Human germ-line gene editing

Conclusions and Recommendations

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Introduction

Recent research and expected further studies in gene editing raise high expectations, especially regarding possible therapeutic applications in humans. Most promising is the prospect of somatic gene editing, which may prove to be a game changer not only in the treatment of a whole range of serious genetic, esp. Mendelian, disorders, but also in the treatment of cancer and infectious diseases. At the same time, its possible future application in the human germ-line raises serious concerns. Initiatives have been taken worldwide to exchange views about responsible innovation using human gene editing. The European Society of Human Genetics (ESHG) and the European Society of Human Reproduction and Embryology (ESHRE) consider it to be their professional responsibility to contribute to further discussion by means of a set of Recommendations, based on a Background paper, focusing on human germ-line gene editing (GLGE).

The aim of this contribution is to inform and stimulate ongoing societal debates, as well as provide guidance, taking account of technical aspects of GLGE, its different possible applications, relevant clinical experience regarding the handling of reproductive risk, legal regulations and ethical and societal issues and concerns linked with GLGE. Because of the relevance of the latter, both the ESHG and ESHRE invited their relevant committees (the Public and Professional Policy Committee resp. the Ethics Committee) to take the lead in writing the Background paper and the Recommendations. These were discussed in both committees. They will be online to solicit comments from the second half of October until the 1st of December 2016. After integrating the comments, the Recommendations will be endorsed by both Societies.

This Document has a provisional nature, and is to be evaluated regularly, taking account of relevant scientific developments, possible future clinical experience, and further societal discussions and ethical reflection.

Recommendations

In preparing this Document, it was considered to be crucial to make a distinction between non-reproductive GLGE and possible future clinical (reproductive) GLGE.

I. Non-reproductive germ-line gene editing

Non-reproductive GLGE includes both basic and preclinical research. Although a sharp demarcation between these forms of research is difficult to make, basic research in this context is characterized by a focus on fundamental questions regarding human embryology and the methods applied in gene editing. Reproductive treatments in health care and adequate patient counseling may be served by a better knowledge of early embryo development. There are good reasons to allow basic research in this area, subject of course, to societal oversight and taking account of relevant ethical guidelines and (inter-)national legal regulations. We should rethink these regulations, also given the value of freedom of research. While the research use of human embryos *in vitro* is more controversial than the research use of human somatic cells and (precursor cells of) gametes, human embryo research may be a justified part of such basic research. A categorical prohibition of the making of human embryos specifically for research purposes ('research embryos'), as stipulated in the Oviedo Convention, is debatable also from an ethical point of view. The use of research embryos can be morally justified if this is necessary to reach the aim(s) of scientifically sound research. Given the sensitivity of human germ-line interventions, a specific consent of the providers of the gametes and embryos should be obtained.

Pre-clinical GLGE research involves investigation of the safety and efficiency of gene editing in view of possible future reproductive applications of GLGE (and other germ-line modifications in mtDNA, including spindle transfer/mitochondrial donation). This is important in order to identify and eliminate, or at least reduce, avoidable risks for applicants and future children thus conceived. As a precondition for the transition to possible clinical applications, preclinical GLGE should be allowed. Here again, the use of research embryos can be morally justified.

'Comprehensive' pre-implantation genetic testing (PGT) of embryos using whole genome sequencing might be an integral part of adequate pre-clinical research on the safety and specificity of GLGE to investigate potential off-target effects. The issue of how to handle possible incidental findings regarding the genetic make-up of the providers of the gametes or embryos should be addressed in the informed consent, taking account of relevant guidelines.

II Reproductive germ-line gene editing

Depending on the outcomes of preclinical research and taking account of societal risks and implications (see below), the step to the clinic may be considered. If so, this should be embedded in a formal research trajectory as soon as doing so is reasonably possible. According to the Clinical Trials Regulation EU No.536/2014, Article 90 "No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity." The implication of this regulation may well be that adequate clinical GLGE research will be impossible in the EU and that clinicians continue these applications outside proper research protocols and outside the EU.

If safe and effective, GLGE may have important benefits for prospective parents at high risk of having a seriously affected child.

Categorical deontological objections to GLGE - in terms of being at odds with e.g. naturalness, human dignity, or the preservation of the human gene pool as a common heritage - seem unconvincing. A better understanding of these objections is needed to inform the public debate and the counseling of individual patients.

Consequentialist objections, regarding both A) health risks and B) societal concerns, need more scrutiny and debate.

