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The Brave New World: Should we tread down the path to human germline editing?

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Gene-editing tools such as the CRISPR-Cas9 system create an opportunity for individuals to have their DNA edited for specific purposes. Somatic cell editing targets specific cells in an individual, and is aimed at providing a therapeutic mechanism to correct a genetic disease or condition. Germline editing refers to the editing of the DNA of embryos or gametes, which creates edits that are heritable. Following the announcement in 2018 that the Chinese scientist He Jiankui had proceeded to gene-edit human embryos, a moratorium on germline editing was quickly proposed. While an objective of the moratorium was to prevent clinical application of germline editing, it also served as an opportunity to engage in global debate on the issues inherent in gene editing. Heritable editing has become an ethically controversial topic in bioethics, and this article undertakes to provide a primer in the existing national and international legal framework for gene editing, as well as description of the prominent current views of heritable germline editing.

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In his novel *Brave New World*, Aldous Huxley states that 'We are not our own any more than what we possess is our own. We did not make ourselves, we cannot be supreme over ourselves. We are not our own masters.'[1] Huxley imagined a technologically advanced, but unkind, version of the future, which can serve as a warning for our current state of affairs. He imagined a world where the use of a drug would enable the control of society by creating a false sense of happiness, and supressing dissent. However, in many ways our world has surpassed Huxley's vision. Human gene editing now makes it possible to control our genetic characteristics. Molecular machines such as the CRISPR-Cas9 (clusters of regularly interspaced short palindromic repeats-associated enzyme 9) system allow scientists to alter the genetic make-up of an existing organism, known as somatic gene editing, or germline editing where it is used on gametes or embryos.[2] The distinction between the two forms of gene editing is that somatic gene editing will only cause genetic corrections in an existing individual, while germline editing will perform corrections that are heritable by future generations of that organism.[3] In 2012, the CRISPR-Cas9 system was modelled on the cellular defence system used by bacteria to detect and destroy DNA from invading bacteriophages.[4] Since its development, the gene-editing tool has been fraught with controversies, including intellectual property litigation over the patent rights to the system.[5] However, the most pervasive controversies over using CRISPR-Cas9 have revolved around ethical and legal issues. This article considers that the extant law does not directly apply to gene editing. However, owing to concerns about social exclusion, legal amendment should only follow once vigorous public engagement on the topic has been undertaken. The ethics of human gene editing (HGE) is beyond the scope of this article, which serves to report on extant law and the value of community engagement informing legal reform. Because germline editing is heritable by an organism's offspring, there must be global discussion between all stakeholders: between ourselves. There has been response – an international commission and World Health Organization (WHO) committee were established to develop governance standards for potential future application of HGE. However, these initiatives involve a narrow selection of stakeholders, and focus on issues such as risk-opportunity assessments. Questions of when and how HGE application may be appropriate must also be considered. The global discussion has begun, and this article considers the most prominent and recent approaches in the debate.

From past to present

In 2015, the organising committee of the International Summit on Human Gene Editing determined that HGE should not proceed without broad societal consensus on its inherent issues.[6] Rather than enforcing this conclusion by allocating resources and programmes to achieve this consensus, it has been noted that this intention to achieve consensus has since been weakened.[7] This is evident by the statement[8] released by the same committee in 2018, following the news that Chinese scientist He Jiankui had proceeded to perform gene editing on human embryos. The statement made by the committee at the Second International Summit on Human Gene Editing instead called for a 'translational pathway' to germline editing.[9] It is possible that the basis of the organising committee's proverbial change of heart was the perception that it was too late to engage in debate. HGE was here. It had happened, and we now needed to create a damage control mechanism in order to ensure oversight. However, this approach was not adopted by everyone. In 2019, a call was made for a global moratorium on HGE.[10] While the authors of the article did not propose a moratorium on somatic gene editing, this was their suggestion in the case of HGE. They proposed an uninterrupted pause during which the technical, scientific, medical, societal, ethical and moral issues inherent in germline editing could

be considered, as well as allowing an opportunity to develop an international regulatory framework. This call was supported by the National Institute of Health, Academy of Sciences, Engineering and Medicine and the Nuffield Council on Bioethics. The WHO convened a panel on gene editing tasked with developing global standards for governance and oversight of HGE.[11]

