Gremlins in the Germline

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Bryan Cwik shows the importance of asking questions such as: what is goal of a given germline intervention? Does the specific method of intervention have its own idiosyncratic ethical texture? Are there alternative means of producing the same end that are less risky and less morally contentious? In this commentary I argue that the considerations underlying Cwik's position indicate that: (i) when we think about the ethics of germline interventions, we should make use of a general set of tools that inform how we should think about risk; and, (ii) once we see this, we see that there are no ethical concerns that are unique to the category of germline genetic interventions (Lewens 2020).

In support of these claims, let me begin with a minor point. Cwik suggests that: 'interventions that target nonpathogenic (otherwise healthy) genes must at minimum not be in equipoise with other interventions relative to the same goal.' The notion of equipoise is most at home in the context of clinical research. According to one influential definition, equipoise denotes 'a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial' (Freedman 1987: 141). Usually the *presence* of equipoise—not its absence—is required for clinical research to go ahead. The standard rationale is that if there were no such uncertainty—if it was clear that standard treatment was superior to an experimental intervention—then clinical research exposing people to the experimental intervention would be impermissible. This reminds us that one way in which gene editing might not be in equipoise with other available interventions would be if the investigator was confident that gene editing was an *inferior* option. Evidently absence of equipoise does not count in favour of gene editing in such circumstances.

It seems Cwik has simply mis-phrased things here: I assume that when he requires absence of equipoise, what he really means is that we should have good reason to think germline intervention is superior to existing alternative measures. This approach already underlines the United Kingdom Human Fertilisation and Embryology Authority (HFEA) guidelines on the use of MST (Maternal Spindle Transfer) and PNT (Pronuclear Transfer) for preventing the inheritance of mitochondrial disease. MST and PNT are not the only ways to help women with defective mitochondrial genomes to have healthy children who share their nuclear genomes. It is also possible to use preimplantation genetic diagnosis (PGD) to select healthy embryos with low proportions of defective mitochondria. But PGD cannot help women who happen to have very high proportions of defective mitochondria: such women may be unable to produce any healthy embryos. That is why the HFEA expert panel recommends that MST and PNT, 'should in the first instance be offered to selected patients for whom

preimplantation genetic diagnosis (PGD) would be inappropriate, or unlikely to succeed' (HFEA 2016: 6).

Reflection on MST and PNT is useful for other reasons. Cwik notes that, 'Because mitochondrial DNA has a more limited impact than nuclear DNA on some of the more interesting traits of an individual, [PNT and MST] may not raise issues that editing of nuclear DNA does.' The true degree of difference will vary with context. Whether a trait is 'interesting' is likely to reside in the eye of the beholder. It is, after all, defective mitochondrial DNA that causes some instances of mitochondrial disease, and the fact of suffering from mitochondrial disease is likely to be of exceptional significance to the individual affected. That said, so far as we know it is not possible to modify fine-grained aspects of cognitive ability, personality and so forth via changes to the mitochondrial genome. It remains unclear whether such modifications are possible via changes to the nuclear genome. It is also important to stress that sometimes mitochondrial disease itself can be traced to defects in nuclear genes that influence mitochondrial function (NCOB 2012). We can, therefore, envisage goals for the editing of nuclear DNA that are exactly the same as the goals for MST and PNT. As things stand, a patient with serious mitochondrial disease in the UK needs to find out whether the low functioning of their mitochondria is a result of defective nuclear, or mitochondrial, genes in order to determine whether their predicament can be aided within the law. Nonetheless, Cwik is right to note that even if their goals are identical, gene editing and PNT/MST raise some different ethical issues: for example, gene editing does not involve three genetic contributors, and consequently gene editing does not raise the same set of risk-based issues around the potential need for 'haplotype matching' (HFEA 2016; Lewens 2019).

I have deliberately avoided using the term 'Mitochondrial Replacement Therapy' (MRT) to label PNT and MST, because that term encourages misunderstandings (Lewens 2015: 7). Cwik tells us that, 'In MRT, mitochondrial DNA from a female donor is transferred into an oocyte from a second female.' This describes a technique called 'cytoplasmic transfer', but it does not accurately describe PNT and MST. Instead, nuclear material from the woman who suffers from mitochondrial disease is transferred into either an enucleated embryo (PNT), or an enucleated egg (MST), donated by a woman with healthy mitochondria (NCOB 2012). Cwik suggests that, 'Presumably the questions outlined…about transfer of mitochondrial DNA would be sharped and augmented by further issues in the (still hypothetical) case of transfer of nuclear DNA.' In fact, the dominant 'MRT' techniques under discussion today already involve the transfer of nuclear DNA.

Cwik tends to phrase his approach in terms of drawing important ethical lines *within* the category of germline gene editing. His discussion thereby invites the question of whether there is anything ethically distinctive about germline genetic interventions as a category. Should we simply ask—for medical interventions that affect germline genomes, and for those that do not—the same sorts of questions about goal, risk and clinical rationale that Cwik recommends? In support of this suggestion, consider that:

- Germline genetic interventions are often distinguished from somatic interventions on the grounds that (i) only the former can affect individuals across several generations and (ii) future individuals who are so affected cannot give consent. But

public health measures can also affect multiple individuals, and again consent is often impossible to obtain. In many cases these effects occur within a single generation, but it is also clear that (for example) measures taken to control the spread of COVID-19 are broad-ranging enough that they simultaneously affect several generations, in ways whose downstream effects are unpredictable.

- Public health measures can also persist across generations after their initial enactment. Educational campaigns can have effects that are sustained through forms of social learning. Other public health interventions are effected via the building of physical infrastructure (such as systems of sanitation) that remains for longer than a single generation.

- Finally, some evidence suggests that alterations to germline *genes* are not the only ways in which changes to the germline can persist across generations (Miska and Ferguson-Smith 2016). Research on transgenerational epigenetic inheritance suggests that a subset of changes to non-genetic structures within the germline may also persist.

In all of these cases we are rightly cautious about the prospect of interventions whose effects ripple through many individuals, often with uncertain impacts that we may struggle to control. We ask ourselves just the same kinds of questions that Cwik recommends for germline gene editing: what do the interventions aim at, what are the risks, do specific features of the techniques bring idiosyncratic ethical worries, and are there better alternatives (Lewens 2020)? These final considerations also reinforce Cwik's scepticism about slippery slope arguments: we have long been on a slope—less slippery than some may think—whose terrain comprises the array of interventions that influence the physiology of numerous individuals spread over space and time.

References

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