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The use of new genetic technologies in human beings

Report[1]
Committee on Social Affairs, Health and Sustainable Development
Rapporteur: Ms Petra De SUTTER, Belgium, Socialist Group

Summary

New genetic technologies are developing very rapidly: recent discoveries related to the human genome have opened the door to new opportunities and unprecedented ethical concerns. The current scientific consensus is that these techniques are not yet "safe" enough to establish a pregnancy with germline cells or human embryos having undergone intentional genome editing, but deliberate germline editing in human beings would also cross a line viewed as ethically inviolable.

The Parliamentary Assembly should thus recommend a five-step plan to the Committee of Ministers:

– urging member States which have not yet ratified the Oviedo Convention to do so without further delay, or, as a minimum, to put in place a national ban on establishing a pregnancy with germline cells or human embryos having undergone intentional genome editing;

– fostering a broad and informed public debate;

– instructing the Council of Europe Committee on Bioethics (DH-BIO) to assess the attendant ethical and legal challenges;

– developing a common regulatory and legal framework;

– recommending that member States, on the basis of the other steps, develop a clear national position on the practical use of new genetic technologies, setting the limits and promoting good practices.

1. Reference to committee: Doc. 13927, Reference 4176 of 25 January 2016.

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A. Draft recommendation[2]

1. Genetic engineering techniques have been applied in the medical field for several decades now. However, new technologies are developing very rapidly: recent discoveries related to the human genome have opened the door to new opportunities and unprecedented ethical concerns. On the one hand, this improved knowledge of our make-up as human beings brings with it welcome potential to diagnose, prevent and eventually cure diseases in the future. On the other hand, it raises complex ethical and human rights questions, including – but not limited to – unintended harm which may result from the techniques used, access and consent to such techniques, and their potential abuse for enhancement or eugenic purposes.

2. In particular, recent advances in genome editing are bound to result in germline interventions in human beings quite soon, for example with the birth of children whose genome has been altered with some unforeseeable consequences in such a way that their descendants are also affected. The scientific consensus at the moment is that these techniques are not yet "safe" enough, leading to a *de facto* moratorium until a germline intervention could meet the risk/benefit standard for authorising clinical trials. However, other techniques, such as pronuclear transfer technology (the "three-parent" technique to avoid maternal inheritance of mitochondrial diseases), have already resulted in babies being born, despite considerable scientific uncertainty about long-term effects.

3. Deliberate germline 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 29 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 modifications in the genome of any descendants". The convention does, however, also establish a specific procedure for its amendment (Article 32), which should be read in conjunction with Article 28, which 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".

4. Numerous scientific and ethical bodies are starting to make recommendations to establish an appropriate regulatory framework for genome editing and germline interventions in human beings, including most recently the United States National Academy of Sciences and National Academy of Medicine, and the European Academies Science Advisory Council (EASAC). The current prohibition on interventions aimed at modifying the germline in human beings in all European Union and many Council of Europe member States is not going to stop genome-edited babies from being born elsewhere.

5. The Parliamentary Assembly thus recommends that the Committee of Ministers:

5.1. urge member States which have not yet ratified the Oviedo Convention to do so without further delay, or, as a minimum, to put in place a national ban on establishing a pregnancy with germline cells or human embryos having undergone intentional genome editing;

5.2. foster a broad and informed public debate on the medical potential and possible ethical and human rights consequences of the use of new genetic technologies in human beings;

5.3. instruct the Council of Europe Committee on Bioethics (DH-BIO) to assess the ethical and legal challenges raised by emerging genome editing technologies, in the light of the principles laid down in the Oviedo Convention and the precautionary principle;

5.4. develop a common regulatory and legal framework which is able to balance the potential benefits and risks of these technologies with the aim of finding cures for serious diseases, while preventing abuse or adverse effects of genetic technology on human beings;

5.5. recommend that member States, on the basis of the public debate, the DH-BIO assessment and the common regulatory and legal framework devised, develop a clear national position on the practical use of new genetic technologies, setting the limits and promoting good practices.

2. Draft recommendation adopted unanimously by the committee on 25 April 2017.

B. Explanatory memorandum by Ms Petra De Sutter, rapporteur

1. Introduction

1. New technologies in the medical field are developing exponentially: recent discoveries related to the human genome and in the science of genetics have opened the door to a new paradigm. While this improved knowledge of our make-up as human beings brings with it welcome potential to diagnose, cure or even eradicate diseases in the future, it also creates ethical and human rights risks related to the techniques used.

