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Heritable genome editing in human beings

Report[1]
Committee on Social Affairs, Health and Sustainable Development
Rapporteur: Mr Stefan SCHENNACH, Austria, Socialists, Democrats and Greens Group

Summary

In the eyes of the Parliamentary Assembly, deliberate germ line editing in human beings would cross a line viewed as ethically inviolable. The Council of Europe's Convention on Human Rights and Biomedicine (ETS No. 164, "Oviedo Convention") only allows an intervention seeking to modify the human genome for certain purposes, and only if its aim is not to introduce any modifications in the genome of any descendants.

There is a broad consensus in the scientific community that the current technology is not yet safe and effective enough to establish a pregnancy with cells having undergone heritable genome editing, and no country explicitly permits it. In the last five years, there has, however, been a noticeable push by many scientists for a "translational pathway for heritable human genome editing" to be developed. This is unacceptable from an ethical and human rights point of view, now and in the future.

The Assembly should thus urge the Committee of Ministers to call all upon Council of Europe member States to embrace a clear and total prohibition of establishing a pregnancy with germ line cells, their precursors, or human embryos having undergone intentional genome editing of their nuclear DNA, by introducing legislation at the national level, and opposing permissive regulation at European and international level.

1. Reference to committee: Doc. 15217, Reference 4563 of 19 March 2021.

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A. Draft recommendation[2]

1. In November 2018 it was announced that, as a result of unsanctioned work by a Chinese researcher, at least two twin girls had been born with modified genes with the aim of conferring on them immunity to the HIV/AIDS virus. The act was strongly criticised by ethicists and scientists worldwide due its premature nature and high risk of unwanted side effects. This led to renewed calls for a worldwide moratorium on establishing a pregnancy with germ line cells or human embryos having undergone intentional genome editing of their nuclear DNA.

2. The Parliamentary Assembly recalls its Recommendation 2115 (2017) "The use of new genetic technologies in human beings", in which it pointed out that deliberate germ line editing in human beings would cross a line viewed as ethically inviolable. Indeed, the 1997 Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No. 164, "Oviedo Convention"), binding on the 30 member States which have ratified it, posits in its Article 13 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".

3. The Council of Europe's Steering Committee for Human Rights in the fields of Biomedicine and Health (CDBIO) assesses the ethical and legal challenges raised by emerging genome editing technologies regarding the Oviedo Convention. The Assembly commends the clarifications agreed by CDBIO in 2022, that Article 13 applies in the research as well as the clinical context, and that any intervention that seeks to modify the human genome may be carried out only for preventive, diagnostic or therapeutic purposes – and that gametes, embryos or their precursors that have been subject to such an intervention may not be used for the purposes of procreation.

4. There is a broad consensus in the scientific community that the current technology is not yet safe and effective enough to establish a pregnancy with germ line cells or human embryos having undergone intentional genome editing of their nuclear DNA, and no country explicitly permits it. In the last five years, there has, however, been a noticeable push by many scientists for a "translational pathway for heritable human genome editing" to be developed, namely the opening of clinical trials when certain minimum standards are met in the future.

5. The Council of Europe has a mandate that encompasses the promotion and protection of human rights of all individuals and is thus responsible for carefully weighing the human rights implications of heritable genome editing in human beings. The risks are serious and manifold, and cannot be ethically justified. For the Assembly, even if and when the technology is considered safe and effective enough, the ban on establishing a pregnancy with germ line cells, their precursors, or human embryos having undergone intentional genome editing of their nuclear DNA should thus be upheld.

6. The Assembly thus recommends that the Committee of Ministers:

6.1. urge member States which have not yet ratified the Oviedo Convention to do so without further delay;

6.2. remind the States Parties to the Oviedo Convention of their obligation to give life to its Article 28 through the promotion of a broad and informed public debate on heritable genome editing in human beings; the protection of the human genome as the heritage of humanity, as well as future generations' human rights also need to be debated;

6.3. call upon Council of Europe member States to embrace a clear and total prohibition of establishing a pregnancy with germ line cells, their precursors, or human embryos having undergone intentional genome editing of their nuclear DNA, by introducing legislation at the national level, and opposing permissive regulation at European and international level.

