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Global Governance of Human Germline Editing: A Statement by the Marsilius Winter School Participants

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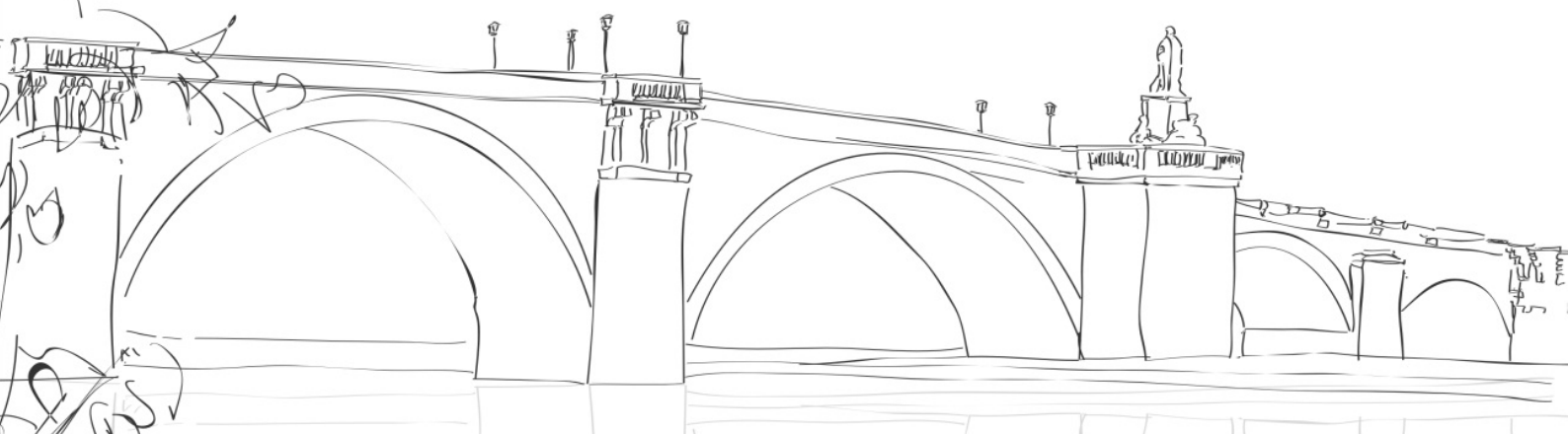

Global Governance of Human Germline Editing: A Statement by the Marsilius Winter School Participants

Author list[1]

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Abstract

Germline editing is a technique that holds immense potential to affect our current society and future generations. Not to be confused with somatic gene therapy, human germline editing involves the application of molecular biological methods, such as CRISPR/Cas9, to edit the genome of germline cells. These edits can then be passed on to future generations. While this technique is very promising to eradicate hereditary diseases and even possibly improve certain traits of the human genome, its use remains highly debated. "Global governance of human germline editing" was the topic of the Marsilius Winter School 2018, which brought together a group of young academics from a variety of disciplines to discuss the issues raised by the potential application of this technology.[3] In a one-week program, experts were invited to present on different aspects of germline genome editing and its governance to the participants of the winter school. The participants worked together to develop a joint position on global governance of human germline editing which is presented in this paper. Overall, a consensus was reached on advising to allow germline genome editing for research and possibly for medical applications under specifically defined circumstances, including an informed public opinion.

Main

Biomedical research has made considerable progress in the past few decades, clarifying the genetic basis of several human diseases and how inheritable genetic mutations influence the development of human pathologies. Genome editing, a technique that may be able to correct these mutations, is a promising approach for treating disease. In germline genome editing, a permanent change is introduced into the genome of a germline cell, leading to the inheritance of these edits by future

[1] This paper solely reflects the views and opinions of the winter school participants. The organizers and the scientific coordinators of the winter school were not part of the development of this statement and thus, do not subscribe to its content.

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[3] The winter school took place before the first claims of successful germline editing by Jian-kui He became public.

Generations.[4] However, this technique presents several risks. For example, unintended alterations of the DNA of the recipient could happen despite the increasing accuracy of the technique. Also, the societal consequences, resulting from the application of this technique, are unpredictable. Therefore, it requires thought and discussion from the legal, politic, ethical, and communication perspectives vis-à-vis the general society.[5]

In the present statement, we outline the requirements that should be met before proceeding with research on and medical application of human germline editing. Moreover, we propose to stimulate public engagement and develop clear regulations able to reflect the multifaceted implications of this technique, and that consider the societal and cultural differences worldwide. Together, we agreed on the fact that germline genome editing should be allowed for research, and possibly for medical applications, under certain strict circumstances.

Over 10,000 inheritable, monogenic diseases cause critical health issues to individuals and place a massive burden on healthcare systems.[6] Although some approved treatments relieve disease symptoms, there is no cure, i.e. the removal of disease cause, for most hereditary genetic diseases yet available.[7] The rapid development of germline genome editing technology, including preliminary, but seminal experiments that attempted to edit the human genome in human germ cells,[8,9] may lead to the ability to correct these disease-causing genetic mutations in human germline cells.[10] In order to find out whether this prediction proves correct and to know if the technology could ever have this capability, we believe that the medical community ought to be able to perform genome editing research on embryos.

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[4] c.f. Deborah M. Thurtle-Schmidt and Te-Wen Lo: *Molecular biology at the cutting edge: A review on CRISPR/CAS9 gene editing for undergraduates*, in: *Biochemistry and Molecular Biology Education* 46(2) (2018), pp. 195-205, doi: 10.1002/bmb.21108.