2. I believe it is urgent to have a political debate on new genetic technologies – some of which are already being applied to human beings. This is why I encouraged the Committee on Social Affairs, Health and Sustainable Development to table a motion for a recommendation[3] on the subject in November 2015, and welcome the two hearings organised by our committee on the subject: the first on "Manufacturing a new human species?" in October 2015 with the participation of scientists, politicians and a representative from the Council of Europe's Committee on Bioethics (DH-BIO),[4] and the second on "The use of new genetic technologies in human beings" in January 2017, with a different set of experts and representatives.[5]

3. My aim in this report is to study the health, ethical and human rights risks and challenges related to the techniques' use and regulation with a view to making the appropriate recommendations to the Committee of Ministers on possible action to be taken to provide a common framework for the use of these technologies.[6]

2. The current situation

2.1. International law and the work of international and regional organisations

4. The mandate of the Council of Europe encompasses the promotion and protection of human rights, democracy and the rule of law. Also, its recognition of subsidiarity, and its mission of promoting good practice amongst member States, places the Organisation in an ideal position to address any possible violation of human rights at the European level.[7]

5. 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"), establishes a European legal framework for the protection of human rights in the field of biomedicine, which is binding on the 29 member States which have ratified it.

6. This convention should be used as the reference guiding instrument with regard to the use of genetic technologies. Article 13 of the convention establishes 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". In addition, "where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo" (Article 18.1), and the creation of human embryos for research purposes is prohibited under Article 18.2.

7. The Oviedo Convention does not take any position on genome research on human embryos. Its Article 13 is, however, generally understood as *de facto* prohibiting the transfer of an embryo with (intentional) genome modification into the uterus of a woman with a view to giving birth to a child.[8]

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3. Doc. 13927.
4. See the declassified minutes of the hearing: AS/Soc (2015) PV 05 add 2. Hearing held with the participation of Mr Jean-Yves Le Déaut, Parliamentary Assembly General Rapporteur on science and technology assessment; Mr Robin Lovell-Badge, Group Leader at the Francis Crick Institute (formerly MRC National Institute for Medical Research), United Kingdom; Mr George M. Church, Professor of Genetics at Harvard Medical School and Director of personalgenomes.org, United States (by video link); Mr Luigi Naldini, Director of the Division of Regenerative Medicine, Stem Cells and Gene Therapy, San Raffaele Scientific Institute, Italy; and Mr Mark Bale, Chairperson of the Council of Europe Committee on Bioethics.
5. Hearing held with the participation of Ms Mair Crouch, Geneticist and Academic Lawyer, University of Glasgow, United Kingdom; Ms Anne Forus, representative of the Council of Europe Committee on Bioethics, and Mr Cor Oosterwijk, Secretary General of the Patients Network for Medical Research and Health (EGAN). The minutes of the hearing (AS/Soc (2017) PV 01 add) were declassified on 24 March 2017.
6. Paragraph 3 of the motion for a recommendation.
7. The European Convention on Human Rights (ETS No. 5) binds all 47 member States of the Council of Europe.

8. Article 28 of the convention requires that Parties see to it that the "fundamental questions raised by the developments of biology and medicine are the subject of appropriate public discussion". Monitoring of scientific developments is foreseen under Article 32.4, and is carried out by the Committee on Bioethics, which represents 47 European States. At its 8th meeting, from 1 to 4 December 2015 in Strasbourg, the Committee adopted a "Statement on genome editing technologies",[9] in which it declared itself "convinced that the Oviedo Convention provides principles that could be used as reference for the debate called for at international level on the fundamental questions raised by these recent technological developments" and agreed, as part of its mandate, "to examine the ethical and legal challenges raised by these emerging genome editing technologies, in the light of the principles laid down in the Oviedo Convention". This work is ongoing, and could possibly lead to an amendment of the convention, as is foreseen in its Article 32.

9. The Parliamentary Assembly started working on the issue at hand more than thirty years ago, and adopted two texts: Recommendation 934 (1982) on genetic engineering and Recommendation 1512 (2001) on the protection of the human genome by the Council of Europe.

