicable to all situations of risk, but only to those that present two main characteristics: that, as a premise, there is a context of scientific uncertainty about the consequences of the activity, and that, in addition, there are suspicions about the possibility of a risk of particularly serious and possibly uncontrollable and irreversible contingent damage."

Besides, precaution does not necessarily imply prohibition in a narrow sense, not, at least, without prior and sufficient evidence of considerable risk (NASEM, 2017):

> "Although heritable germline genome editing trials must be approached with caution, caution does not mean prohibition."

The same applies to the principles of proportionality and responsibility, since, as has already been said, Lulu and Nana did not suffer yet from any disease; therefore, the mere possibility of suffering from more serious pathologies or malformations than the one that was intended to be avoided entailed unnecessary and disproportionate hazard.

4.1.3. Legal framework

Finally, the SBC dedicates point five to two international treaties[5]:

> "(...) the Universal Declaration on the Human Genome and Human Rights 1997 and the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine 1997 (...)".

[5] Furthermore, see Directive 98/44/EC of the European Parliament and of the Council, of 6th July 1998, on the legal protection of biotechnological inventions, art. 6.2: "On the basis of paragraph 1, the following, in particular, shall be considered unpatentable: b) processes for modifying the germ line genetic identity of human beings; (…)"; and Charter of Fundamental Rights of the European Union (2000/C/364/01), art. 3.2: "In the fields of medicine and biology, the following must be respected in particular: (...) the prohibition of eugenic practices, in particular those aiming at the selection of persons; (...)."

Even if the references to the beginning of human life are particularly rare (de Miguel Beriain, 2017: 671), is true that those texts mention indirectly gene editing and that, at first sight, it could be understood GGE as prohibited in the light of them (Bellver Capella, 2008: 408; Andorno, 2005: 140). Despite this, the fact that ECHRB is binding only for the signatory States – the 29 members, most of them European – and the interpretation of some of its dispositions may call into question the referred international consensus. Among these norms, the most significant one is article 13, which establishes:

> "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."

As can be inferred, this precept alludes, among the permitted interventions, the preventive ones, so it would be agreeable with the first of its mandates. On the second one, it quotes literally the genome of the descendants, without referring to the germline. Frequently, these terms are used indistinctly, and are understood as equivalent; nevertheless, the germline can be modified without changing the genome of the offspring, e.g., if Lulu and Nana decide not to have children in the future, or they are infertile (de Miguel Beriain, Armaza Armaza & Duardo Sánchez, 2019: 228). Even though their germline were altered, what would be modified would be the individual genome of the twins, and not the genome of humanity, as no novation would be introduced in the human gene pool (de Miguel Beriain, 2018: 3):

> "There is a big difference between changing the genome of a human being and changing the human genome (...) If the final result of the intervention—for instance, replacing a mutated gene to restore its original function—does not introduce any novelty into the human gene pool, then it is inaccurate to speak of an alteration in the human genome."

Furthermore, in some occasions it happens that the affectation of the germline is an indirect consequence and is subordinated to the intended clinical result, that is to say, the cure of a pathological condition, without wanting to deliberately introduce any modification in the genome of the descendants[6]. When this happens, it could be thought that such an intervention is permissible.

[6] So it is with radiotherapy or chemotherapy, increasingly prescribed to eliminate any cancerous tumour. See the Oviedo Convention Explanatory Report, art. 92, which

Although ECHRB is the most important one in this area, there are a few references in the Spanish legal system[7], even if has no specific and explicit regulation on gene editing, also because of the territorial decentralization. However, criminal law is an exclusive competence of the State. In accordance with the above, offences of genetic manipulation are regulated in articles 159-162 of the Criminal Code, but the prevention of serious illnesses are atypical or not punishable because they do not harm the bodily integrity of the individual (Romeo Casabona, de Miguel Beriain & Duardo Sánchez, 2020: 398).

In the meantime, Austria, Germany and Italy did not sign ECHRB because they considered it too permissive, advocating a ban on the use of human embryos for research; the same occurs in France, Portugal and the Netherlands, unless the research is carried out with embryos that are not suitable for implantation. The opposite situation is embraced by Belgium, United Kingdom and Sweden, which considered ECHRB extremely restrictive, authorizing the creation of embryos for research, if they have therapeutic purposes (de Wert *et al*., 2018: 6). In the USA the limit is constituted by therapeutic purposes, while Russia and China have soft laws (Deuring & Taupitz, 2018: 73).