2. Draft recommendation adopted unanimously by the committee on 19 September 2023.

B. Explanatory memorandum by Mr Stefan Schennach, rapporteur

1. Introduction

1. "[R]ecent advances in genome editing are bound to result in germ line interventions in human beings quite soon".[3] These were the words of the Parliamentary Assembly's former rapporteur Ms Petra De Sutter (Belgium, SOC) introducing her 2017 report on the use of new genetic technologies in human beings, which were also reflected in the adopted recommendation. One year later, her prediction had already become a reality. In November 2018, it was announced that, as a result of unsanctioned work by a Chinese researcher, at least two twin girls had been born with modified genes with the aim of conferring on them immunity to the HIV/AIDS virus. The act was strongly criticised by ethicists and scientists worldwide due the premature nature and high risk of unwanted side effects (on-target and off-target effects). This led to renewed calls for a worldwide moratorium on establishing a pregnancy with germ line cells or human embryos having undergone intentional genome editing[4], but also to calls for a "rigorous, responsible translational pathway toward clinical trials" for when heritable genome editing in human beings is considered "safe enough".

2. If, and this needs to be expected, the technology develops further to the point that unwanted side effects no longer pose a common and obvious problem, voices will be raised in favour of lifting the current more or less official moratorium. There has been a shift in the scientific community and among those involved in risk evaluation to move from the notion of "safe" to the notion of "acceptable risks" to greenlight a move towards possible application. The evaluation of the risks at stake and the question of who should decide on whether these are "acceptable" remain a key issue. The question is no more "whether" but "how". In fact, voices are already being raised in favour of the creation of a regulatory pathway to permit germ line modifications, even though a survey published in 2020 showed that 75 of the 96 countries which have policy documents relevant to the use of genome editing to modify early-stage human embryos, gametes, or their precursor cells prohibit their use to initiate a pregnancy – and no country explicitly permits it.[5] The position the Council of Europe wants to take in future concerning intentional heritable genome editing in human beings must thus be made clear already now, before use of the technology can be deemed "safe".

3. It is my opinion that our member States should maintain and reinforce the clear position of prohibition of any intervention seeking to introduce a modification in the genome of any descendants, postulated in Article 13 of the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No. 164, "Oviedo Convention"). This is the necessary response to protect the human genome, safeguard future generations' human rights and enforce shared bioethical principles. The Council of Europe should also take this message to the rest of the world via its Committee of Ministers, Parliamentary Assembly, and Steering Committee for Human Rights in the fields of Biomedicine and Health (CDBIO).

2. Heritable genome editing in human beings: definition and context

4. Gene editing technologies constitute promising tools both in the fields of biomedical research and clinical application.[6] These techniques are opening the pathway to genetically personalised, or "precision" treatments. However, the early promise of such treatments has not, or not yet, been fully realised.[7] This is because there are very few genetic diseases which are well understood and involve only single genes. Most genetic diseases are multifactorial, involving several genes and also environmental factors. With so few beneficiaries for "precision"-treatments of rare genetic disorders, the cost of research and treatment is very high – which in turn has sparked questions of whether the money would not be better invested in public health measures to fight more common (non-genetic) diseases.[8]

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3. Recommendation 2115 (2017), paragraph 2.
4. Human germ line editing and heritable human genome editing are synonyms. I have decided to privilege the latter term, since it is more easily understandable. Germ line editing interventions are always hereditary, except with the "one-generation" germ line editing technique currently in development.
5. Françoise Baylis, Marcy Darnovsky, Katie Hasson and Timothy M. Krahn: "Human Germline and Heritable Genome Editing: The Global Policy Landscape", in *The Crispr Journal*, Volume 3, Number 5, 2020, pp. 365-377.
6. In the last decades, numerous techniques to intervene on human genetic material emerged: somatic nuclear transfer, induced pluripotent stem cells, spindle and pronuclear transfer and, ultimately, gene editing. The completion of the Human Genome Project in 2001 revolutionised the understanding of clinical use of genetic technologies, leading to the launching of the Precision Medicine Initiative by the United States National Institute of Health in 2015.
7. There is one successful treatment case in the USA: Victoria Gray who had sickle cell anaemia: www.npr.org/sections/health-shots/2021/12/31/1067400512/first-sickle-cell-patient-treated-with-crispr-gene-editing-still-thriving.