[5] c.f. Deutscher Ethikrat: *Germline intervention in the human embryo: German Ethics Council calls for global political debate and international regulation* (2017), URL:https://www.ethikrat.org/fileadmin/Publikationen/Ad-hoc Empfehlungen/englisch/recommendation-germline-intervention-in-the-human-embryo.pdf (16.03.2020).

[6] c.f. N.N.: „WHO | Genes and human disease"; URL: https://www.who.int/genomics/public/geneticdiseases/ en/index2.html (28.03.2019)

[7] c.f. Julie S. Cohen and Barbara B. Biesecker: *Quality of Life in Rare Genetic Conditions: A Systematic Review of the Literature*, in: *American Journal of Medical Genetics* (2010), pp. 1136-1156, doi: 10.1002/ajmg.a.33380.

[8] c.f. Puping Liang et al: *CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes,* in: *Protein & Celll* 6(5) (2015), pp. 363-372, doi: 10.1007/s13238-015-0153-5.

[9] c.f. Hong Ma et al: *Correction of a pathogenic gene mutation in human embryos,* in: *Nature* 548 (2017), pp. 413-419, doi: 10.1038/nature23305.

[10] c.f. Stella Baliou et al: *CRISPR therapeutic tools for complex genetic disorders and cancer (Review)*, in: *Int J Oncol.* 53(2), pp. 443–468, doi: 10.3892/ijo.2018.4434.

The possible application of pre-existent legal and regulatory frameworks is yet to be clarified for all uses of genome editing in humans. In countries where there is explicit legislation, the regulatory limitations on research prevent genome-edited gametes or embryos being used in clinical applications, i.e. the modification of gametes or embryos that would be allowed to survive and then be implanted to create a pregnancy. In at least 12 countries, jurisdictions allow research on the embryo for only 14 days, at which point the embryos must be destroyed,[11] while research on germline cells is forbidden in many others. In some countries, it is not even allowed to donate human embryos for research purposes at all,[12] hindering scientific progress. As the technique itself is not yet mature, basic research into human germline genome editing should be permitted and needs to precede its clinical application; this should include research into the frequently reported off-target side effects.

We therefore propose that research on human germline genome editing should be carefully regulated and should operate in a clear policy and regulatory framework. Medical applications of germline editing should also be allowed eventually, but given the public concern about the risks, its application needs to have clear boundaries or, at least, clear regulations on how to deal with possible risks. In legislating for the use of this technology in research it is important not to confuse medical applications of therapeutic germline editing with germline enhancement. Although enhancement applications that raise significant ethical issues (aside from issues that concern the therapeutic approach) might still be far away in terms of research, we propose a strict line between the two by evaluating the medical requirement for germline editing. For example, this could imply allowing germline genome editing only to treat severe monogenic hereditary diseases. In other words, we advocate allowing germline genome editing only in research and therapeutic applications.

Before progressing to the clinical use of germline genome editing several minimum requirements need to be met. Firstly, adequate evidence on the safety and effectiveness is required, to balance the risks with the benefits in human clinical trials. Secondly, regulation is necessary in order to ensure that research and all the subsequent steps are carried out in a responsible manner, due to the peculiar ethical implications of this technique and its applications. A multidisciplinary approach to drafting such regulation is required, drawing on expertise including law, natural sciences and ethics. Lastly, engagement of the public is required to obtain democratic support.

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[11] c.f. Insoo Hyun, Amy Wilkerson and Josephine Johnston: *Embryology policy: Revisit the 14-day rule*, in: *Nature 533* (2016), pp. 169–171, doi:10.1038/533169a.

[12] c.f. European Court of Human Rights: *Banning a woman from donating embryos obtained from in vitro fertilisation to scientific research was not contrary to respect for her private life*, URL: https://hudoc.echr.coe.int/eng-press?i=003-5156393-6373024#{%22itemid%22:[%22003-5156393-6373024%22]} (23.12.2019).

With the emergence of feasible and efficient genome editing protocols and the resulting possible future scenarios of applications in medicine and human enhancement, the debate about a standardized global germline policy has become a subject of public interest. Thus, for gaining societal support and consensus on a legal framework that permits specific cases of germline interventions, (i) inclusive means of public information and engagement must be established, (ii) the public's opinion must be obtained by methods such as standardized surveys and deliberative dialogue, and (iii) these results must be taken into account by the corresponding policies.

The development of a clear international legislation on human germline editing is deemed fundamental to enable an optimal and comprehensive adherence. Additionally, establishing a flexible legislation that can expand over time and differentiate between basic scientific research and clinical application will enable the development of the technology and its applications at an unobstructed pace. In formulating such regulation, we must carefully negotiate an approach combining precaution and openness to development by using stepwise legislation. The social and cultural differences worldwide further point out the importance of considering flexibility in the design of the regulatory framework. Therefore, we advise to combine international regulation with local ethics committees, responsible for developing the criteria for germline genome editing. In this way, a balance between the international principles and local priorities can be established.

In conclusion, we recommend that editing of the human germline should be allowed for research purposes under strict regulation. We further recommend that the progress and implementation of germline genome editing in a clinical setting be pursued when basic scientific research shows that it is safe, ethical concerns are agreed upon, and suitable regulations are in place.

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