In the latter country, genetically modified human embryos are banned by a 2003 ministerial order, but this does not have the force of law, which has led its authorities to rush, in the face of the numerous criticisms received, to tighten their regulation (Cyranoski, 2019a; Cyranoski, 2019b).

5. FINAL REMARKS

To sum up, some conclusions can be drawn from the fields of science, ethics and law. Firstly, scientists have warned in several occasions about

states: "On the other hand the article does not rule out interventions for a somatic purpose, which might have unwanted side-effects on the germ cell line. Such may be the case, for example, for certain treatments of cancer by radiotherapy or chemotherapy, which may affect the reproductive system of the person undergoing the treatment."

[7] See Law 14/2006 of 26 May, on assisted human reproduction techniques, art. 13.1: "Any intervention for therapeutic purposes on the live pre-embryo in vitro may only have the purpose of treating a disease or preventing its transmission, with reasonable and proven guarantees;" and Law 14/2007, of 3 July, on Biomedical Research, art. 74: "C) These are very serious infractions: a) The performance of any intervention aimed at introducing a modification in the offspring's genome."

the lack of control over CRISPR-Cas9 repair mechanisms, as well as the limited knowledge about polygenic diseases, in which a multiplicity of genes interact. This is the reason why, before applying this tool to humans, basic science research should be reinforced, limiting itself, for the moment, to *ex vivo* trials. Indeed, responsible research should be encouraged, requiring authors to follow appropriate, contrasted and relevant guidelines and procedures. In any case, it should be taken into account that there is no "zero risk" in medicine, so it seems difficult to imagine a future stage that does not involve any harmful consequences to health.

Secondly, it does not seem entirely clear that the GGE can be qualified as morally rejectable for the cure of a disease (German Ethics Council, 2019: 26), even though it is in the future; in this case, treatment and prevention – as the factual assumption might be – should be praiseworthy based on a strictly ethical consideration. On the contrary, what makes intervention reprehensible is, on the one hand, the existence of major harms than the benefits that twins could obtain – risks/benefits criterion –, and, on the other hand, the existence of reasonable and safe alternatives.

Thirdly, at the legislative level, three proposals have been carried out to date: one, the general ban on GGE (Annas, Andrews & Isasi, 2002); two, a five-year moratorium to prevent the clinical use of heritable gene editing during this period (Lander, Baylis, Zhang, Charpentier, Berg *et al.*, 2019); and three, the creation of a world register on gene editing by the World Health Organization (Reardon, 2019). Nonetheless, in our view, none of them would provide a definitive solution. To begin with, the general veto would exclude forever the benefits of this promising biotechnology; moreover, it has already been explained that the low cost and simplicity of the technique will feed the black markets. To go on, a moratorium would only postpone the problem, without forgetting the uncertainty that its application could generate depending on the legal framework and jurisdiction of each country (Schaefer, 2019). With regard to the creation of a world register, in which the experiments carried out are published, it would provide transparency, although it should be accompanied by some kind of coercive measure to avoid non-compliance – such as fines, prohibitions on obtaining public funding and disqualifications from practice –; otherwise it would again be left to the willingness of scientists.

The overall conclusion is that it is necessary to establish a binding and legal pathway, given that the rules in force are very much older than the new gene editing technologies and the way of interpreting them is cumbersome (de Miguel Beriain & Romeo Casabona, 2020: 379). To this

end, the protection of human rights and the rights of future generations (Koplin, Gyngell & Savulescu, 2019: 58) must be the basis. In this context, in the event of the collision of different legal interests – on the one hand, the right to life or to the highest attainable standard of health; on the other hand the preservation of the human genome and the right to genetic identity – the legislator must weight them and opt for the one that deserves the highest protection.

Be that as it may, the need to make a process of deliberation and better governance, in which citizens participate and express their opinion before applying gene editing, fostering public empowerment (Andorno, Baylis, Darnovsky *et al*., 2020) should not be overlooked. Only in this way it will be possible to unify scientific development with public freedoms and social justice, for which law must act in pursuit of a decision that will certainly transform the future of humankind.

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