5. When used to modify the human germ line, these new technologies, such as CRISPR-cas9, raise crucial legal and ethical implications.[9] These techniques can be used to make alterations of the human genome itself: that is to say the alterations made will be inherited by future generations. Because of the potential unintended, unpredictable, and undetectable effects both on the person born with the modified genome and the descendants, such as off-target effects and mosaicism, at the present stage their use in human beings is still considered unsafe by scientists.[10]

6. Human genome editing has different fields of potential application. If unwanted side-effects could be eliminated, germ line editing would be a new option to prevent, diagnose or treat genetic diseases. In most of the cases germ line editing is, however, not the only possible option for parents wishing for a child, including those seeking to have a genetically related child unaffected by a genetic disease. Apart from adoption, egg, sperm or embryo donation, the treatment of the genetic disease directly in the affected child (somatic gene therapy, working at the level of epigenetics, or, possibly, by "one-generation" germ line editing) would provide alternatives.

7. Another possibility is in vitro fertilization (IVF) combined with pre-implantation genetic diagnosis (PGD) which, however, requires the ethically disputed PGD-selection of embryos. In the very rare cases, where both parents' germ cells carry the defect (and the gene involved is dominant), deliberate germ line editing could be the only option for these parents to have a genetically related child without the genetic disease – but would also require PGD, since the success rate of genome editing is never 100%.[11] Even if side-effects can be eliminated in the future, the technique may have unknown effects on future generations.[12]

8. There are three possible forms how deliberate germ line editing in human beings could be conducted: modifications could be either directed directly on the embryo in the pronuclear or one-cell-stage, on the germ cell, for example an egg or a sperm cell, or on a stem cell (precursor cell). According to the general understanding, germ line editing interventions imply that the genetic alterations are hereditary and thus transferred to future generations. Some researchers are exploring the option of "one-generation germ line therapy" whereby future descendants remain unaffected by the genome editing intervention.[13]

9. Another possible field of application of deliberate germ line editing is human enhancement, namely the optimisation of certain characteristics and abilities via genetic modification. As will be examined in more detail in chapter 5, the deliberate alteration of the human genome to enhance the human species would cross the line of ethical inviolability and could foster the "production" of individuals or groups with specific genetic characteristics or qualities, thus enlarging the pathway to discrimination and throwing into doubt the survival of the human race as we know it.

3. The Oviedo Convention and the international prohibition of heritable genome editing in human beings

10. The International Committee of Bioethics (IBC) was founded by UNESCO in 1993 and tasked with devising an international instrument to protect the human genome. Given the controversies surrounding genomics research and the number of open and partly hidden conflicts during the preliminary work of the IBC, it soon became clear that UNESCO would not be able to adopt a legally binding convention.[14] Instead, States opted for a declaration, and the Universal Declaration on the Human Genome and Human Rights was adopted unanimously and by acclamation at UNESCO's 29th General Conference on 11 November 1997.

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8. Ned Carter Niles: "'Very little yield': has genetically targeted medicine really made us healthier?", in: *The Observer*, 9 September 2023. www.theguardian.com/society/2023/sep/09/precision-medicine-targeted-personal-human-genome-genetics-tailored.

9. Among the developing techniques, CRISPR-cas9 is considered the most promising one. The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) are sections of the genetic code containing repetitions of base sequences. The protein Cas9 is an enzyme which guides RNA to introduce double strand break at a specific location, thus acting as a kind of "molecular scissors".

10. H. Ledford, "CRISPR gene editing in human embryos wreaks chromosomal mayhem". Three studies showing large DNA deletions and reshuffling heighten safety concerns about heritable genome editing, in *Nature*, 2020.

11. Normally, however, 25 to 75% of descendants of parents with a monogenic disease do not suffer clinically from the disease, making IVF and PDG a possible alternative.

12. Cantz T., "Introduction to Genome Editing in Induced Pluripotent Stem Cells", in Dederer HG. and Frenken G (eds.) *Regulation of Genome Editing in Human iPS Cells*. Springer. 2022 (in print).

13. See Schleidgen S. et al., "Human germline editing in the era of CRISP-Cas: risk and uncertainty, intergenerational responsibility, therapeutic legitimacy". *BMC Medical Ethics*. 2020. 21(87).

14. www.forskningsetikk.no/en/resources/the-research-ethics-library/legal-statutes-and-guidelines/unescos-declaration-on-the-human-genome/.

The Declaration was endorsed by the UN General Assembly the following year. The Declaration regards the human genome as the "heritage of humanity". It should be protected and passed on to future generations and advances in science need to be considered in the light of human rights. Further to this, the IBC believes that interventions on the human genome should be admitted only for preventive, diagnostic or therapeutic reasons and without enacting modifications for descendants and has called for "a moratorium on genome editing of the human germ line".[15]

11. The only internationally binding framework in this field is the 1997 Oviedo Convention, binding on the 30 member States which have ratified it. Its Article 13 posits 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 modifications in the genome of any descendants".

