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RESEARCH ARTICLE

Navigating the Ethics of Genome Editing and Heritability

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ABSTRACT

This article explores the role of ethics in contributing to a deliberative discussion on the necessary principles that ought to shape future governance of an emerging technology – Heritable Human Genome Editing ('HHGE'). An ethical evaluation will be undertaken to identify some of the considerations pertaining to its intergenerational impact. This will be explored through the lens of genetic exceptionalism, human dignity and welfare as guiding ethical principles. The identification of and compliance with key ethical principles reflects a deontological approach. In practice, these principles are applied to achieve an outcome that maximises the welfare of future offspring. While this underlying rationale reflects a utilitarian approach, the practical enforcement of these ethical theories raises questions pertaining to their potential permeability. It is recognised these theories are rightly independent schools of thought. However, *in practice*, they can be permeable. Ethics, as applied *in practice*, does not necessarily require a "one theory fits all" approach to an ethical evaluation of this technology. While an outcome which maximises the welfare of future offspring is paramount, the means to achieve this are also important. These principles should inform the basis of an ethical evaluation in determining permissible uses of HHGE. Specifically, to prevent, treat or correct genetic disease.

Introduction

This article explores the role of ethics in contributing to a deliberative discussion on the necessary principles that ought to shape future governance of an emerging technology – Heritable Human Genome Editing ('HHGE'). An ethical evaluation will be undertaken to identify some of the considerations pertaining to its intergenerational impact. This refers to a unique attribute of germline genome editing – any edits made to the genome will be inherited by subsequent generations. A primary consideration raised by its intergenerational impact is the interests of future offspring. This will be explored through the lens of genetic exceptionalism, human dignity and welfare as guiding ethical principles. Together, it will be argued these principles ought to form the basis of an ethical evaluation in determining permissible uses of HHGE.

Ethics may be perceived as an anchor through which society identifies reasons for action or opinion. Julian Savulescu and Peter Singer defined ethics as 'the study of what we ought to do'¹. In contrast, science offers us facts and justification for observed phenomena. Ethics and science should not be divorced from one another. Rather, ethics provides a conduit to communicate issues and questions and a framework to facilitate a response. This article will highlight the ways in which ethics manifests into key ethical principles informing deliberative discussions and a pathway forward.

It is recognised that the specific field of genomics and genome editing is associated with an increased risk in the exaggeration of claims^{2,3}. This is often expressed in media headlines involving designer babies and superhumans. This article seeks to frame ethical considerations in a neutral way, as they arise in areas of potential applications of HHGE that are reasonably foreseeable.

This article will solely focus on HHGE, which refers to the editing of germline cells for reproduction purposes⁴. This is distinguished from the general term germline genome editing, which refers to the editing of germline or reproductive cells (either in human embryos or gametes) for non-reproduction purposes⁴. Unlike HHGE, this indicates there is no intention to implant these modified cells to achieve a pregnancy.

Following an ethical analysis of the intergenerational impact of HHGE – two conclusions will be made. First, ethics underpins the innate sense of judgement exercised when determining whether a specific application of HHGE is ethical. This is proceeded by an evaluation of the process

identifying the means to achieve a positive outcome. Second, a deontological approach is advocated, to ensure adherence to universally accepted ethical principles. In practice, these principles are applied to achieve an outcome that maximises the welfare of prospective parents and their future offspring. While this underlying rationale reflects a utilitarian approach, the practical enforcement of these ethical theories raises questions pertaining to their potential permeability. It is recognised these theories are rightly independent schools of thought. However, *in practice*, these ethical theories can be permeable. It is argued that ethics, as applied *in practice*, does not necessarily require a "one theory fits all" approach to an ethical evaluation of HHGE. While an outcome which maximises the welfare of future offspring is paramount, the means to achieve this are also important.

Contextualising the Ethics of Human Genome Editing

At the 2023 Third International Summit on Human Genome Editing, David Baltimore aptly noted "new technologies continue to challenge our society"⁵. The ethical deliberations of a new technology and the nature of the challenges posed by them are arguably more complex. In light of the ongoing advancements in CRISPR technology and more specifically, its application in germline cells, it is important to consider the ethical challenges that accompany this progression⁶.