10. The United Nations Educational, Scientific and Cultural Organization (UNESCO) has provided several related recommendations on the issue, including the Universal Declaration on the Human Genome and Human Rights in 1997, the International Declaration on Human Genetic Data in 2003, and the Universal Declaration on Bioethics and Human Rights in 2005.[10] Indeed, UNESCO's International Bioethics Committee has proposed a moratorium on germline applications and hereditary modifications.[11]

11. Shortly thereafter, an international group of scientists meeting in Washington in December 2015 for the "International Summit on Human Gene Editing" also called for a moratorium on making inheritable changes to the human genome. The meeting was 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.[12]

12. Finally, there are national regulations, although very few countries legislate on new technologies, mainly because technology is moving at a faster pace than regulators can keep up with. However, the consequence of the lack of regulation is the absence of technology control. Often, the actors involved "auto-regulate" the technology, which jeopardises the accepted principle of the need for control by an independent (and transparent) authority.

13. Most recently, the Committee on Human Gene Editing of the US National Academy of Sciences and the National Academy of Medicine finalised a report on "Human Genome Editing: Science, Ethics, and Governance" which includes a number of principles and recommendations for governance of human genome editing,[13] which may come to set the *de facto* global standard in time. Concomitantly, the European Academies' Science Advisory Council (EASAC) also finalised a report on "Genome editing: scientific opportunities, public interests and policy options in the European Union", setting out different policy recommendations, especially regarding human germline (heritable) genome editing.[14]

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8. The convention can be interpreted in a way that such a transfer could be allowed if the intervention seeking to modify the human genome is undertaken for preventive, diagnostic or therapeutic purposes, and it is not its aim to introduce any modifications in the genome of any descendants, but this interpretation is not supported by the convention's explanatory report.

9. DH-BIO/INF(2015)13 FINAL.

10. There are also other international codes of conduct in the field of clinical research and bioethics, such as the Declaration of Helsinki of the World Medical Association on Ethical Principles for Medical Research Involving Human Subjects, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organisations of Medical Sciences.

11. Report of the UNESCO International Bioethics Committee on Updating Its Reflection on the Human Genome and Human Rights, October 2015.

12. The academies have no regulatory power, but their moral authority on this issue seems very likely to be accepted by scientists in most or all countries. Nicholas Wade for the *New York Time*s, "Scientists Seek Moratorium on Edits to Human Genome That Could Be Inherited", 3 December 2015, www.nytimes.com/2015/12/04/science/crispr-cas9-human-genome-editing-moratorium.html?_r=0.

13. A pre-publication copy of the report is available via the website of The National Academies Press, www.nap.edu. All references to the report are based on this copy, downloaded on 24 February 2017.

14. www.easac.eu/home/reports-and-statements/detail-view/article/genome-editi.html. The Federation of European Academies of Medicine (FEAM) has also just published the report of a 2016 workshop on "Human Genome Editing in the EU" held at the French Academy of Medicine (in which I had the honour of taking part), and which contains interesting information on applicable EU regulations and discussions on different interpretations of the Oviedo Convention. www.interacademies.net/File.aspx?id=31273.

2.2. State of the developments of the use of new genetic technologies on humans

14. The human genome is the complete set of DNA within the 23 chromosome pairs in cell nuclei and in a small DNA molecule found within individual mitochondria. After the mapping of the human genome was completed in 2003, approximately three billion bases of the DNA code were analysed, and around 20 000 human genes were identified and mapped (using bioinformatics and experimental research). However, there are still many gaps in the sequence, and the function of many genes is totally unknown, including the basic gene regulation for growing and reproducing cells.[15]

15. A genetic disease is any disease that is linked to an abnormality in an individual's genome. Some genetic disorders are inherited from the parents, while other genetic diseases are caused by acquired changes or mutations. The defect will only be passed down if it occurs in the germline. Over 4 000 human diseases are caused by single-gene defects with recognisable patterns (autosomal dominant, autosomal recessive, and X-linked), but the majority of diseases are related to the implication of several genes and the influence of the environment.

16. The recent development of a new technology, CRISPR-Cas9, a genome editing tool, has made it possible to edit DNA faster, more cheaply and more accurately than with previous such techniques.[16] It acts like "molecular scissors" in a "specific" place of the DNA, and it is supposed to excise a gene mutation which can then be replaced by the correct genetic sequence. However, while the excision is quite effective for a target gene, the homologous recombination step that happens later in the reproduction of the cells is more critical to repair than the defective gene, leading to potential problems of accuracy with unintended consequences (so-called "off-target" effects).

17. In the case of (rare) genetic diseases linked to the maternal inheritance of mitochondrial diseases, mitochondrial replacement therapy has been used to avoid passing down such diseases. There are two ways: pronuclear transfer technology[17] and maternal spindle transfer.[18] 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.