12. Further, the Oviedo Convention provides for the freedom of scientific research, subject to the protection of human rights.[16] Yet, "where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo" (Article 18'1)). The creation of human embryos for research purposes is prohibited under Article 18(2).

13. Article 28 imposes on States Parties to see to it that "the fundamental questions raised by the developments of biology and medicine are the subject of appropriate public discussion in the light, in particular, of relevant medical, social, economic, ethical and legal implications, and that their possible application is made the subject of appropriate consultation". In conjunction with this, the Oviedo Convention establishes a specific procedure for its amendment in Article 32.

14. CDBIO assesses the ethical and legal challenges raised by emerging genome editing technologies regarding the Oviedo Convention. According to the Strategic Action Plan 2020-2025, adopted at the 16th meeting of its precursor committee, the Committee on Bioethics (DH-BIO), on 19-21 November 2019, it is of the greatest importance to embed human rights in technologies with an application in biomedicine. Hence, the actions promoted include examining the practical and legal implications of Article 13 of the Oviedo Convention in the light of the developments in genome editing as well as analysing the necessity of an amendment to this Article.

15. In accordance with Article 32 of the Oviedo Convention, in 2020, DH-BIO started re-examining Article 13 of the Convention, with a view to "providing for clarifications on terms or aspects of the provisions of Article 13 without revising its wording".[17] DH-BIO set up a drafting group in 2021 to provide clarifications on the terms "preventive, diagnostic and therapeutic" and to avoid misinterpretation of the applicability of this provision to "research".

16. At its 1st plenary meeting in 2022, the CDBIO concluded the final step of the re-examination process of Article 13 of the Oviedo Convention, with the adoption of the clarifications on the scope of the provisions with regard to research and the purposes limitation provided for any intervention on the human genome. As regards "research", the main clarifications are that the provisions of Article 13 apply to any intervention seeking to modify the human genome, including in research, and that the limitations of permittable purposes to "preventive, diagnostic and therapeutic" also apply in research. With regard to the permitted purposes for genetic alteration, the CDBIO has clarified the following: an intervention for a "preventive" purpose has the aim of avoiding the occurrence of a disease or disorder. The term "disease" refers to a disease or disorder defined in accordance with internationally accepted medical standards. An intervention for a "diagnostic" purpose should be understood as intervention undertaken to identify a disease or disorder, or a genetic variant or factor associated with the development of a disease or disorder, again identified in accordance with internationally accepted medical standards. An intervention undertaken for a "therapeutic" purpose will aim at controlling symptoms of a disease or disorder, slowing or reversing its progression or provide a cure, for example by removing its underlying cause.[18] The clarifications were presented to the Committee of Ministers on 27 September 2022.

17. In light of these clarifications, it can be concluded that the Oviedo Convention constitutes an international legal framework and a guiding set of ethical principles which restrict the scientific use of gene editing technologies in human beings and impose a strong precondition of legal and ethical legitimacy for such activities. Therefore, these shared ethical principles should drive the international debate on germ line and

15. Report of the IBC on updating its reflection on the Human Genome and Human Rights, 2015.
16. Explanatory Report to the Oviedo Convention, paragraph 96.
17. DH-BIO/Abr RAP17, paragraph 22.
18. CDBIO, "Intervention on the Human Genome, Re-Examination Process of Article 13 of the Oviedo Convention: Conclusions and Clarifications".

embryo editing in human beings: as already highlighted by the Assembly in its 2017 Recommendation, the member States which have not done so should ratify the Oviedo Convention, as well as develop a clear national position of prohibition of germ line and embryo editing in human beings in order to avoid a vacuum of legal and ethical certainty both at the international and national levels.[19]

4. Opinions in the international debate

18. The issue of germ line editing in human beings is one of the major bioethical dilemmas of today and it is the object of a widespread international debate. Many international fora and groups of experts are addressing it: the main ones are the IBC, the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing of the World Health Organization (WHO), the European Group on Ethics in Science and new Technologies (EGE) and the International Commission on the Clinical Use of Human Germline Genome Editing.