Following the Third Summit, the Organising Committee published a statement of their concluding remarks, noting:

Heritable human genome editing remains unacceptable at this time. Public discussions and policy debates continue and are important for resolving whether this technology should be used. Governance frameworks and ethical principles for the responsible use of heritable human genome editing are not in place. Necessary safety and efficacy standards have not been met⁷.

Further, they concluded:

Preclinical evidence for the safety and efficacy of heritable human genome editing has not been established, nor has societal discussion and policy debate been concluded ... Heritable human genome editing should not be used unless, at a minimum, it meets reasonable standards for safety and efficacy, is legally sanctioned, and has been developed and tested under a system of rigorous oversight that is subject

to responsible governance. At this time, these conditions have not been met⁷.

As of March 2023, HHGE remains legally, ethically and scientifically impermissible^{4,8}. In the absence of preclinical evidence and interrogation on a transnational level of the ethical and social implications, HHGE cannot and will not be undertaken.

While germline genome editing is acceptable for basic research purposes⁷, concerns relating to its ethics and governance for reproduction remains at the forefront of global debate. It is important to emphasise two points, to contextualise this form of editing for ethical purposes and to highlight the uncertainty attached to a new technology is not unfamiliar.

First, mitochondrial donation is classified as a type of germline and heritable genome editing. Upon its conception, it also received significant scrutiny in relation to its ethical and regulatory implications. Over time, it has become an accepted technology, with legislative backing to enforce a governance framework (*Mitochondrial Donation Law Reform (Maeve's Law) Act 2022 (Cth)*).

Second, CRISPR technology was trialled in somatic cells, which was met with similar technical, ethical, social and public concerns. Recently, the Organising Committee concluded that "remarkable progress has been made in somatic human genome editing, demonstrating it can cure once incurable diseases"⁷. Despite this progress, the technology requires further research to improve understanding of risks and unintended consequences⁷. While risks associated with genome editing may be "reducible" by further research – "... it is only through research that we may find way[s] to overcome [risks]"¹⁰.

Ongoing research and human clinical application will enable the collation of evidence regarding safety and efficacy¹¹ and alleviate ethical concerns. In the context of HHGE, its intergenerational impact is a strong source of concern. While safety and efficacy may be centric to this ethical issue, other principles such as genetic exceptionalism, human dignity and welfare are closely associated. Although clinical applications may resolve or address some ethical concerns, it must be ensured that "the risks are small enough and the potential benefits great enough to justify taking this step"¹². Ethics will inevitably form part of the benefit-risk assessment.

These points reiterate that society has long been confronted with ethical issues raised by emerging technologies. Previous experiences should offer reassurance in society's ability to deliberate and address ethical implications associated with a new technology. Further, it suggests that the framework for an ethical evaluation exists to assist in traversing the ethics of HHGE.

The Ethical and Social Dimension of Heritable Human Genome Editing

This article focusses on one prominent ethical and social issue raised by HHGE – its intergenerational impact. This distinct feature of HHGE will be explored because the heritability of genome edits imposes a significant responsibility upon researchers and society. This responsibility requires the consideration of measures that may be undertaken to address and manage the uncertainty attached to HHGE. An overview of the literature examining the ethical and social impact of this issue will be provided.

Genome editing has been characterised as a "disruptive"^{3,14} and "transformative"¹⁵ technology, with the "... potential to create unintended disruptive effects"¹⁶. The debate has been said to be "located at the interface between science, technology, and society"¹⁷. Often, the prospects of an emerging technology are also accompanied by uncertainty and ambivalence, which may lead to polarised views within society¹⁸.

The literature concerning the ethics of HHGE has been described as "rich and expansive"^{13,19}. This "long history"^{20,21} of debate has now extended beyond pure "theoretical interest"²⁰ to reality.

