Goldilocks, polygenic risk scores and moral imperatives

Heritable genome editing (HGE) is officially here. “Lulu” and “Nana”, born in China, are the first children whose genomes have been intentionally modified. A third gene edited baby may have already been born. Scientists in Russia are planning similar applications.

We recently argued that HGE should be judged by the same ethical standards that we apply to other technologies. [1] There is a moral imperative to improve the health of future generations, to reduce inequalities, and improve standards of living. If we can use HGE to achieve these aims, we should. We want to thank Sarah Chan, Peter Mills, Rachel Horton, and Anneke Lucassen for their thoughtful criticisms of our paper. We would also like to thank the editors of the Journal of Medical Ethics for helping facilitate this detailed discussion. The moral questions posed by HGE, are complex, multifaceted and difficult. They required focussed attention, which formats like this encourage.

Our responses to each of the commentaries are detailed below

Horton and Lukassen

We agree with the following points made in Horton and Lukassen’s paper “*The moral argument for heritable genome editing requires an inappropriately deterministic view of genetics”* [2]

- Until we better understand what determines the penetrance of genomic variants, HGE is premature
- Many variants used in gauging polygenic risk are markers of disease risk, rather than agents of pathogenesis themselves,
- The impact of any given variant will depend on its context within a genomic background, and the influence of environmental factors, some of which will be stochastic

These are some of the reasons why we say HGE targeting polygenic diseases is decades away.[1] The technical challenges seem daunting. But science can move quickly, and often does so in bounds. Our capacity to capture and analyse genetic data is rapidly expanding. Over the next five years, genomic data from over 60 million patients are expected to be generated through clinical practice alone, not to mention the hundreds of millions of genome sequences through direct to consumer testing.[3] At the same time our ability to analyse genetic data is being aided by advances in artificial intelligence, which is already analysing genomes for disease predispositions in clinical settings. What is foreseeable in genomic medicine in 10 years will be very different from what is foreseeable today. For these reasons, we believe it is important to analyse the ethics of HGE from a wide lens, even if some applications seem distant.

Horton and Lukassen state “most diseases cannot simply be attributed to specific genetic variants that we could edit away”. This may well be true, but this doesn’t mean that certain combinations of genetic variants will not provide disease resistance to specific individuals, facing known environmental conditions. For example, in populations where blood cholesterol is a known contributor to heart disease, individuals may benefit from genetic variants that reduce levels of blood cholesterol. Such targeted intervention will become more plausible as our knowledge of genetics increases.

Horton and Lukassen’s claim that we endorse an ‘*inappropriately deterministic view of genetics’* is difficult to make sense of. Our argument is based on the moral parity between genetic and environmental influences on disease. There are no *conceptual* differences between reducing rates of diseases through genetic or non-generic means, and we should employ whichever method is most

effective and safe. We fail to see how arguing that we should reduce the incidents of polygenic disease by reducing genetic risk implies an inappropriately deterministic view of genetics, any more than arguing that we should fight climate change by reducing deforestation implies a deterministic view of the impact of forests on global climate. For complex problems, like climate change and polygenic disease, there are complex interactions at different casual levels. But, if an intervention works, it doesn't matter which casual level it operates from.

There is nothing deterministic in this moral argument for HGE.

Mills

In our article, we argue that a strength of the Nuffield report was that "it outlines quite specific moral principles; rather than merely appeals to broad concepts." (1) In his response "Goldilocks and the two principles" Pete Mills, Assistant Director of the Nuffield Council, states that this praise rests on a misreading of the report. The principles offered by Nuffield should be read "not as conditions that must be satisfied but as orientation principles for the development of practical governance"[4].

He elaborates:

> *" A neglected aspect of the report is the dialectical relation of the three sets of considerations through which it advances…Gyngell et al.'s analysis does not attend to how the second principle …. interacts with the first…. It also ignores the important implication of the refusal of a final synthesis (which would be that heritable genome editing – HGE – is categorically at odds with the interests of humanity)…"*

Seeing the principles not as conditions, but as orientation principles, makes the report much more difficult to apply to specific application of HGE (and much more like the many reports on HGE that preceded the Nuffield Council) The basic difficulty is that everyone will agree that things like welfare, social justice, solidarity, and fairness are important. But people will have radically different ideas about how those values bear on specific questions. Appealing to what feels like the 'right mix' of considerations is not a helpful way to guide policy, just as instructions to make porridge so that it is 'just right' is a bad recipe.