19. The IBC set out its position in the 2015 Report on updating its reflection on the Human Genome and Human Rights. On this occasion, it reiterated its support for a moratorium on germ line editing in human beings, recalling the necessity to consider scientific development in light of human rights. By identifying the human genome as "one of the premises of freedom itself and not simply raw material to manipulate", numerous arising ethical challenges were taken into consideration, such as the respect for autonomy and privacy, the threats to principles of justice and solidarity and the responsibility towards future generations. More recently, IBC has adopted a report on the principle of protecting future generations: affirming that the principle of intergenerational justice must go hand in hand with the precautionary principle, it recalled that such germ line editing in human beings must not be applied until it is scientifically validated and considered ethically acceptable. It finally recommended that States build a shared global standard and pass regulation to protect the human genome and to prohibit genetic alterations of the human germ line.

20. In December 2018, WHO established the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing ("WHO Committee") to examine the scientific, ethical, social, and legal challenges associated with human genome editing (somatic and germ line).

21. The WHO Committee reaffirmed the statement by the WHO Director-General in March 2019 that it would be irresponsible at this time for anyone to proceed with the clinical application of germ line genome editing. The WHO Committee recommends that WHO should work with others to institute and develop international collaboration for effective governance and oversight. In addition, germ line editing should only take place in jurisdictions with domestic policy and oversight. The WHO Committee further suggests creating and hosting a registry for human genome editing used in clinical trials, which should include data from germ line editing technologies if at some point, they should be approved.[20] WHO thus supports the call by the EGE to "establish a public registry for research on germ line genome editing".[21]

22. In the United States, the International Commission on the Clinical Use of Human Germline Genome Editing, a collaboration by the Academy of Medicine, the National Academy of Sciences, and the Royal Society, published a report on the issue in 2020. According to the report, germ line editing should be prohibited until it has been clearly established that it is possible to make precise genomic changes efficiently and reliably without undesired changes in human embryos. Further, any clinical use should proceed cautiously, with initial uses restricted to a limited set of circumstances, *inter alia*, severe monogenetic disease and no or very poor alternatives for having a genetically related child without the disease. The report calls for every country to ensure that the requirements have been met for initial responsible use, prior to approving the use of germ line editing. The report hence entails a certain openness leaving the decision at a country-level while establishing an international scientific advisory panel and an international body for related discussions and international oversight.[22]

23. The human rights framework for germ line editing in the European Union is the Charter of Fundamental Rights which in Article 1 secures everybody's rights to be treated with dignity. Article 3 prohibits "eugenic practices, in particular those aiming at the selection of persons". The EU Clinical Trials Directive bans gene

19. This line was followed by Ms Petra De Sutter in the explanatory memorandum which was at the origin of Recommendation 2115 (2017).
20. WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.
21. European Commission, EGE, "Ethics of Genome Editing", 2021.
22. National Academy of Medicine, National Academy of Sciences, and the Royal Society. "Heritable Human Genome Editing". The National Academies Press, 2020.

therapy trials "which can result in modifications to subject's germ line genetic identity".[23] It is, however, unclear whether this ban applies to germ line gene editing research. In general, the regulatory framework is considered patchy and lacking coherence.[24]

24. The international debate has been enriched by the EGE, an independent and multidisciplinary body which advises the European Commission. In a recent position paper, EGE addressed the need to consider the numerous bioethical implications arising, and proposed a balance between potential benefits and risks in the use of germ line editing techniques in human clinical application.[25] By putting the accent on the principles of social justice and equality, the heritability of genetic intervention by future generations has been declared a potential challenge to human biodiversity and a potential doorway to genetic make-up and human enhancement. Consequently, EGE has recommended that EU member States be engaged in global governance initiatives and promote an inclusive debate on germ line editing.

25. In addition, the European Society of Human Genetics and the European Society of Human Reproduction and Embryology have expressed similar opinions. After having supported the moratorium on establishing a pregnancy with genetically modified germ line cells or human embryos,[26] both societies widely examined the bioethical implications, also highlighting potential societal risks, such as the breach of the dignity of people with disabilities, the risks of human enhancement and the growth of inequalities. However, these societies would be in favour of regulating the use of germ line editing in human beings if and when safety concerns are overcome.