In framing the issue of intergenerational impact, it is important to ensure the ethical considerations do not fall victim to "futuristic speculations"²², recognising that many of these familiar debates may be interrogated within a "context of alarmism"^{23,24}. Specifically, it is increasingly accepted that genetics "... seems to be particularly prone to enthusiastic predictions"².

This identifies a unique challenge accompanied by HHGE – "the task of separating hype from reality, and distant possibilities from early, practical applications"²⁵. Given the complexity attached to the technical functionality of CRISPR technology, public engagement and education to increase understanding and scientific literacy is paramount. This must be actively considered when engaging in a public dialogue concerning the ethics of HHGE.

The Importance of Ethics

If ethics is perceived as an anchor identifying reasons for action or opinion, it is reasonable to conclude that the notion of what we ought to do is governed by an innate sense of judgement. This refers to the “*geography of ethics*”, which indicates the principles and values guiding our innate judgement is very much context-specific. When confronted with a new technology and its accompanied concerns or issues, whose ethics are we applying? This specifically raises the impact of factors such as culture, religion, politics and positionality, upon the perception of an emerging technology. This was observed by Howard et al:

As we have learned from other ethically sensitive areas in the field of genetics and genomics, such as newborn screening, reproductive genetics or return of results, normative positions held by different stakeholders may be dissimilar and even completely incompatible. This might be influenced by various factors, such as commercial pressure, a technological imperative, ideological or political views, or personal values ... it is clear that associated values often differ between different stakeholder groups, different cultures and countries ... making widespread or global agreement on [the ethical and social issues] very difficult, if not impossible to reach ¹⁴.

Similarly, the Committee on Human Gene Editing observed that “... while science is global, it proceeds within a variety of political systems and cultural norms” ²⁶. The identification of fundamental principles that inform our ethical perception of an emerging technology is “no easy task” to ensure that a given principle can “transcend these differences and divisions while accommodating cultural diversity” ²⁶. While some principles may be deemed universal, the way in which they are translated in practice is often reflected in a governance approach. The governance of a new technology arguably reflects the boundaries of acceptable and unacceptable applications. Adherence to and prioritisation of these ethical principles is contingent upon context and culture. The Committee on Human Gene Editing further noted:

Achieving consensus around overarching ethical principles to undergird specific recommendations for action can be difficult, whether because no one theory of ethics has been accepted by philosophers and theologians or because no one algorithm for deriving principles from those theories has been found ²⁶.

Similarly, Jeremy Sugarman acknowledged the “repetitive” nature of debates concerning germline editing and HHGE, noting the importance of extending beyond the particulars associated with an emerging technology ²⁷. Notably, Sugarman highlighted the need to “articulate general principles” that are capable of being applied to a developing technology ²⁷. This flexibility would facilitate a necessary discretion for each international jurisdiction to undertake an individualised ethical evaluation of HHGE in accordance with their culture, values, ethics, political and religious status and social fabrics.

It is also important to highlight that the utility of clinical applications of genome editing is fundamentally premised upon accuracy and precision ²⁹. Generally, the “de facto global consensus” ³⁰ pertaining to HHGE is that it ought to be impermissible until greater knowledge concerning the safety, efficacy, risks and benefits is obtained ^{29,31,32}. Further, a “broad societal consensus” on ethical issues must be achieved ^{24,31,33}. However, difficulties arise in reaching a broad societal consensus when determining the relevant ethical principles that should inform acceptable uses of HHGE. For example, some caution against a myopic application of safety and efficacy as the predominant guiding principles ³¹. Rather, human dignity, the right to life, autonomy, justice, freedom of research, non-discrimination and solidarity are relevant principles that should guide a reflection of ethically permissible applications ³⁴.

This reinforces the innate context-specific nature of ethics. For this reason, it has been challenged whether a global societal consensus can be achieved through the application of universal guiding principles ³¹.

Despite the ethical teething challenges, the promise of HHGE is clear. Doudna highlighted this reality, “... we are entering an era in which genome-editing tools will be used to inactivate or correct disease-causing genes in patients, offering life-saving cures to people who have genetic disorders” ²⁹. Other commentators focus on the value of research in facilitating the development of precise therapies or treatments to cure heritable diseases and prevent heritable predispositions to disease ^{1,16,30,35–37}. In light of this, it is argued that research and development of germline genome editing, with the aim to transition to HHGE, is ethically justified ³⁵.

