Deutscher Ethikrat

Germline intervention in the human embryo: German Ethics Council calls for global political debate and international regulation

AD HOC RECOMMENDATION

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The technical opportunities offered by genome editing (for example the CRISPR-Cas9 method) raise complex and fundamental ethical questions particularly where they are used to modify the human germline. Last year there was still by and large agreement – for instance at the annual conference of the German Ethics Council devoted to this topic – that there would be sufficient time for the necessary thorough and comprehensive reflection since applications in humans were still far away from actual implementation. Recent developments, however, demonstrate that, in this particularly sensitive area, research has advanced far more quickly than expected and precedents are being created at least in some countries. As, however, this touches not only on national interests but also on the interests of mankind as a whole, there is a need for broadly-based discussion and international regulation.

In August 2017 an international research group led by the Oregon Health & Science University in Portland (USA) published research findings on the germline treatment of a dominant hereditary disorder in the earliest stage of human life.[1] The goal of the researchers was to correct a gene defect which causes a serious hereditary myocardial disease using what is known as genome editing ("genetic scissors"). The genome editing was done as part of artificial fertilisation. According to the researchers, the sperm cells used to produce the embryos carrying the disease gene came from an adult cardiomyopathy patient whose disease is treated in the usual way, with a defibrillator and medication.

Already in April 2015 and April 2016 Chinese research groups had published the results of experiments involving the correction, by means of genome editing, of a genetic predisposition for the blood disorder thalassemia in human embryos[2], and the generation of genetic resistance to HIV[3]. In comparison to these experiments, however, the American-Chinese-South Korean consortium of scientists around the US-American stem cell researcher, Shoukhrat Mitalipov, have since reported far better results. Mitalipov's group observed that the proportion of what are known as mosaic embryos – embryos in which the desired genetic modification could only be implemented in some of the cells – could be considerably reduced. Furthermore, there were no unintended (off-target) modifications in other genes in the, albeit, few embryos examined.

Although the results of the recent experiments have since become the subject of controversial debate[4], one thing is sure: these experiments are about the long-term goal of making in vitro treatment possible in the earliest stage of human life by means which will also correct the embryo's sperm and/or egg cells and thereby allow the modifications to be passed on to potential progeny. In other words, this research will lead to modifications to the human germline which are as precise and effective as possible and are undertaken systematically and intentionally. They are, therefore, to be judged in a morally different way to random mutations that are tolerated as side effects of, for instance, chemotherapy or radiotherapy.

Even if the embryos used in the current study were produced specifically for this purpose in order to demonstrate the viability of the method used, and were destroyed afterwards, the implications of this kind of genetic manipulation in humans are considerable. At the present time, they can only be surmised and elude the predictive power of scientific studies. More even, for the first time in the history of science, medical procedures are to be developed and perhaps applied which will affect not only an adult who is able to give his or her informed consent or – and this is already ethically controversial – a born or unborn child who is not yet able to give his or her informed consent but also generations of an indeterminate number of still to be conceived progeny.

These intentions give cause for intensive reflection. This also and particularly applies if the results might not yet be ready for application. In this context, the first Chinese research activities attracted major attention not only in the global scientific community but also, for a short period of time, amongst the general public. This triggered an intensive factual and broadly led debate about the scientific and social implications of experiments of this kind. Leading researchers, even those who are usually willing to push the boundaries of research into areas prohibited elsewhere, advocated caution and moratoria on the application of genome editing in human embryos.[5] In October 2015 the UNESCO International Bioethics Committee called on the member states to agree on a joint moratorium on germline modification by genome editing.[6] Civil society organisations and religious representatives were also concerned about the intention to systematically intervene in the human genome.

1 Ma, H. et al. (2017): Correction of a pathogenic gene mutation in human embryos. *Nature*, 548 (7668), 413-419. The disease is MYBPC3-associated cardiomyopathy; the numerous different forms of hereditary myocardial diseases affect, in total, around one in 500 people.

2 Liang, P. et al. (2015): CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein & Cell*, 6 (5), 363-372.

3 Kang, X. et al. (2016): Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. *Journal of Assisted Reproduction and Genetics*, 33 (5), 581-588.