A) Health risks

In this context health risks should be taken to refer to the first and possible later generations. Different types of possible adverse effects (off-target and pleiotropic, genetic and epigenetic) need investigation. Part of the problem is the present uncertainty about the reversibility of possible adverse effects. In view of the many unknowns, any use of germline gene editing methods for clinical purposes, including any reproductive use of gametes derived from edited pluripotent somatic cells, should be regarded as premature and therefore presently unacceptable.

Clinical applications can only be morally justified if adequate pre-clinical safety research, including (human) embryo research, shows clinical GLGE to be sufficiently safe and efficient. The proper standard for the evaluation of possible residual risks ('how safe is safe enough for starting clinical applications?') needs further clarification.

If comprehensive PGT of edited embryos on the basis of whole genome sequencing would be included as a safeguard in future clinical GLGE, this testing should be targeted at possible off-target effects. A possible broadening of the analysis of the raw data generated by such PGT raises complex additional ethical issues and needs further multidisciplinary analysis and debate. The proportionality of such broader analysis should not be taken for granted.

Furthermore, any possible future reproductive GLGE requires prospective data collection of reproductive outcomes and long-term follow-up studies on the health of children thus conceived. Possible practical barriers and limits (in terms of for example lack of funding or tensions with familial and children's privacy) may render this challenging, as with long-term follow-up of children conceived through new reproductive technologies generally.

B) Societal concerns

The major societal risks often mentioned in this context are inequity, the undermining of reproductive autonomy, and possible misuse of GLGE for non-medical applications.

Equal access to health care has to be decided on the level of society. Public funding, as some countries have provided for PGD, can mitigate the concerns regarding inequity. If limited funding is available for health care, prioritization is needed. It is conceivable that presently somatic gene editing would be prioritized as many current severe health problems could be targeted.

Reproductive autonomy should be maintained and respected by both adequate counseling and provisions for disabled people. Moreover, while some fear the undermining of reproductive autonomy, it should be noted that GLGE may well promote the reproductive autonomy of prospective parents at high risk of having a child affected with a serious disorder, as it would increase the number of reproductive options.

The experience with regulating PGD and other reproductive technologies may help to build a sound strategy for regulating acceptable possible future clinical applications of GLGE, including a licensing system and obligatory regular reporting by licensed clinics about their handling of applications for GLGE, in order to strengthen societal oversight. If clinical GLGE is considered to be sound, priority should be given to the editing of highly penetrant genes for serious disorders. As the distinction between serious and less serious disorders is unclear, feeding fears of a slippery slope, further multidisciplinary reflection on the demarcation of serious disorders is needed. In addition, the distinction between therapy and enhancement is not always clear-cut and decisions will need to be made about intermediate subtypes of medical enhancement, such as strengthening the human immune system or editing carrier status for recessive disorders or structural aberrations. With regard to fears regarding future 'designer babies', it is important to acknowledge that the prospect of enhancing complex traits (like intelligence) is to a large extent science fiction, and that possible efforts to enhance complex traits would run a disproportional risk of (antagonistic) pleiotropy. Public debate and education is needed to lower the risk of commercial companies exploiting prospective parents' possible preference for a 'perfect child'.

In view of the medical and societal risks of and concerns regarding GLGE, it is important to take account of other reproductive options for people at high risk of having an affected child. Considering the preference of most prospective parents to have a healthy, genetically related child, PGD, aimed at a selective transfer of an unaffected embryo, may be a good 'preventive' option in most cases. Still, there may be situations where GLGE might be useful and justified, depending upon, amongst others, the genetic status of the prospective parents, their experiences with clinical PGD, their weighing of the possible risks and burdens of a next cycle of ICSI/PGD, and their moral preferences, also with regard to minimizing embryo loss. A further ethical and societal evaluation of relevant aspects, including possible health risks of GLGE, is needed in order to define possible indications for future clinical GLGE as an alternative for PGD aimed at selectively transferring an unaffected embryo.

Possible future routine comprehensive PGT of IVF-embryos using whole genome sequencing, aimed at selecting 'the best embryo' for transfer, needs proactive ethical and societal debate. Such testing could, assuming a further improvement of the efficiency of editing embryos, well function as a driver for future routine GLGE, at least among some (wealthy) social groups. After all, there will always be something to be edited, as all embryos, like humans, are 'fellow mutants'.

III. Governance

A process of ongoing public debate about material and procedural ethical and societal issues raised by both non-reproductive and reproductive human GLGE is of the utmost importance. Such debate should be inclusive; apart from scientists and clinicians, other stakeholders should be invited to

participate, including patients' organizations, the public, policymakers, and scholars in the medical humanities.

These current Conclusions and Recommendations build a first, joint, contribution of both ESHRE and the ESHG to the suggested ongoing trajectory of public deliberations. The Conclusions and Recommendations have a provisional nature and are to be evaluated regularly and systematically.