The importance of ethics cannot be undermined. While the geography of ethics renders the task of uniformly prioritising and applying principles difficult, if not impossible, this does not diminish its

importance. Rather, it reinforces that ethics provides the necessary framework to assess new technologies and guide its permissible uses.

Intergenerational Impact

One of the prevalent ethical concerns raised by HHGE is its intergenerational impact on future offspring. This is captured by the reality that the impact of HHGE “may not be fully known until a certain number of generations have inherited [the edits]”³⁸. Further, the complexities of gene frequency and microevolution render the possibility of predicting the impact of HHGE almost impossible³⁷. It has been a recurring topic of discussion within the literature concerning genome editing. For example, the French Comité Consultatif National D'éthique identified intergenerational impact as “... the main ethical question ... that is not part of a eugenic attempt to transform the human species”³⁹. In contrast, others acknowledged intergenerational impact can be perceived as an advantage compared to somatic genome editing^{19,40}.

Friedmann et al raised the ethical imperative to establish mechanisms to assess the long-term impact of HHGE⁴¹:

The requirement that the results of an experiment be susceptible to analysis and characterization before further applications are undertaken cannot be met with human germ-line modification with current methods because the results of any such manipulation could not be analyzed or understood for decades or generations – a situation incompatible with ethical imperatives and with the scientific method⁴¹.

The significant uncertainty attached to HHGE may render the assessment of intergenerational impact incompatible with the scientific method. Although uncertainty accompanies all innovative and emerging technologies, the case of HHGE would require a participant and a “... future person for whom adverse outcomes may be difficult, if not impossible, to redress”⁴². This reinforces the abstract nature of this ethical issue – one must consider the interests of individuals who are yet to exist.

The notion of uncertainty was identified as a distinct feature rendering governance of an emerging technology difficult¹⁸. This uncertainty has been described as the “... inescapable lack of knowledge about the range of possible outcomes or ... the likelihood that any particular outcome will ...

occur”¹⁸. This is a strong premise underpinning the ethical concerns of intergenerational impact.

In their systematic review on the ethics of germline genome editing, van Dijke et al identified one of the most commonly reported concerns was the “... safety risks for the child and subsequent generations due to off-target and on-target effects”¹³. Of the one hundred and eighty articles included in the review, a total of seventy-six articles referred to the intergenerational impact of HHGE as an ethical concern¹³. For example, some articles raised the technical limitations as an argument against HHGE¹³. Others noted the safety risks may be unpredictable, and the current difficulty in ensuring safety prior to HHGE or relying upon preimplantation genetic diagnosis to assess unintended effects¹³. Articles also raised that the implications of intergenerational impact extend to the imposition of long-term monitoring mechanisms to assess its safety in subsequent generations¹³.

Carolyn Brokowski, in her review of sixty-one ethics statements published by the international community, identified the intergenerational impact as involving possible “irrevocable” and unforeseen risks for future generations, which was inextricably linked to the “... preservation of human dignity and individuality”³¹.

In light of the unforeseen consequences of a germline edit throughout generations, this is a strong basis underpinning ethical opposition to HHGE⁴³. For example, Lanphier et al opposed the use of germline genome editing and HHGE, arguing “... genome editing in human embryos using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable”⁴⁴.

The intergenerational impact of HHGE is particularly relevant to future generations. It invokes a number of considerations pertaining to the interests of future offspring, genetic exceptionalism, human dignity and welfare. Of particular importance is the welfare of the future offspring, in light of the significant uncertainty attached to HHGE. In their concluding remarks, the Nuffield Council on Bioethics observed that there are circumstances in which HHGE may be ethically permissible, if appropriate measures to safeguard the welfare of the future person are implemented⁴². This conclusion was premised upon detailed consideration of various ethical principles, including respect for reproductive autonomy and a desire for prospective parents to have a genetically related child⁴². The interests of future offspring raise a number of ethical principles relevant to

intergenerational impact. These will be explored as a means to highlight how the issue of intergenerational impact may be influenced by these principles.