4 Egli, D. et al. (2017): Inter-homologue repair in fertilized human eggs? *bioRxiv*, DOI: 10.1101/181255.

5 Lanphier, E. et al. (2015): Don't edit the human germline. *Nature*, 519 (7544), 410-411; Baltimore, D. et al. (2015): A prudent path forward for genomic engineering and germline gene modification. *Science*, 348 (6230), 36-38.

6 International Bioethics Committee (2015): Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights. http://unesdoc.unesco.org/images/0023/002332/233258E.pdf [2017-09-18].

The open questions were discussed internationally in a diverse manner.[7] In Germany, for example, the Berlin-Brandenburg Academy of Sciences and Humanities[8] published an opinion in July 2015 as did, in September 2015, the German National Academy of Sciences Leopoldina together with the German Research Foundation, the National Academy of Science and Engineering and the Union of the German Academies of Sciences and Humanities.[9] The German Ethics Council extensively discussed the ethical challenges posed by this topic at several public meetings and in a close exchange with other national ethics committees.[10] On the international level the debate reached an initial milestone at the International Summit on Human Gene Editing ("Washington Summit") in December 2015. It is worth noting that the lead organisers were the national science academies in those countries that use genome editing in embryo-consuming research particularly intensively at present and will surely continue to do so in the future: the USA, the United Kingdom and China. Contrary to some expectations no moratorium was announced in the final statement; reference was merely made to the considerable remaining risks and the regulatory ambiguities – up to the level of international law – which would constitute obstacles to clinical germline interventions.[11] However, there was also no likelihood of clinical use in the foreseeable future: the risks still seemed to be uncontrollable in the long term and the chances of success too limited. Furthermore, in many countries pre-implantation genetic diagnosis offers an – albeit itself controversial – alternative of preventing the propagation of severe hereditary disorders in individual cases.

This guarded evaluation of genome editing for the purpose of germline intervention was also the tenor of numerous statements given at the annual conference of the German Ethics Council in June 2016. On that occasion the Ethics Council deliberately chose to discuss genome editing in the format of a large public event, under the title "Access to the human genome. New possibilities and their ethical evaluation".[12] The broadly shared evaluation that, in moral terms, this was a highly controversial technology that was, however, still far away from application, probably contributed to the marked cooling down of the, at times, heated debate on the topic of genome editing of the human germline amongst the public at large and in the scientific community.

Against this backdrop, the recommendations drawn up in February 2017 by a committee jointly convened by the US National Academy of Sciences and National Academy of Medicine appear surprising[13]. They advanced, for instance, the hypothesis that germline interventions, within strictly regulated risk limits and when coupled with accompanying research on the risk, were ethically defensible if the intervention constituted "really the last reasonable option" for a couple of having their own healthy, biological child, commented committee co-chair Alta Charo.[14]

The report reveals a subtle but, at the same time, important shift in the evaluation of ethical accountability. It switches from "not allowed as long as the risks have not been clarified" to "allowed if the risks can be assessed more reliably". It is clear that the US-American academies are no longer focusing on a partially fundamental, partially risk-related strong rejection of germline therapy by genome editing but on a fundamental permission guided by individual formal and material criteria. The most recent study of the consortium around Oregon University from August 2017 on germline therapy can already be interpreted as an expression of this change in attitude. It was not preceded by any extensive debate amongst the general public in which agreement would have been reached on the fundamental permissibility of germline interventions, despite the Washington Summit having expressly called for this type of discussion. Apparently, speculations now concentrate less on whether but rather only on when the first human genetically modified by genome editing will be born.

It is noticeable that policymakers on the national and international levels are adopting a cautious stance when it comes to the demand made in almost all statements – up to the Washington Summit – for broad public debate and for necessary regulations. At the Washington Summit, for instance, the prevailing attitude was that intervention in the human genome could not

7 Cf. by way of example, the discussion process of the British Nuffield Council on Bioethics on https://nuffieldbioethics.org/project/genome-editing.

8 Berlin-Brandenburg Academy of Sciences and Humanities (2015): Human genome surgery – towards a responsible evaluation of a new technology. https://edoc.bbaw.de/files/2486/2015_Analysis_HumanGenomeSurgery.pdf [2017-09-18].

9 German National Academy of Sciences Leopoldina et al. (2015): The opportunities and limits of genome editing. https://www.leopoldina.org/uploads/tx_leopublication/2015_3Akad_Stellungnahme_Genome_Editing.pdf [2017-09-18].