18. The first baby with genes that came from pronuclear transfer (the three parents technique) was recently born in Mexico,[19] the second in Ukraine.[20] The United Kingdom became the first country in the world, as of 29 October 2015, to permit such babies to be born from pronuclear transfer technology[21] (while in the United States it is completely forbidden), and has also licensed the research use of embryos that have been genetically modified (by gene editing).

19. New technology is also blurring the previous strict dichotomy of somatic and germline cells, as somatic cells can now be reprogrammed into pluripotent stem cells, and possibly in the future further into gametes. Changes can even be made with a combination of *in vivo* and *in vitro* technology, leapfrogging conventional approaches in relation to *in vivo* gene therapy.[22]

20. Similarly, there is a problem with the blurring of the lines between basic and applied research in genetics. There used to be a great difference between basic research in the laboratory or on embryos, and clinical trials with applications leading to pregnancy and the birth of a child. In the past, new genetic

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15. Design and synthesis of a minimal bacterial genome, Clyde A. Hutchison et al., *Science*, March 2016.
16. The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) are sections of genetic code containing short repetitions of base sequences followed by spacer DNA segments. The CRISPR associated protein 9 (Cas9) is an endonuclease, a synthetic guide RNA to introduce a double-strand break at a specific location within the genome.
17. This technology creates an embryo containing the pronuclear DNA of the intended parents and the healthy mitochondria from the female donor's egg (implying the creation of two embryos).
18. With this technology, the nuclear DNA of a donor egg is removed, leaving the healthy mitochondria, and is replaced with the nuclear DNA from an egg of the woman with a mitochondrial disease, and then the fertilisation is performed (this creates only one embryo).
19. "World's first baby born with new '3 parent' technique", *New Scientist*, September 2016, https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/.
20. Worryingly, this highly experimental technique was used in Ukraine for an infertile couple with no mitochondrial disease. See BBC report of 18 January 2017, "IVF: First three-parent baby born to infertile couple".
21. The first UK licence to create such a "three-person baby" was granted by the fertility regulator in March 2017; the procedure could be offered by the Newcastle clinic concerned as of summer 2017. See article in the *Guardian* of 16 March 2017 by Ian Sample, "First UK licence to create three-person baby granted by fertility regulator".
22. Cells from patients are isolated, genetically modified in the laboratory with CRISPR-Cas9, and then re-injected into the patient (this has the advantage of checking the changes before reintroducing the cells). Other alternatives include generating normal sperm from abnormal ones via tissue culture and gene editing.

technologies were only used in very developed countries, but today biotechnology is more accessible, low-cost and makes inserting, removing, and editing human genes much easier. Also, with globalisation, it is possible for patients and scientists to travel easily to private clinics in countries without (strict) bioethics regulations.

21. In May 2015, a first paper was published using genome editing (CRISPR-Cas9) on non-viable human embryos in China.[23] February 2016 saw the world's first endorsement of a national regulatory authority for research on human embryos using genome editing, in the United Kingdom.[24] In the United States, the National Institute of Health decided, however, not to fund any use of gene-editing technologies in human embryos.[25] But all this demonstrates how human germline gene modification is starting to move out from the theoretical field to clinical research applications.

22. As regards future developments, pre-implantation genetic diagnosis is generally used to avoid the transfer of embryos carrying a genetic disease to the uterus, but it cannot be used in all cases.[26] In those cases, in order to prevent passing the defect mutation to further generations, a new technology may be required for treatment purposes.[27]

3. The potential benefits and risks of new genetic technologies

23. There are many possible positive uses of new genetic technologies, which could be applied to infectious diseases stemming from viruses, bacteria, prions and fungi (for example by making cells resistant to infection by Hepatitis B and HIV). Also, in relation to the fight against vectors of diseases like zika or malaria, there are already several developments which aim to stop the reproduction of certain types of disease-carrying mosquito. In oncology, a new type of advanced therapy using specific immune cells reprogrammed to target and kill cancer cells looks promising. Add to this the use of patient-specific induced pluripotent stem cells (undifferentiated cells which can differentiate in any given direction) in combination with genome editing, which offers unique opportunities for developing personalised disease models for research.

24. There are also many promising uses for the CRISPR-Cas9 technology:[28] the therapeutic potential would combine the latest technological developments in the field of stem cells and future clinical applications. The use of patient-specific induced pluripotent stem cells (iPSCs) in combination with bioengineering advances and genome editing offers unique opportunities for developing personalised disease models and tissues for regenerative medicine.