The Interests of Future Offspring

This intergenerational impact is particularly relevant to future generations. The notion of a future person, their identity, dignity and capacity to hold rights has been the subject of philosophical debate^{42,45,46}. This article does not explore the literature concerning the moral status of a future child, or their capacity to be a 'bearer of potential rights'⁴⁵. Rather, it is argued the welfare – which refers to the social and health betterment of a future child⁴⁷, should be one of the relevant ethical principles guiding the permissibility of HHGE. In making this conclusion, the end does not itself justify the means. The process by which the technology moves forward, while ensuring responsible use and ethical adherence remains paramount²⁹.

In the context of the future offspring's interests, the ethical dilemma is nuanced. On the one hand, opponents to HHGE argue the uncertainty and safety risks render any use ethically impermissible. In contrast, alternative forms of reproduction are not risk-free. Proponents have highlighted the inherent dangers of sexual reproduction and current assisted reproductive techniques – which also carry uncertainty and risks⁴⁸. For example, the Danish Council on Ethics highlighted the undesirable impacts associated with "ordinary assisted reproduction" techniques, which "... even after 30 years of use – remain to be clarified fully"⁴⁹. Noting these uncertainties and possibility of increased disease risk later in life, they observed that "[i]n everyday practice of assisted reproduction, these safety questions do not weigh heavily"⁴⁹.

Two principles will be applied to intergenerational impact and the interest of future offspring – genetic exceptionalism and human dignity. These may be perceived as inviolable ethical red lines against permissible uses of HHGE. Alternatively, they may be ethical imperatives, justifying permissible uses of HHGE. In this way, they could be viewed as positive obligations to pursue specific applications of HHGE. With respect to intergenerational impact, they support the principle of welfare as an ethical anchor to justify specific applications of HHGE. These are the prevention, treatment or correction of genetic disease.

GENETIC EXCEPTIONALISM:

Genetic exceptionalism may be perceived as a barrier to distinguishing genome interventions from other medical interventions⁴². This term is used to

describe genetic information as "special or unique" and distinctly different from other medical information^{42,50}. This is relevant to the inquiry as to the special status attached to genome interventions, when compared to other non-genome interventions. This was raised by Ormond et al, who sought views from different disease group stakeholders²⁸. Results indicated that some stakeholders argued that ascribing "... too much ethical weight ..." on gene editing, as opposed to other treatments or lifestyles constitutes a form of genetic exceptionalism²⁸.

Other arguments highlighted the innate ability to alter the biological or genetic lineage of generations warrants serious consideration of acceptable genetic edits⁴². Our perception of identity and dignity are arguably the underlying factors prompting this line of argument, as our genetics should not be vulnerable to manipulation without ethical impunity. In opposition to this, is the notion that there are many other non-technological means to alter the biology of a future person⁴².

This raises the well-known nature versus nurture argument. The biological composition of an individual can be influenced by a number of factors, the impact of which is observed through the expression of a given gene. The term "ecogenetics" has been adopted to describe these factors, which together, may divert an individual's path of health²⁵. These factors include epigenetic changes, gene interactions, naturally occurring mutations, environmental exposures (such as chemicals, upbringing and diet) and social milieu (socio-economic status, educational opportunities, culture and religion). While HHGE represents a technological solution, it is distinct from the abovenamed factors only in its mechanism of delivering an alteration to DNA. In applying a deontological lens to genetic exceptionalism, it may be argued any means to adhere to this principle ought to be explored. However, a utilitarian approach would contend that any attempt to promote the welfare of future offspring is ethically justified. If welfare is maximised, the ethical grounding to pursue HHGE is established.

The special status attributed to DNA is also influenced by the ethical concept of naturalness. Our biological composition upon conception is a product of nature – the culmination of complex biological processes to create an embryo capable of sustaining life. Some commentators argued that interfering in the human genome is a transgression to the divine laws or an act of playing God^{30,40,49,52,53}. This article does not explore the ethical, theological or philosophical considerations attached

to the moral status of an embryo, nor does it engage with literature concerning the sanctity of life. This does not imply that these issues are irrelevant or insignificant to the ethical evaluation of HHGE.

