Is the 'serious' factor in germline modification really relevant? A response to Kleiderman, Ravitsky and Knoppers

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ABSTRACT

Should we use human germline genome modification (HGGM) only when serious diseases are involved? This belief is the underlying factor in the article written by Kleiderman, Ravitsky and Knoppers to which I now respond. In my opinion, the answer to this question should be negative. In this paper, I attempt to show that there are no good reasons to think that this technology should be limited to serious diseases once it is sufficiently proven to be safe and efficient. In fact, opting otherwise would negatively harm human beings' right to the highest standard of health that unmodified embryos could promote. Therefore, the issue should not be so much to define adequately what a serious disease is, but rather to elucidate whether this concept should play any role beyond the context of preimplantation genetic testing (PGT). This paper argues that we should not accept the similarity between technologies such as PGT and HGGM because they face different challenges and offer totally different possibilities. Therefore, we are in urgent need to build a completely new ethical architecture that covers the application of germline editing in human embryos. As a part of that process, a much deeper debate on the necessity of distinguishing different disease types is required.

The paper by Kleiderman, Ravitsky and Knoppers[1] is an excellent piece; it adds important reflections to the debate on assisted reproductive technologies. First of all, they are quite right to underline the importance that the documents produced by important institutions, including Quebec's Commission on Ethics in Science and Technology,[1] the US National Academies of Sciences, Engineering and Medicine[2] and the German Ethics Council,[1] provide to the concept of 'serious diseases'. Moreover, their efforts to build a new approach to this concept that overcomes the obstacles that have traditionally hindered its development are particularly praiseworthy.

In my opinion, however, the article also has an underlying error that should be highlighted. Kleiderman, Ravitsky and Knoppers accept as a fact that human germline genome modification (HGGM) should only be performed in cases of serious diseases. I believe that this supposition is not necessarily true or, rather, that it may be clearly mistaken. Moreover, except in those cases in which HGGM may be the best or only option for couples to have a healthy, genetically related child, the success of this innovative technique will be measured precisely by its ability to go beyond the fight against serious diseases through the modification of human embryos.

In my opinion, the error of these authors is based on the parallel they draw between preimplantation genetic testing (PGT) and HGGM. Indeed, they state that 'past experience with the normative analysis and governance of PGT and prenatal testing can serve as a model to guide similar debates surrounding the acceptability of HGGM'.[1] I believe that accepting this parallelism is a mistake with serious consequences. The point to keep in mind is that in the context of PGT—but only in this specific context—is where the distinction between serious diseases and other diseases that cannot be considered as such makes sense for various reasons.[3]

The first reason is that PGT is an invasive procedure that injures the embryo and can lead to its loss.[4] Moreover, it is possible that PGT provokes long-term consequences on the human being who suffered it in the embryonic state.[5] Therefore, from the point of view of the welfare of the embryo and the person it will produce, it makes sense to limit the circumstances in which this technique should be applied. Furthermore, it is important to remember that PGT does not in any case improve the health of the embryo and/or the person it generates. PGT is a technique that only provides us with the capacity to discriminate between embryos, and thus it clearly operates as a negative selection mechanism.[6] Therefore, it is only worth using when we suspect the presence of factors with enough weight to justify this screening. This last assessment is particularly important if we bear in mind that its very selective nature makes PGT often accused of being a refined form of eugenics.[6] Moreover, and as the authors express, the fact that a pathology is included in the catalogue of serious diseases incompatible with a reasonably good life 'could lead to further stigmatisation of people with disabilities' (p. 4).[1] For all these reasons, it makes sense to limit the possible the use of PGT as much as possible so that it is only used in cases where there seems to be no other reasonable option. Thus, PGT makes perfect sense only in the context of serious diseases.

The question then, is the same true for HGGM? In my opinion, the answer is clearly negative, for multiple reasons. The fundamental one is that this technique, unlike PGT, is clearly therapeutic, in the sense that it allows us to improve the health of human beings.[7] Therefore, if the technique is safe and effective—the hypothesis on which the whole reasoning of the article I am now criticising is built—it is hard to understand why it should apply exclusively to serious diseases and not to all diseases. If we accept that there is a 'right to the highest attainable standard of health' and that HGGM 'could be perceived as a form of preventive personalised medicine and a tool to foster the realisation of the right to health' (p. 3),[1] then why should we limit its use exclusively to dealing with serious diseases? I do not find any good reason for such a restriction, especially if we bear in mind that, precisely for those serious diseases, there is already a more or less functional tool (with all the issues exposed), namely PGT. Consequently, it seems reasonable to conclude that the value of HGGM comes mainly from its ability to go much further than what PGT is and will be able to accomplish. However, if this possibility is the case, limiting its applicability to serious diseases is depriving the technique of its raison d'être, which, in turn, implies renouncing to facilitate the 'right to the highest attainable standard of health' mentioned above.