Take the case of He Jiankui, and editing the CCR5 gene in an attempt to make children resistant to HIV. Two of us had discussed this specific example many times before He Jiankui's announcement [5–8], and argued that it would not be an appropriate target for HGE. CCR5 is not mentioned once in the Nuffield Report. Nor is it clear to us now whether, under the current Nuffield guidelines, such an application would lead to the "refusal of a final synthesis", and thus be impermissible.

In our response, we suggested the Nuffield's second principle should be modified to rule out applications that could lead to collective action problems, including changes to genes that govern innate immunity (like CCR5). We find it very surprising that Mills did not engage with this very practical suggestion, and instead focus on vague theoretical debates. In all, we are not sure if (and why) Mills disagrees with our stance of the permissibility of the practical application of HGE, in reducing polygenic disease, and reducing inequalities.

Furthermore, we find many of the theoretical concerns offered by Mills difficult to follow. Mills claims that our argument "rests on how welfare figures in the moral appraisal of the potential uses of HGE".

But this can't be, giving our argument doesn't include the term 'welfare', and we only use the term when referring the Nuffield paper. Our arguments rest on the similarities between genetic and non-genetic causes of disease and inequality.

Chan

Dr Chan's concern is not with our argument, but rather with its framing. HGE raises questions that are difficult and have historical aspects that need to be carefully considered. However, we strongly believe that we must follow moral arguments where they lead. We should not shy away from difficult ethical questions, like whether there is a moral difference between increasing cognitive ability through genetic and non-genetic means. There are dangers in accepting a moral status quo because it is convenient, rather than because it is correct. We believe this is the case with many perceptions around genome editing and the difference between treatment and enhancement.

HGE shouldn't be considered in a vacuum, and we must be conscious of the history of attempts to alter the human germline – in particular, the moral atrocities of the eugenics movement. Two of us have previous considered these issues in great detail in published work [9,10]. In any conversation about HGE, we need to stress the importance of respecting individual autonomy, human rights and recognizing the fundamental equal standing of all humankind.

We want to clarify Dr Chan's use of the term 'genetically weaker'. We never used this term. We do not believe there anything 'weaker' about an individual who requires, say dialysis, to survive. It should also go without saying that requiring dialysis has no bearing on one's moral status, or human rights. But someone on dialysis is less healthy than someone who is not (all else being equal). Our argument is that, if we can reduce the number of people who require dialysis in the future, we have strong reasons to do so. Indeed, this is part of the normal ethical calculus when considering public health measures. We should have the ethical sophistication to separate the position that the future will be better with less disease, from the insinuation that people who have a disease are somehow weaker, or have less moral standing than healthy people.

1 Gyngell C, Bowman-Smart H, Savulescu J. Moral reasons to edit the human genome: picking up from the Nuffield report. *Journal of Medical Ethics* 2019;:medethics-2018-105084. doi:10.1136/medethics-2018-105084

2 Horton R, Lucassen AM. The moral argument for heritable genome editing requires an inappropriately deterministic view of genetics. *J Med Ethics* 2019;:medethics-2019-105390. doi:10.1136/medethics-2019-105390

3 Stark Z, Dolman L, Manolio TA, *et al.* Integrating Genomics into Healthcare: A Global Responsibility. *The American Journal of Human Genetics* 2019;**104**:13–20. doi:10.1016/j.ajhg.2018.11.014

4 Mills P. Goldilocks and the two principles. A response to Gyngell *et al*. *J Med Ethics* 2019;:medethics-2019-105395. doi:10.1136/medethics-2019-105395

5 Gyngell C. Enhancing the Species: Genetic Engineering Technologies and Human Persistence. *Philosophy & Technology* 2012;**25**:495–512. doi:10.1007/s13347-012-0086-3

6 Gyngell C, Douglas T. Stocking the genetic supermarket: reproductive genetic technologies and collective action problems. *Bioethics* 2015;**29**:241–50. doi:10.1111/bioe.12098

7 Gyngell C, Douglas T, Savulescu J. The Ethics of Germline Gene Editing. *Journal of Applied Philosophy* 2017;**34**:498–513. doi:10.1111/japp.12249

8 Munsie M, Gyngell C. Ethical issues in genetic modification and why application matters. *Curr Opin Genet Dev* 2018;**52**:7–12. doi:10.1016/j.gde.2018.05.002

9 Gyngell C, Selgelid M. *Twenty-First-Century Eugenics*. Oxford University Press 2016. doi:10.1093/oxfordhb/9780199981878.013.7

10 Savulescu J. Procreative beneficence: why we should select the best children. *Bioethics* 2001;**15**:413–26.