25. However, unwanted and inaccurate (off-target) mutagenesis is a major concern, because this may produce cancer or rare and unknown diseases. This risk may be minimised by optimising the procedure in the future, but even small changes can be very dangerous for the patient and future generations, with unknown consequences. “Mosaicism”, the presence of two or more populations of cells with different genes, can also create several problems, including rare diseases, as well as practical problems related to the DNA identification for diagnosis, paternity tests and forensic identification.

26. The problem of the impact of the genetic modification of human germline cells is that it may not be fully known until a certain number of generations have inherited these mutations. There are also risks concerning future generations arising from patients who have the new genetic condition and who reproduce amongst themselves, due to the creation of a variety of unknown combinations of genes.

27. The scientific call for a moratorium on the gene editing of embryos leading to pregnancy[29] concluded that it would be “irresponsible to proceed”, until the risks were better understood and that there was “broad societal consensus” about the research – and also because, up to now, we lack precise knowledge about many genes. This position was recently confirmed once more by both the US National Academy of Sciences and National Academy of Medicine and EASAC. Additionally, so far there are no clinical trials of somatic

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23. CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes, Puping Liang et al., *Protein & Cell*, May 2015.
24. UK scientists gain licence to edit genes in human embryos, Team at Francis Crick Institute, Ewen Callaway, *Nature*, February 2016.
25. Statement on NIH funding of research using gene-editing technologies in human embryos, Francis S. Collins, April 2015.
26. Both parents are affected with a disease of autosomal recessive inheritance.
27. The severity of the disorder and the feasibility and predicted success of treatment based on animal models will define the strategy for the research.
28. Such as getting induced pluripotent stem cells.
29. See paragraph 12.

genetic correction *in situ* using the newest gene editing techniques. The gene therapy research and clinical trials with thousands of studies running every year worldwide have not yet succeeded in determining survival rates and life expectancy outcomes.

28. Future regulation depends on the respective context and aim pursued, not solely on the presumed ontology of the cell or tissue.[30] The physiological regulation of the changed genes and the role of epigenetics must be considered. There are changes in gene expression (active versus inactive genes) that do not involve changes to the underlying DNA sequence (like in gene editing technology). Furthermore, changing genes may provide only temporary inhibition of certain functions.

29. In addition, there are grave concerns about possible misuse and abuse of the technology with the intention to produce individuals or entire groups endowed with particular characteristics and required qualities.[31] Germline gene therapy could lead to the acceptance of gene therapy for genetic enhancement – which could lead, in turn, to the spectre of eugenics (genetic selection in order to improve genetic traits). I believe history has taught us where this may lead.

30. Since 1980, it is possible to patent micro-organisms under international agreements. In fact, even during the genome project, the human DNA was intended to be patented. In a landmark decision in June 2013, the Supreme Court of the United States determined that DNA in its natural form cannot be patented,[32] but patents of procedures detecting certain human genes, even the ones able to produce cancer, are possible. There are several cases in court, taking many years to resolve, on claims for intellectual property rights regarding technologies identifying (only the patent holder has the right to sequence that DNA) or changing the human genome, including the controversy regarding the patenting of the CRISPR-Cas9 technology itself.[33]

31. Although this is beyond the focus of this report, I would like to comment in passing that the use of genetic technology in animals and plants indicates a worrying commercial interest with possibly grave environmental consequences[34]. At the moment, public investment in this technology is providing benefits to small public entities or to private companies instead of to society as a whole. Multiple patent-holder claims across the genome are stopping the translation of genetic discoveries into health care benefits, compromising the accessibility and affordability of high-quality health care, which has human rights implications.

32. In addition, there is a natural tendency for scientists to want to be the pioneers of genetic technology developments, to endeavour to publish papers thereon and to reap economic benefits from their research (for example by participating in technological companies). This raises the question of possible conflicts of interest. In my opinion, science provides knowledge, but it should not be left to scientists alone to decide on research policies (for example on where to set the limits of such research) and how the research is used.

33. It is often argued that full transparency in research and clinical trials would compromise patient confidentiality and intellectual property rights. While patient anonymity must be respected, medical knowledge should be published and shared, also in this field. It is, in fact, one of the difficulties of the "gene editing" technology that it is impossible to identify that changes have been made artificially. This creates not only a problem regarding the treatment of patients with genetic changes, but also of traceability in animals and plants.