26. Ultimately, at the international level, the World Medical Association has also called for a germ line editing specific ethical and legal framework while condemning its use in human clinical application at this stage.[27]

27. Three international summits have been held on Human Genome Editing[28], in 2015, 2018 and early 2023. While, in 2015, this international group of scientists called for a moratorium on making inheritable changes to the human genome,[29] in 2018 – despite the shock revelation of the Chinese researcher at the Summit that he had broken the moratorium – the Organising Committee issued the following statement: "The organizing committee concludes that the scientific understanding and technical requirements for clinical practice remain too uncertain and the risks too great to permit clinical trials of germ line editing at this time. 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. A translational pathway to germ line editing will require adhering to widely accepted standards for clinical research, including criteria articulated in genome editing guidance documents published in the last three years. Such a pathway will require establishing standards for preclinical evidence and accuracy of gene modification, assessment of competency for practitioners of clinical trials, enforceable standards of professional behaviour, and strong partnerships with patients and patient advocacy groups."[30]

28. The Organising Committee of the Third Summit – which focused on somatic, rather than heritable human genome editing – went one step further in its statement: "Preclinical evidence for the safety and efficacy of heritable human genome editing has not been established, nor has societal discussion and policy debate been concluded. (In some cases, pre-implantation genetic testing is among the alternatives.) Heritable human genome editing should not be used unless, at a minimum, it meets reasonable standards for safety and efficacy, is legally sanctioned, and has been developed and tested under a system of rigorous oversight that is subject to responsible governance. At this time, these conditions have not been met."[31]

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23. Regulation EU No. 536/2014 of the European Parliament and of the Council of 16 April 2004 on Clinical Trials on Medicinal Products for Human Use, Article 9(6).
24. Almqvist J. and Romano C.P.R., "Regulation of Human Germline Genome Modifications in Europe" in Boggio A., Romano C.P.R., Almqvist J. (eds.) *Human Germline Modification and the Right to Science*. A Comparative Study of National Laws and Policies. Cambridge. 2020.
25. European Commission, EGE, "Ethics of Genome Editing", 2021.
26. European Society of Human genetics, Genetic Editing in human embryos, 2019. The European Society of Human Reproduction and Embryology Response to "Adopt a moratorium on heritable gene editing", 2019.
27. World Medical Association, Statement on human genome editing, 2020.
28. These meetings were convened by the National Academy of Sciences and the National Academy of Medicine of the United States, the Chinese Academy of Sciences and the Royal Society of London.
29. They also set the condition of a "broad societal consensus about the appropriateness of the proposed application".
30. Statement by the Organising Committee of the Second International Summit on Human Genome Editing, 28 November 2018, paragraphs 6-7, www.nationalacademies.org/news/2018/11/statement-by-the-organizing-committee-of-the-second-international-summit-on-human-genome-editing.

29. In May 2021, the International Society for Stem Cell Research (ISSCR) issued updated Guidelines for Stem Cell Research and Clinical Translation. In what can be interpreted as an "important contribution to the project of developing a translational pathway for heritable human genome editing"[32] (an objective proposed by the afore-mentioned Second Summit), a new sub-category "3 A Research activities currently not permitted" was created, and heritable human genome editing research was moved out of the "prohibited" category into this new sub-category.

5. Human rights and ethical issues concerning intentional heritable genome editing in human beings

30. As can be seen in the various reports, recommendations and statements being made (see Chapter 4), many scientists are pushing hard for what is euphemistically called a "translational pathway" to clinical trials with intentionally genetically modified embryos. The birth of human beings whose genome has been intentionally modified – which is, we should recall, prohibited by the Oviedo Convention, as well as 75 countries, and is explicitly permitted by no country in the world – could in their view take place as soon as "reasonable standards for safety and efficacy" are met, "societal discussion and policy debate has concluded", heritable genome editing is "legally sanctioned" and "has been developed and tested under a system of rigorous oversight that is subject to responsible governance". While the green light for inducing such pregnancies has not been given (scientists consider that these minimum conditions have not – yet – been met), preparations are obviously going ahead with this aim in mind.

31. Personally, I find this push shocking. In the past three years, public debate on this issue has been sorely lacking, and understandably so: the world has been preoccupied with fighting a global pandemic and a climate emergency, and dealing with the consequences of Russia's war of aggression against Ukraine. In 2020, I authored a report entitled "Ethics in science and technology: a new culture of public dialogue" (Doc. 15517). The Assembly followed my recommendations, and noted that "Developments in science and technology must respect fundamental values and human dignity, and scientific and technological foresight should no longer remain the exclusive remit of researchers and industry. Public authorities have to involve citizens more widely in decision making on science and technology, and policy options should be subject to public debate and scrutiny, to make sure that new advances in these domains sustain human progress."[33] Indeed, the need for public debate and appropriate consultation is clearly stated as a principle in Article 28 of the Oviedo Convention, and DH-BIO has published a "Guide to public debate on human rights and biomedicine".[34] National parliaments have a key role to play in this process.