However, it is relevant to consider the role of naturalness when applying genetic exceptionalism as a barrier to, or facilitator of, permissible uses of HHGE. The German Ethics Council contended naturalness is premised upon two arguments – the notion that the germline of an individual is representative of the “heritage of mankind” and the consequences of this technology from an evolutionary perspective⁵⁴. The symbolic significance of DNA as a natural product, which should not be derived from, or altered by, technological intervention, is a rationale for this principle. To intervene using germline genome editing would be to “... [impose] limits on human creative will”⁵⁴. Other arguments noted that HHGE “... implies a new level of [interference]” that should be considered irresponsible³⁷.

Despite objections, there will be a cohort of society that argue any form of HHGE will remain unacceptable as it “... involves artificially changing natural processes”¹². The Danish Council on Ethics also raised that opponents may perceive gene editing as the limit to interference with nature, whereby it is “... too complex and incomprehensible for human beings to get involved in”⁴⁹. However, as noted above, this argument loses its strength when considering the many factors that impact gene expression and are heritable. Modern assisted reproductive techniques are also accompanied by “... considerable manipulation of gametes and embryos, manipulations that, at least in the early days, might well have had considerable unintended consequences”²⁸.

The application of genetic exceptionalism to the issue of intergenerational impact refers to the ability to use a technology to alter the germline of a future person. It is argued that genetic exceptionalism is inextricably linked to intergenerational impact – “... we cannot predict with certainty what is going to happen in the future”⁴². The complexity of competing factors – epigenetic, gene interactions, environmental and social impact, culture and biography – all represent forms of genetic intervention. As observed by the Nuffield Council on Bioethics:

... what is at stake are interventions that, along with a number of other factors, have consequences for the kind of life the future person may have. At the margin (e.g. in the case of serious inherited genetic disease),

they can be strongly determinative, but genomic intervention is only one – and probably not the most significant – of the decisions that parents will make that affect their offspring (and it may become progressively less important as other biographical factors intervene, especially to the developing sense of self-identity)⁴².

Rather, we must consider the significance of the uncertainty and its influence over our decision-making when determining permissible uses of HHGE. For example, what if there are cases involving medical necessity to avoid a fatal genetic disease? Our risk tolerance may differ depending on the circumstance. In this instance, it may be that our genetic exceptionalism offers us the opportunity to embrace a new technology, provided it is safe to do so, in order to maximise the welfare of future offspring. There is an argument that technological advancement has strengthened the principle of genetic exceptionalism, to the extent that we may utilise this new genetic knowledge to benefit the welfare of future generations.

HUMAN DIGNITY:

The notion of human dignity has been the subject of ethical interrogation by many commentators^{12,15,20,26,42,54}. Its philosophical roots can be traced to Immanuel Kant, who considered dignity to be a universal principle, creating a categorical imperative upon all citizens to respect and uphold this principle⁴⁷. This highlights the importance of safeguarding dignity as a universal principle, particularly in the context of a transformative technology that holds the capacity to alter our genetic make-up.

The concept of human dignity is also interrelated to identity and how our genetic material contributes to our perception of it. Identity may be perceived as a biological and social construct. Biological identity may refer to our genetic make-up and inheritance, while our social identity may refer to factors such as our personality characteristics. Further, it is the impetus prompting our deliberation concerning the significance of our genetic material and how it may influence our phenotypic identity or humanism.

Dignity, as a right, also derives its strength as a guiding principle from international conventions, including Article 1 of the *United Nations Universal Declaration of Human Rights*. The *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* – known as the *Oviedo Convention*, is a relevant example. Within its preamble, the *Oviedo Convention* reinforces the importance of respecting

human dignity. In order to meet this objective, it recognises that advancements in science may endanger human dignity, reinforcing the need for safeguarding measures to be implemented to counteract this risk. Consequently, the role of human dignity represents "... the essential value to be upheld. It is at the basis of most of the values emphasised in the Convention"⁵⁵.