Against this backdrop, a small pool of scientists and bioethicists has endorsed proceeding with HGE, and have focused on carving the path forward.[12] In late January 2020, a group of public interest advocates including philosophers, scientists and policy-makers drafted the Geneva Statement on Heritable Genome Editing (the Geneva Statement),[7] which suggested an urgent need for changing our approach to HGE. Rather than creating a framework for HGE, we must first ask fundamental questions as to whether or not we *should* proceed. This approach was supported in the Joint Statement on the Ethics of Heritable Human Genome Editing[13] (the joint statement) published by the Comité Consultatif National d'Éthique pour les sciences de la vie et de la santé (National Advisory Committee on Ethics in life sciences and health, France), Deutscher Ethikrat (German Ethics Council) and the Nuffield Council on Bioethics (UK) in March 2020. The statement echoed a concern common among all three institutional bodies, in terms of which they believe that the moral and societal issues raised by HGE necessitate a level of public ethical reflection which is not being met by current initiatives.[14] I agree with the approaches adopted in these statements, that these issues must be placed on the agenda for broad societal debate.

Current legal framework

International law exists as a way for nations to create norms for acceptable behaviour in their engagement with one another, in a manner similar to that of national law, which creates the norms of acceptable behaviour between a nation's citizens as well as between citizens and the state structure. However, international law does not carry the equal force of national law, and states cannot be forced to comply with legal standards that they have not accepted. International law works on the principle of common consent, and it is often difficult for states to achieve common ground on important issues, or to enforce compliance against states which do not adhere to the agreed norms. It is, however, an important attempt to encourage nations to agree to some common standard on issues of shared significance. Regarding the human genome, the United Nations Educational, Scientific and Cultural Organization Universal Declaration on the Human Genome and Human Rights (UDHGHR) states in article 1 that 'the human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity'.[14] This instrument was formally endorsed by the General Assembly of the United Nations, and together with the Oviedo Convention, was put into place to protect the equality of people, as well as to safeguard the physical, psychological and social wellbeing of children.[15] Together, they are an attempt at international level to prevent the resurgence of eugenics. Furthermore, the right to scientific progress is enshrined in international law under both the UDHGHR[14] and the International Covenant on Economic, Social and Cultural Rights,[16] which both include the right to enjoy the benefits of scientific progress. In terms of these instruments, state parties should prevent the use of scientific progress for purposes that are contrary to human rights and dignity, life, health and privacy, but should also ensure equitable access to medical products and technologies. The report of the special rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health commented on the nature of the legal obligations of state parties to the covenant.[17] In terms of the covenant, state parties have core obligation to achieve minimum standards of achievement of the rights contained therein.[16] While it appears that the legal provisions are articulated in a manner that promotes respect for genetic heritage, it can be argued that states are obliged to make gene editing available to citizens in a manner that promotes equal treatment and non-discrimination. This is because the right to health places a positive obligation on states in terms of which they must take steps to achieve progressive realisation of the rights under the covenant. What is significant in international law is that genetic interventions that are therapeutic are favoured, whereas interventions that are heritable are phrased in the language of prohibition. This is clear from article 13 of the Oviedo Convention, which states that 'an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.' This would clearly permit somatic editing, but not germline editing.

In South Africa (SA), the starting point of legal analysis is the Constitution.[18] As the cornerstone of democracy, it is the supreme law of SA, and binds all organs of state as well as persons within its borders. While the Constitution does not directly speak to interventions such as HGE, there are a number of provisions within it that are of importance to the discussion. Chapter 2, which contains the Bill of Rights, contains a number of rights relevant to gene editing. The right to human dignity, contained in s10, is enumerated as the foundation of all human rights. This right is at the heart of prohibition against genetic discrimination and obligation to respect genetic diversity, and is also relevant to scientific research in gene editing and clinical applications. The right to physical integrity, contained in s12, includes the rights *inter alia* to make decisions concerning reproduction, and to not be subjected to scientific experiments without the provision of informed consent. The s12 right, which is often identified as the right to autonomy of the individual, places limitations on medicine, biology and the freedom of scientific research. Therefore it is imperative to consider this right, as it conflicts directly with the right to scientific progress identified in international law. Furthermore, the right to physical integrity extends to the genetic integrity of an individual, and we can compare this with the interference with the integrity of future generations, which is protected under international law.[15] The Bill of Rights also contains provisions that ask the state to consider the merits of HGE. The right to life, which is protected under s11, is relevant in the context of the state being under a positive duty to take action to protect the right to life by decreasing infant mortality. Therefore, if gene editing will potentially result in healthier embryos, and potentially healthy births and reduced mortality rates, the state must take measures to promote it. Further, s27 contains the right to health or access to healthcare facilities. In terms of this section, an individual has a right of access to healthcare services, including reproductive healthcare services.[18] The section binds the state to take reasonable measures that are within its available resources to achieve progressive realisation of this right. In terms of this section, it could be argued that should gene editing be proved