34. Research on animals is mostly performed on mice, but most of the recent advances in genetic technology have not yet even been tested on apes or primates (who share 96% of common DNA with human beings, but also have 40 million differences). Instead, research has jumped directly to research on patients or human embryos. Furthermore, there is a lack of experience in animal research, and the tendency to stop animal research continues to create a barrier in the field of genetics. However, it may be necessary to

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30. "I bet you won't": The science–society wager on gene editing techniques, EMBO reports, Matthias Braun and Peter Dabrock, February 2016.

31. In this way, it would even be possible to "weaponise" the use of new genetic technologies in humans, for example by lowering the need for sleep in soldiers.

32. US National Human Genome Research Institute, Intellectual Property and Genomics, https://www.genome.gov/19016590/intellectual-property/.

33. On 15 February 2017, the Patent Trial and Appeal Board (PTAB) of the US Patent and Trade Mark Office (USPTO) delivered judgment in the interference proceedings between the University of California Berkeley (UCB) and the Broad Institute of MIT and Harvard (the Broad). However, this decision is subject to appeal, and does not bind the European Patent Office (EPO), where similar proceedings are pending. www.lexology.com/library/detail.aspx?g=b2ebd517-92d9-4bf1-90b3-a1d80a7c1677.

34. There are chapters on genome editing in plants and animals in EASAC's March 2017 report.

increase animal research in the genetic field in order to avoid consequences dangerous to humans. On the other hand, research on animals and human embryos alike have the drawback of not allowing a thorough analysis of possible consequences on psychological and behavioural characteristics of genetic modifications.

4. The need for international regulation and respect of the precautionary principle

35. The Asilomar Conference on recombinant DNA, held in California in 1975, and led by the United States, discussed potential biohazards, as well as possible regulation. It was the first time that genetic dangers were brought into the arena for public debate. At the time, the Conference focused on the study of the biohazards and made recommendations about the necessary containment of research on hybrid DNA – but those recommendations were made without a prior political, independent, pluridisciplinary, balanced, and transparent assessment, which would have been desirable.

36. The scientific community has so far agreed on two arguments regarding interventions on the human genome: safety concerns, mainly due to the off-target effects of gene editing (i.e. affecting other genes), and human rights concerns, in particular with respect to the effects on future generations (changing the genome means changing the common heritage of humanity). However, so far, international regulation is sorely lacking.

37. In 4th century BC, Hippocrates established the idea of “to help and do no harm”. The basic principles of bioethics are nonmaleficence, beneficence, respect for autonomy and justice. It is important to explain that the autonomy of the patient is mainly linked to informed consent (absent in the case of future generations) and also the principle of justice (equity of access to treatment) which is linked to fair treatment. Other bioethical principles have been developed regarding health care, like equity and accessibility to new technology, the responsibility of scientists and health professionals, the confidentiality of patient information and the necessary compensation in cases of harm. All of these principles should be balanced with each other, as in the Council of Europe Oviedo Convention.

38. The Committee of Ministers and the Parliamentary Assembly agree that it is necessary to advocate “a culture of precaution incorporating the precautionary principle into scientific research processes, with due regard for freedom of research and innovation”.[35] In this context, the Committee of Ministers recalled in 2008 the undertakings given by the Heads of State and Government of the Council of Europe in the Final Declaration of the 3rd Summit of the Council of Europe to “ensure security for our citizens in the full respect of human rights and fundamental freedoms” and to meet, in this context, “the challenges attendant on scientific and technical progress”.

39. The European Union defines the precautionary principle as enabling a rapid response through preventative decision taking in the case of risk, such as a possible danger to human health, in particular where scientific data does not permit a complete evaluation of the risk.[36] Zero risk does not exist, which is why measures must be proportionate to risk in accordance with the precautionary principle. Due to the lack of evidence-based knowledge regarding the consequences of new genetic technologies, the risk calculation in this area is, however, quite difficult. Nevertheless, any regulation in this area should apply the precautionary principle rather than the prevention principle,[37] which does not go as far in protecting against possible dangers.

40. On this point it is very helpful to have advisory bodies, such as national academies, colleges of scientists or others, able to undertake risk assessments of possible uses of the technology, considering the consequences for the newborn babies, future generations, patients themselves or the environment. Such risk assessments should be made public, also in order to highlight certain dangers and the limits of the research.