10 Event overview and details on http://www.ethikrat.org/themen/forschung-und-technik/genomforschung-genomeditierung and https://www.globalsummit-berlin2016.de/programme and https://www.bka.gv.at/-/treffen-der-deutschsprachigen-nationalen-ethikkommission.

11 National Academies of Sciences, Engineering, and Medicine (2015): On Human Gene Editing: International Summit Statement. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a [2017-09-18].

12 Event details on http://www.ethikrat.org/veranstaltungen/jahrestagungen/zugriff-auf-das-menschliche-erbgut.

13 National Academies of Sciences, Engineering, and Medicine (2017): Human Genome Editing: Science, Ethics, and Governance. Washington, D.C.

14 Kaiser, J. (2017): U.S. panel gives yellow light to human embryo editing. *Science*, DOI: 10.1126/science.aal0750.

be regulated solely on the national level but should also and primarily be regulated on an international level. This idea takes up the concept of the genome as the symbolic heritage of humanity – admittedly, a phrase of uncertain meaning in international law which has been coined emblematically in Article 1 of the "Universal Declaration on the Human Genome and Human Rights" of UNESCO from 1997.[15]

The hesitant attitude of policymakers towards genome editing might also stem from the experience in 2003 involving the failed efforts to globally outlaw reproductive cloning in a binding convention under international law. In Germany this caution can perhaps also be explained by the fact that here research of this kind is prohibited by the Embryo Protection Act and – notwithstanding the initiative by a group of scientists from the National Academy Leopoldina[16] – there is not thought to be any acute national need for action. The 35 countries that ratified the "Convention on Human Rights and Biomedicine" of the Council of Europe (Oviedo Convention), are also unlikely to see any pressing need for action as, pursuant to Article 13 of the Convention, interventions seeking to modify the human genome which also introduce modifications in the genome of descendants are prohibited.[17]

In contrast to reproductive cloning, the rapid advances over the last two years have moved genome editing much closer to application. This situation seems to carry far more urgency because of its potential consequences. Given the real application opportunities, there must be a debate about and a decision on whether systematic, transgenerational modifications to the human genome are to be prohibited or authorised and, if they were to be authorised in principle, the extent to which they would need to be limited by conditions and restrictions. For even though man intervenes time and time again in the highly complex fabric of evolution in an increasingly intensive, accelerating and irreversible manner and the current geological epoch is already and rightly being described as "Anthropocene", the genome nonetheless takes on a factually and symbolically special, even if not exceptional, role because of its impact on individual and collective self-images of mankind. Hence, despite its mutability and diversity, its modification cannot be evaluated on the basis of the common categories for the bearing of responsibility for consequences of human actions but requires more extensive reflection processes. As research is being conducted worldwide and has, therefore, global consequences, debates of this kind should not be limited to Germany. They must instead be conducted internationally beyond individual nations' initiatives.

Scientific research, the results of which could have such fundamental effects on humanity's self-image, must be embedded in society. It is not an internal affair of the scientific community. Nor is it a matter for one country alone – not just because research happens in international networks but, moreover, because the consequences of these research activities affect everyone. That is why the scientific community, in turn, must endeavour to engage in open-ended discussions with all relevant groups amongst the public at large. In parallel to this, the political institutions can and must find ways and initiate processes to discuss the numerous, as yet, unanswered questions and possible consequences of systematic genome manipulations through genome editing in an intensive, differentiated and, above all, global manner, and draw up the necessary regulatory standards as quickly and comprehensively as possible.

Before any further precedents are created, the consequences of which may become irreversible at some point, the decisive issues and problems, like the following ones, must be answered and clarified on all levels up to the politically constituted global community:

- What are the serious diseases for whose treatment germline intervention methods offer a realistic chance in the foreseeable future because they cannot be treated with traditional methods? What risks and perhaps harm can the individuals, who are the potential participants in the first relevant experiments, be expected to bear for the sake of the scientifically and medically valuable goals (like the treatment of those serious diseases)? To what extent can such risks and harm realistically be reduced or avoided? Does it make any difference whether an intervention is made in unfertilised gametes, germline cells or an embryo? What different considerations could possibly play a role here? To what extent do experiments of this kind once again raise the fundamental question about the moral and legal status of the embryo in vitro?
- The question must also be raised about where the boundary lies between calculable and not foreseeable, between justifiable and unjustifiable risks. The concept of acceptable risk must, therefore, be specifically determined for these interventions. Here, special consideration should be given to the scientific findings of system biology and epigenetics according to which gene activity depends on many factors and external factors, too, can influence gene function for

15 UNESCO (1997): Universal Declaration on the Human Genome and Human Rights. http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html [2017-09-18].