to be safe, the state would be required to make it available at clinical level, progressively, so that it becomes affordable to everyone. The s12 right also provides compelling argument for the introduction of gene editing at state level, as it refers to the freedom to decide when and if to reproduce, and the right to access to safe, effective methods of family planning, which includes the right of access to healthcare services to promote safe child birth and to provide couples with the best chance of having a healthy infant. There are other rights included in the Bill of Rights that are of importance, including the rights to equality and the prohibition of unfair discrimination. These are important, as much of the conversation around the ethics of HGE focuses on whether these treatments, if sanctioned, would be available to people equally, and whether HGE itself constitutes discrimination against persons living with disabilities. Gene editing also creates the potential to undermine the inherent dignity and identity of persons with disabilities. These issues have also been considered in the context of other reproductive interventions such as preimplantation genetic diagnosis (PGD), and fall outside the ambit of this article.[19]

If we consider the provisions of the National Health Act No. 61 of 2003,[20] there are no provisions for gene editing except in the context of human reproductive cloning. The Act states that gametes, embryos and zygotes may not be genetically manipulated, but this prohibition applies in relation to human reproductive cloning. There are many ways in which legal provisions may be interpreted, and one of these methods takes into account the literal meaning of the words which are used by the legislature. On application of this method of interpretation one could argue that the legislature intended that the prohibition of genetic manipulation apply solely in the context of human cloning, and not gene editing for other purposes. However, there are other methods of interpretation, which include an examination of the purpose of a provision or 'mischief' or issue that the legislature was attempting to address when wording the provision. These approaches would indicate that the objective behind this provision was to prevent genetic manipulation of the human genome in a manner that is heritable, hence the reference to gametes, embryos and zygotes. What the consideration of both national and international law indicates is that there are legal provisions that may directly apply to HGE, but these are rare and, in the case of SA law, absent. What we know about the provisions of international law is that they are interpreted in the context of the technology to which they are being applied. There are many forms of technology that did not exist at the time at which these instruments were drafted and signed. However, the provisions indicate a general approach in international law that leans in favour of therapeutic interventions, and against heritable ones. The same may be said of SA law. The current framework was developed at a time when HGE had not been developed, and while it is debatable whether we may extend the meaning of s57 of the National Health Act to apply to gene editing, it is suggested that because specific applicable law does not exist, we should develop a legal framework that more directly applies to HGE. My suggestion is a two-stage approach, which involves international engagement and debate on HGE, as well as consultation at national level. This approach will serve to make debate as inclusive as possible, and the feedback obtained used to inform national legal reform, as well as consolidated and used to assist with the drafting of international laws on HGE. Furthermore, the two-stage approach is appropriate as it is inclusive, and the end result will be reform of both the international and national framework. While it is important to strengthen the national legal system, it is also appropriate to do so in the context of the international system, as this will create or enhance a sense of global community, that nations are deliberating and proceeding with engagement with these issues with reference to one another and not in isolation.