41. Unfortunately, this is not what is happening today: A Chinese group has had the first clinical trial approved using the revolutionary CRISPR–Cas9 technique.[38] They modified immune cells *in vitro* to attack cancer cells, but these changes to the cell genome will not pass on to the next generation, meaning that any side effects (e.g. attacking normal cells) will impact only the patient. The United States is following the approval procedure for a similar clinical trial through an advisory panel of the US National Institute of Health,

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35. See Assembly Recommendation 1787 (2007) on the precautionary principle and responsible risk management, and the Committee of Ministers’ reply thereto (Doc. 11491), in particular paragraph 4 of the latter.
36. The precautionary principle is detailed in Article 191 of the Treaty on the Functioning of the European Union.
37. This principle is not as far-reaching as the precautionary principle, but it also foresees not only repairing damages after they have occurred, but to prevent those damages occurring at all. However, the prevention principle doesn’t contain the same notion of risk assessment, in particular in cases where the risk is not clearly defined. The United States applies the prevention principle only.
38. CRISPR gene-editing tested in a person for the first time, *Nature*, November 2016.

which already approved the project, the US Food and Drug Administration (FDA) and the license of the University Review Board. However, China mainly follows the hospital internal review board system for approval, without due transparency or respect for human rights. There is a very real danger that countries are running a race to be the first, without considering the human rights perspective, bioethical analysis or possible consequences.

42. In Europe, some countries have special committees dealing with reproductive medicine: for example, in the United Kingdom, the Human Fertilization and Embryology Act created the Human Fertilization and Embryology Authority (HFEA) in 1990, which gives legal answers to scientific progress. Few other countries have a national body regulating new scientific developments, or specific legislation on gene editing.[39]

43. The report on "Human Genome Editing: Science, Ethics, and Governance" of the Committee on Human Gene Editing of the US National Academy of Sciences and National Academy of Medicine[40] proposes seven overarching principles which should "undergird the oversight systems, the research on, and the clinical uses of human genome editing": promoting well-being, transparency, due care, responsible science, respect for persons, fairness, and transnational co-operation[41]. While it is difficult to disagree with these principles (except that other principles of equal or higher importance in my view are missing, such as a human rights perspective and the precautionary principle), their application to the field of "heritable genome editing" leads to more questionable recommendations. The report concludes, for example, that "[h]eritable germline genome editing trials must be approached with caution, but caution does not mean they must be prohibited"[42], and thus formulates recommendations on what is entailed by a "robust and effective regulatory framework" which should permit clinical trials using heritable germline genome editing. However, the Committee on Human Gene Editing itself admits that "it would be surprising if everyone were to agree with this recommendation".[43] Indeed, the President of EASAC has categorised these recommendations as "controversial", and requiring "considerable further public engagement by the scientific and medical communities to debate issues and perspectives".[44]

44. Interestingly, the final criterion of the recommendation (5-1) is "reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition"[45]. Again, the Committee admits that there are "those who think the final criterion … cannot be met, and that once germline modification had begun, the regulatory mechanisms instituted could not limit the technology to the uses identified in the recommendation". Indeed, the committee concluded that if it were not possible to satisfy the criteria in the recommendation, in the committee's view "germline genome editing would not be permissible".[46]

45. The committee also admitted that heritable germline genome editing "also raises concerns about premature or unproven uses of the technology", and thus the emergence of "regulatory havens" that would "tempt providers or consumers to travel to jurisdictions with more lenient or non-existent regulations to undergo the restricted procedures". The committee, in consequence, highlights the need for comprehensive regulation[47] – which, I would argue, would ideally be international, and based on a Council of Europe model.

46. As regards the possible clinical use of germline interventions, EASAC comes to a similar conclusion: "These applications pose many important issues including the risks of inaccurate or incomplete editing, the difficulty of predicting harmful effects, the obligation to consider both the individual and future generations who will carry the genetic alterations, and the possibility that biological enhancements beyond prevention and treatment of disease could exacerbate social inequities or be used coercively. It would be irresponsible to proceed unless and until the relevant ethical, safety and efficacy issues have been resolved and there is broad societal consensus."[48]

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39. Editing policy to fit the genome?. R. Isasi et al., *Science*, January 2016.
40. See paragraph 14.
41. Pre-publication copy downloaded on 24 February 2017, pp. 139-140.
42. Recommendation 5-1, ibid., p. 145.
43. Ibid., p. 145.
44. Foreword by Thierry J-L Courvoisier to the March 2017 EASAC report on genome editing, p. 1. The report's chapter on "slippery slope, risk and proportionality" also seems relevant in this respect (pp. 21-22).
45. Ibid., p. 145.
46. Ibid.
47. Ibid.
48. March 2017 EASAC report on genome editing, pp. 2-3.