16 Bonas, U. et al. (2017): Ethical and legal assessment of genome editing in research on human cells. https://www.leopoldina.org/uploads/tx_leopublication/2017_Diskussionspapier_GenomeEditing.pdf [2017-09-18].

17 Council of Europe (1997): 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. https://rm.coe.int/168007cf98 [2017-09-18].

generations. A question of special relevance in this context is the role which the genome assumes both de facto and symbolically in the understanding of being human – without either succumbing to the simplifying assumptions of genetic determinism or qualifying the genome as a random biological system component. In Germany a special law, the Genetic Diagnosis Act, ascribes this kind of special status to the genome on the grounds that it contains particularly sensitive information about the affected individuals and their biological relatives, information which therefore merits special protection.

- Furthermore, what is the normative relevance of the circumstance that, in contrast to the usual practice for medical procedures or research projects, the persons who will be affected by the procedures cannot give their consent, because they have not even been conceived yet?
- There must also be discussion of whether pre-implantation genetic diagnosis is to be classified as a less problematic alternative because, while it prevents serious hereditary disorders by regularly discarding embryos, it does not, in contrast to gene manipulation, entail any comparable risks for possible later progeny. Under what circumstances could the therapeutic approach of genome editing, which theoretically does without embryo "discarding", outweigh these risks? And what is the role, in this context, of the consideration that (additional) pre-implantation genetic diagnosis would still be necessary for the foreseeable future in order to verify the success of genetic germline modifications?
- Which systematic germline modifications made possible by genome editing should be allowed? Should therapy during the earliest stage of human life – I.e. the avoidance and, ideally, complete healing of disease of the later individual – be restricted only to monogenetic diseases, or should the therapeutic goals be widened to include multifactorial hereditary disorders, too? The latter are far more common but their development is also far more complex. In order to markedly reduce the risk of these disorders by means of germline interventions, several genes would probably have to be manipulated at the same time.
- Another battery of questions has to do with whether the ethical assessment and a possible regulation of these technologies is impacted when they not only help to create therapies as options for medical treatment but also offer a tool for more far-reaching "improvements" of man (enhancement).
- This then raises the topic of accountability given the potential social and cultural consequences. Could germline modifications exacerbate social and health inequalities thereby bringing into play a weighty problem for social justice? Does the possibility of germline treatment alter the understanding and the practice of human reproduction if the genetic make-up of progeny can be actively shaped? Could this lead to social pressure on future parents to make use of these intervention options?
- Consideration must also be given on how to handle communication and regulation, given the fact that many people have major reservations about such profound and systematic intervention in an important part of the "naturally given" biological basis of humanity.
- Which (globally relevant) institution should make the decision about possible modifications to the genetic foundations of mankind? Beyond possible international regulations, is there an additional need for separate national regulations to accommodate, for instance, specific historical experiences or cultural peculiarities?

It is foreseeable that, given the cultural and ideological plurality, these questions will be discussed in a highly controversial manner and the individual answers given will differ markedly. Nonetheless, already the articulation and discussion of these questions is of enormous importance for the culturally pluralistic self-image of mankind. On the one hand, they should, therefore, be debated by local, regional and national groups and professional audiences. On the other hand, attention should also be drawn to them on a level in keeping with their global importance: the level of the politically organised world community in the shape of the United Nations. Different formats are possible: from a large international conference that could put across the message that genome editing for the purpose of therapeutically motivated germline modifications is, in principle, a question of global and not just scientific relevance, to the laying down of globally binding safety standards or even to possible resolutions or international conventions. Given the importance of this topic, the fact that this kind of process promises to be wearisome and cumbersome should not serve as an excuse to not take any initiatives of this kind at all.

The German Ethics Council will continue to intensively monitor research on possible genome editing interventions in the human germline and use this as the basis for further reflection. At the same time, it urgently recommends that the German Bundestag and the Federal Government take the initiative as soon as possible in the forthcoming legislative period to position the topic of possible germline interventions in humans also and above all on the level of the United Nations, and to work there towards implementing the measures outlined above (organisation and staging of an international conference and adoption of binding global rules or conventions under international law).

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