Discussion

The authors of the Geneva Statement[7] affirm the need for broader societal consensus before any decision to proceed with HGE can be made. They suggest that public engagement must be inclusive, global, transparent, informed, open in scope, supported by resources and given adequate time. They call for a 'course correction' that must function along three dimensions. Firstly, there must be a thorough and meaningful attempt made to address and clarify the various misrepresentations and misunderstandings that have distorted the public's understanding of heritable germline modification. Secondly, the conversation must be reoriented by focusing on the consequences of germline editing on society, as well as the threat to equality that it poses.[7] Finally, criteria for public engagement must be identified that will promote democratic governance through shared decision-making. The joint statement[13] issues a call to governments and stakeholders worldwide to prioritise ethical considerations in any future discussion and development of global governance of HGE, and to proceed with caution, responsibility and transparency. Together, these statements serve as an important symbol of necessary co-operation and global discussion.

These points cannot be undermined. Much of the public is uninformed as to what gene editing really entails, and many have been distressed by the idea of babies being designed, and the resurgence of eugenics. The nature of HGE is not therapeutic. It will not treat, cure or prevent disease in existing people the way that somatic gene therapy may treat a patient. Germline therapy can only modify the genes of future persons, by creating a modified genome that will be expressed in a person's offspring. For this reason, the authors of the Geneva Statement claim that it is not a medical intervention in the true sense, but merely satisfies our desire to control the characteristics of future people. I suggest that we step back and ask ourselves whether germline editing represents an unwarranted intervention in reproduction. It has been pointed out that there are existing alternatives available for persons who are unable to reproduce naturally, such as the use of third-party gametes and adoption. Additionally, *in vitro* fertilisation (IVF) exists as a means of assisted reproduction, and can be combined with interventions such as PGD where an individual is at risk of passing on genetic disease to their offspring. PGD is a procedure that detects chromosomal abnormalities in early embryos, and raises ethical issues of its own. There is some thought that these ethical issues will only be intensified with the addition of germline editing. This reasoning is correct, as we must ask whether it is justifiable to use an additional intervention where interventions such as IVF and PGD have not been successful. The presentation of HGE as an alternative to PGD in reproduction is misleading and unethical. The writers of the statement call for informed and engaged debate. This will be difficult, but it is necessary. Public debate on these issues will determine where society stands in relation to the idea of performing HGE and thereby exercising control over generations.

Immediate measures are suggested by the joint statement,[13] which considers four points:

(*i*) HGE must be brought within the control of relevant public authorities, and its abuse must be subject to appropriate sanction;

(*ii*) there should be no clinical attempt to use HGE until the acceptability of the intervention has been broadly debated;

(*iii*) there should be no further attempts at clinical use of HGE until research has reduced the considerable uncertainty about its inherent risks; and

(*iv*) before clinical trials of applications of HGE are permitted, the risks of adverse effects must have been appropriately assessed, and there must be measures put in place to monitor and review these.

These measures have also been identified by researchers in SA. In 2018, the Academy of Sciences of South Africa (ASSAf) released a report on 'Human genetics and genomics in South Africa: Ethical, legal and social implications', which was based on a consensus study undertaken by a panel appointed by ASSAf.[21] The findings of this preliminary study largely corroborate with the suggested measures of the authors of both the joint statement[13] and Geneva Statement.[8] The study highlighted the importance of, *inter alia*, engagement on the issues, protecting the public through regulation of marketing and the provision of services, and the development of policies and guidelines suitable for the African context. In this regard the committee proposed that 'legislation and policies should be developed in an inclusive and cross-cutting framework, taking into account national, regional and international contexts, and should avoid stifling innovation.' A second consensus study is currently being conducted by ASSAf.

Conclusion

Gene editing has the ability to permanently improve human health. However, our deliberations on the issues are specific to somatic or germline editing. With regard to germline editing, I am in agreement with the proposals of the statements that have recently been released. They provide reasons for effecting a pause, and engaging in vigorous public debate. The present article demonstrates the chronological development of the discussion at international level, as well as the existing national and international framework. What these aspects highlight is the fact that the decisions we make regarding heritable germline editing have high stakes for our shared future. Engagement must be global, to obtain as much participation in the conversation as possible. However, we must be conscious of the obstacles we will encounter in this endeavour. Cultural and traditional barriers will necessitate engagement models being tailored to suit various societal systems. Our DNA makes us similar, while our cultures and traditions make us different. The task we undertake in terms of public engagement is an attempt at reaching consensus via a balance of these two factors. It will be an onerous exercise, but a necessary one. The engagement has already started in SA and elsewhere, and must continue.

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