5. Conclusions and recommendations

47. Genetic sciences are developing quickly, but we are only just beginning to understand them, with much research trying to find out the genetic functions and possible treatments for genetic and hereditary diseases. We need to evaluate the possible risks and consequences of the application of these new technologies through a pluridisciplinary, independent, balanced, transparent and political assessment. The general public needs to be properly informed in order to have a broad public debate on the state of scientific knowledge regarding new genetic technologies. Human rights, including bioethical principles, the rule of law and democratic principles should be an integral part of this debate.

48. Specific and independent bodies (with the necessary knowledge on the new developments in science) should advise parliamentarians, the regulatory authorities and public institutions. Member States should develop a clear position on the practical use of new genetic technology, setting the limits and promoting good and accountable practices in full respect of the precautionary principle. The absence of regulation should not be an option. It would be appropriate to take a position (including preventive measures) sooner rather than later, otherwise technologies will be widely applied without appropriate analysis.

49. There is an explosion of genetic studies and information on "big bio-data" that needs to be better understood before being applied to human reproductive cells or to newborn babies, with unknown consequences. To create an embryo with a genome modification and to transfer it into a womb cannot yet be considered a safe practice. Humans should not be used as experimental entities without there being an existing knowledge of the consequences following tests on animals, because there is not enough research and animal experiment experience using new genetic technology. The current self-declared and self-imposed moratorium on making inheritable changes to the human genome should thus be upheld. In States which do not yet have a *de jure* moratorium or a ban in place, this moratorium should be included in legislation/ regulation on the matter, in order to ensure that it is the State (rather than an individual scientist or a group of scientists) which has the power to lift that moratorium. Unfortunately, with the pace of scientific progress, this may be unrealistic.

50. Arguably, deliberate germline editing in human beings would cross a line viewed as ethically inviolable. However, I do not believe we are going to be able to agree amongst ourselves on whether there should be only a moratorium or rather a ban on the deliberate use of germline editing in human beings, as proscribed in the Oviedo Convention. However, the current prohibition on interventions aimed at modifying the germline in human beings in all European[49] and many Council of Europe member States is not going to stop genome-edited babies from being born elsewhere. The US National Academy of Sciences and National Academy of Medicine have recently enunciated a number of principles and recommendations for governance of human genome editing. These may in time come to set the *de facto* global standard, if Europe cannot offer a better alternative.

51. I believe that an international legal framework is necessary to set the limits and complement national legislation/regulation, and that Europe should lead the way with a common regulatory and legal framework which is able to balance the potential benefits and risks of these technologies with the aim of enabling the eradication or cure of serious diseases, while preventing abuse or adverse effects of genetic technology on human beings. The Council of Europe is the ideal organisation to develop this framework, which – if sufficiently compelling and widely accepted in Europe –, may well become the global standard.

52. A fifth of the human genome is subject to patent claims, generating a huge barrier for research, diagnosis and therapeutic use. We need new legislation to prevent intellectual property rights being recognised in relation to the identification and modification of the human genome. Public investment in this technology is providing benefits to small public entities or to private companies instead of to the whole of society, while human sciences and medicine should be an open source of shared knowledge. The public interest should prevail over the interests of third parties, while taking into consideration the danger of "sacrificing" individuals for a perceived common good.

53. I thus believe that the Parliamentary Assembly should recommend a five-step approach to the Committee of Ministers which is compatible with the divergent views in and amongst the Council of Europe's 47 member States while assuring an outcome which is consistent with Council of Europe values and principles. Step 1 would be to urge those member States which have not yet ratified the Oviedo Convention to do so without further delay, or, as a minimum, to put in place a national ban on establishing a pregnancy with germline cells or human embryos having undergone intentional genome editing.

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49. Ibid., p. 23.

54. Step 2 would be to foster a broad and informed public debate on the medical potential and possible ethical and human rights consequences of the use of new genetic technologies in human beings, so that there is a fact-based and democratic basis for Step 3 – an assessment by the Council of Europe Committee on Bioethics of the ethical and legal challenges raised by emerging genome editing technologies, in the light of the principles laid down in the Oviedo Convention and the precautionary principle.

55. Step 4 would be the development by the Council of Europe of a common regulatory and legal framework which is able to balance the potential benefits and risks of these technologies with the aim of enabling the eradication or cure of serious diseases, while preventing abuse or adverse effects of genetic technology on human beings. Finally, Step 5 would hand the power back to the member States, on the basis of the public debate, the assessment of the Committee on Bioethics and the common regulatory and legal framework devised, to develop a clear national position on the practical use of new genetic technologies, setting the limits and promoting good practices. The only challenge will be time, which is not on our side.