There are, of course, some possible objections to this argument. For instance, one might reply that I am forgetting the relevance of the risk/benefit criterion.[2] Following this principle, we should use HGGM only when the potential benefit far exceeds the risk inherent in the use of this technique. Evidently, the more serious the disease to be faced, the lower the ratio and, therefore, the more advisable the use of HGGM. However, this objection

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is based on a contradiction of what the authors assume in their text, namely that HGGM will at some point be 'safe and efficient'. If we do not arrive at such a scenario, its use will be unethical for all diseases. In other words, if the relevant safety conditions are not met, the distinction between one type of disease and another will be completely irrelevant.

A second objection—which may be more substantial in my view—is that the monitoring of all human beings to whom HGGM has been applied for many years will only be possible if the number of cases to follow is low. Hence, it seems appropriate to apply the technique only to the most serious diseases. The question here, however, is whether it is necessary to perform this control on each and every modified human being.[8] This debate is complex because while it is true that risk is inherent in science and that we can hardly know the long-term consequences of HGGM, it is also true that it does not seem necessary to extend this type of control to all cases, but rather to a significant sample. Moreover, it is worth remembering that we were not aware of the long-term effects of assisted human reproduction techniques when we started to use them, but this fact never provoked a general veto for their use. Why should we opt for a different approach in the case of HGGM?

Finally, it is objectionable to my argument that 'the notion of serious may be useful in determining who has the most urgent claim to HGGM (eg, families suffering from serious genetic diseases) and therefore should be assisted or favoured to enable equitable access' (p. 5).[1 9] However, this objection has at least two weaknesses. First, it should only apply to publicly funded interventions: there seems to be no reason to prohibit a person or couple from using these techniques to improve the health of their offspring if they are willing to finance them from their own pocket. Second, we can accept that this criterion—opting first to deal with serious diseases—may be reasonable within the framework of a public health service, but I very much doubt that it is necessary to externalise this relevance by producing a standard or recommendation of the type cited in the article. It is indeed a general criterion of efficiency in the use of public resources that they are allocated to cases in which the cost/benefit ratio is optimal. Therefore, it is not necessary to generate new specific regulations for HGGM to achieve this goal.

In short, my conclusion is that, although the article I am now criticising makes commendable contributions, it is worth seriously considering whether its underlying assumption—that HGGM should be applied at least preferably to serious diseases—is reasonable. I am inclined to think that it is not, although it is true that there are some factors that operate for the other side of the argument. In any case, I believe that a more in-depth discussion on this subject is advisable, at least if we want to reach a broad consensus on it.[10]

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REFERENCES

1 Kleiderman E, Ravitsky V, Knoppers BM. The 'serious' factor in germline modification. *J Med Ethics*.
2 National Academies of Sciences, Engineering, and Medicine. *Human genome editing: science, ethics, and governance*. Washington DC: The National Academies Press, 2017.
3 Knoppers BM, Bordet S, Isasi RM. Preimplantation genetic diagnosis: an overview of socio-ethical and legal considerations. *Annu Rev Genomics Hum Genet* 2006;7(1):201–21.
4 Zacchini F, Arena R, Abramik A, *et al*. Embryo biopsy and development: the known and the unknown. *Reproduction* 2017;154(5):R143–48.
5 Beriain DM I, Ishii T. Should gene editing replace embryo selection following Pgd? some comments on the debate held by the International Society for prenatal diagnosis, prenatal diagnosis, forthcoming issue.
6 Beriain DM I, Penasa S. The embryo survival criterion: a moral obligation or a eugenic practice? *Rom J Leg Med* 2018;26(2):212–7.
7 Savulescu J, Pugh J, Douglas T, *et al*. The moral imperative to continue gene editing research on human embryos. *Protein Cell* 2015;6(7):476–9.
8 Howard HC, van El CG, Forzano F, *et al*. One small edit for humans, one giant edit for humankind? points and questions to consider for a responsible way forward for gene editing in humans. *Eur J Hum Genet* 2018;26(1):1–11.
9 Farrelly C. Genes and equality. *J Med Ethics* 2004;30(6):587–92.
10 Baylis F. 'Broad societal consensus' on human germline editing. *Harvard Health Policy Review* 2016;15(2):19–22.