32. What little debate has happened – both in parliaments and in society at large – seems to me to have been pushed, possibly in a manipulative way, by researchers and industry, seeking scientific glory and profits, with little regard to human rights, human dignity, and human progress. This may sound overly harsh, but how else to describe the proposal of defining "reasonable standards for safety and efficacy", that is to say something that is "safe enough" and "effective enough" when we are talking about a technology which, with its possible side-effects which may only become apparent after several generations, could end up wiping out the human race as we know it? A technology which could easily be abused for eugenic or military purposes? And to do what – help the extremely rare couples with a monogenetic disease to have a genetically related child without the genetic disease, where both parents' germ cells carry the defect (and the gene involved is dominant), and somatic or "one-generation" gene therapy doesn't work? I would like to recall that, in any case, there is no "right to a child", and even less to a genetically related one.

33. Even if the safety concerns are eliminated in the future, the human rights concerns, in particular with respect to the effects on future generations, will persist. The Council of Europe has a mandate that encompasses the promotion and protection of human rights of all individuals and is thus responsible for carefully weighing the human rights implications of heritable genome editing in human beings. The CDBIO has withstood calls to "revise" Article 13 of the Oviedo Convention which contains the prohibition of any intervention seeking to introduce a modification in the genome of any descendants. In 2022, it clarified that Article 13 applies in the research as well as the clinical context, and made clear that any intervention that seeks to modify the human genome may be carried out only for preventive, diagnostic or therapeutic purposes.

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31. Statement from the Organising Committee of the Third International Summit on Human Genome Editing, 8 March 2023, penultimate paragraph, https://royalsociety.org/science-events-and-lectures/2023/03/2023-human-genome-editing-summit/.
32. Françoise Baylis: "Heritable human genome editing is 'currently not permitted', but it is no longer 'prohibited': so says the ISSCR", in *Journal of Medical Ethics*, 4 October 2021.
33. Resolution 2333 (2020) "Ethics in science and technology: a new culture of public dialogue", paragraph 2.
34. www.coe.int/en/web/bioethics/guide-on-public-debate.

34. Allow me to quickly summarise the human rights concerns which underpin the position of CDBIO: first, germ line modifications mean irreversible modifications to future generations which might not even be foreseeable. This, on the one hand, means changing the common heritage of humanity. Making genetic modifications on humans might have unexpected evolutionary consequences which cannot be reversed. Since the entire effects of these modifications might not become apparent for years or even generations, permanently altering the germ line of human beings is considered an unbearable risk. Further, the future generations affected are not able to give their informed consent to these alterations. This is clearly contradictory to the idea of the autonomy of a patient, a principle which has been a core to research regulation for centuries.

35. Further, germ line editing even for therapeutic or preventative measures opens the door to human enhancement.[35] Even if an application is carried out for therapeutic reasons, the question will arise as to whether the treatment goal (for example regaining lung capacity) should be oriented towards the average of society or towards the optimum. What is understood as a severe disease or a therapeutic measure depends on subjective decision making. Commercial, military, or scientific interests could in some cases influence the evaluation. In addition, parents might feel pressured to accept such germ line therapy on their future children. Enhancement measures in general violate human dignity as they imply that the "natural" human is less valuable than its genetically modified self. The technology could be misused to produce individuals or entire groups with particular qualities, which could even lead to a "weaponisation" of the use of certain genetic technologies, for example to reduce the sleep required of soldiers.

36. Another potential societal consequence of the use of germ line editing in human beings is the breach of the principles of justice, equality, and non-discrimination. The techniques in question would most certainly not be accessible to the entire population and not be fairly distributed. In line with the human enhancement scenario, this would aggravate the existing social and economic inequalities, thus prolonging the existence of discrimination and imposing a negative impact on society.

6. Conclusions and recommendations

37. In 2015, the UK Parliament amended the Human Fertilisation and Embryology Act to permit the use of mitochondrial replacement therapy, making the United Kingdom the first country in the world to officially permit this form of intentional germ line modification.[36] In the case of rare genetic diseases linked to the maternal inheritance of mitochondrial diseases, this therapy can be used to avoid passing down such diseases. There are two ways: pronuclear transfer technology and maternal spindle transfer. A child born from this latter procedure has three genetic parents (with one providing the new genes of the healthy mitochondria). Although the traits of a child are inherited from the nuclear DNA of its parents and not the mitochondrial DNA, the interrelation and function between the genome of the nuclei and the mitochondria is still uncertain. The procedure is thus still considered a risky and experimental intervention that carries serious risks, and should not be undertaken lightly – and certainly not out of commercial motivations.

38. On 31 July 2023, two researchers published a paper which contends that the model followed to persuade the UK Parliament (and later the Australian Parliament) to authorise this procedure – in their view, prematurely – is now being used to influence perception and incrementally shift public consensus towards creating a regulatory pathway to allow heritable genome editing in human beings which changes the DNA of the nuclei (not just the mitochondria).[37] I am personally not in favour of allowing mitochondrial replacement therapy, but the dangers associated with this therapy are far fewer than with allowing heritable genome editing in human beings which changes the DNA of the nuclei. The risk involved with the necessary public debate on whether or not to allow heritable genome editing in human beings being unduly influenced by researchers and the fertility industry is thus also far higher than with the debate on whether or not to allow mitochondrial replacement therapy.

39. We must remember that just because we "can" do something does not mean we "should" do it, and even less that there should be a "right" to do it. Mere technical possibility should not lead to a *per se* acceptance of a technology. An example is deliberate cloning of human beings, which is – independent of the

35. This was actually one of the main concerns of the drafters of the Oviedo Convention, hence the limitation to medical purposes of any intervention.

36. Many authors would argue that this is not "genome editing" as you are not touching the DNA. It could be considered as a modification of the genetic characteristics of the cells as a whole namely genetic material in the nucleus and in the mitochondria.

37. Shoaib Khan and Katherine Drabiak: "Eight Strategies to Engineer Acceptance of Human Germline Modifications", in: *Bioethical Inquiry*, 31 July 2023.

technological possibility – banned by the Additional Protocol to the Oviedo Convention on the Prohibition of Cloning Human Beings (ETS No. 168) as it would "give up the indispensable protection against the predetermination of the human genetic constitution by a third party" and would endanger human dignity by instrumentalisation.[38] The statement in the Explanatory Report to the Additional Protocol that "as naturally occurring genetic recombination is likely to create more freedom for the human being than a predetermined genetic make up, it is in the interest of all persons to keep the essentially random nature of the composition of their own genes", also holds true for deliberate human germ line intervention.

40. Different voices raise the argument that in cases of severe genetic diseases, the right to life secured in Article 2 of the European Convention on Human Rights (ETS No. 5) as well as the right to enjoy the benefits of scientific progress and its applications (for example in Article 15(1)(b) of the International Covenant on Economic, Social and Cultural Rights) should be read as permitting heritable genome editing. One must, however, keep in mind, that there are always alternative options to heritable genome editing. There does not seem to be a case in which these alternatives, including possibly "one-generation germ line editing", could not sufficiently secure human rights. Indeed, human rights law does not recognise a "right" to a child, much less to a genetically related one.

41. The Assembly and the Council of Europe as a whole should thus take a clear position today in case heritable genome editing is considered "safe enough" by the scientific community in the future. We need to consider that neither those affected by germ line interventions have the possibility of consent, nor can long-term influences on humanity be prevented. Allowing heritable genome editing is a slippery slope towards the "improvement" of humanity. In line with the decision at the 17th DH-BIO meeting not to amend Article 13 of the Oviedo Convention, the ban on establishing a pregnancy with germ line cells or human embryos having undergone intentional genome editing (with the possible exception of mitochondrial replacement therapy and, in the future, "one-generation germ line editing") should thus be maintained in my opinion, even when the technology underlying it is considered "safe" in the future.

42. For activities not prohibited by Article 13 of the Oviedo Convention, such as certain forms of genome research and, if technically feasible, "one-generation germ line editing", comprehensive laws and regulations seem required to prevent the possible misuse of the technology.

43. I thus suggest that the Assembly should consider the adoption of the three following recommendations to the Committee of Ministers:

43.1. to urge member States which have not yet ratified the Oviedo Convention to do so without further delay;

43.2. to remind the States Parties to the Oviedo Convention of their obligation to give life to its Article 28 through the promotion of a broad and informed public debate on heritable genome editing in human beings and the protection of the human genome as the heritage of humanity, as well as on future generations' human rights;

43.3. to call upon Council of Europe member States to embrace a clear and total prohibition of establishing a pregnancy with germ line cells, their precursors, or human embryos having undergone intentional genome editing of their nuclear DNA, by introducing legislation at the national level, and opposing permissive regulation at European and international level.

38. Explanatory Report to the Additional Protocol on the Prohibition of Cloning Human Beings.