A deontologist would argue a principle or right is absolute. However, in law and practice, no human right is absolute. There are instances in which rights may conflict with one another or interference is authorised. The permissibility of HHGE would be one instance in which a basic principle, such as human dignity, may be infringed. In reality, while rights and principles are not necessarily absolute, they may conflict or balance with one another. Consequently, a governance response would need to ensure this infringement is ethically justifiable and proportionate.

An argument in opposition to HHGE is that it violates human dignity^{27,42}. This is premised, in part, by the notion that all future offspring ought to have a human right to inherit a genotype that has not been intentionally edited¹². In addition, it has been argued germline genome editing diminishes human dignity, as it undermines a respect for genetic diversity²⁶. It has also been argued that intentional edits to the germline fails to appreciate the natural order and devalue the status of what it is to be human²⁶. Consequently, it was contended that dignity "... affirm[s] that humans have value simply by virtue of being human and not because of their capacities, and thus cannot be treated as instruments of another's will"²⁶. A Kantian view of dignity endorses this argument, as human agency and free will were perceived to be fundamental tenets of human dignity²⁶.

These arguments highlight that genetics shapes our biological and social identity, contributing to the rich gene pool of a society. To manipulate our genes, is to alter our identity and genetic contribution to society. Subsequently, any edits made to our genes should only be undertaken in circumstances that respect the dignity and welfare of future offspring, such as disease prevention, treatment or correction.

The veracity of arguments claiming to violate dignity weakens in light of the plethora of factors causing genomic changes, including epigenetics, gene interactions, environmental exposures and social milieu. These arguments also lose strength if applied in the context of using HHGE to correct genetic defects to restore the health of future generations⁴⁰. In this instance, choice becomes a

relevant ethical consideration, as prospective parents will exercise decision-making autonomy to undergo HHGE. In light of this, "it is difficult to see how this would show a lack of respect for human dignity"⁴⁰. This represents a strong argument for the following proposition: the use of HHGE as a means to prevent, treat or correct genetic diseases preserves human dignity.

It has been acknowledged that critical questions pertaining to human dignity cannot be answered "... in a uniform way owing to profoundly different notions of the concept of dignity"²⁷. Therefore, it may be argued that human dignity cannot be used to justify a blanket condemnation on all forms of HHGE⁴⁰. A more nuanced approach must be adopted, which relies on the application of ethical principles to guide permissibility.

Julian Savulescu noted we have a moral imperative to continue genome editing research in embryos. In contrast to a deontologist, a utilitarian agenda would argue that any use of HHGE which maximises welfare and the betterment of global health is ethically permissible. In this vein, Savulescu and colleagues reasoned:

To intentionally refrain from engaging in life-saving research is to be morally responsible for the foreseeable, avoidable deaths of those who could have benefitted. Research into gene-editing is not an option, it is a moral necessity⁵⁶.

In light of this, Savulescu et al recognised the transformative potential of HHGE to reduce the global disease burden and benefit millions of individuals⁵⁶. More recently, this argument was framed in terms of intergenerational justice. Christopher Gyngell, Hilary Bowman-Smart and Savulescu suggested there is a "... strong moral imperative ..." to develop HHGE for the benefit and interests of future generations, as a "... matter of intergenerational justice"⁵⁷. In this context, intergenerational justice is a utilitarian concept which is achieved by fulfilling our societal obligation to future generations to avoid genetic disease. The authors offered the following rationale for this moral imperative – as advances in modern medicine continue to arise, selection pressures that have historically confronted humans will be mitigated or removed⁵⁷. Consequently, this may lead to an increased rate of random mutations in a given gene pool⁵⁷. Gyngell et al argued that:

As we develop effective and accessible treatments for disease, we all but guarantee that the incidence of those diseases will increase in future generations. This is because mutations which arise that

contribute to those diseases are no longer selected against⁵⁷.

By embracing HHGE, the authors contended that future generations will be able to avoid a “medicalised future”, enjoying “... the same level of genetic health ...”⁵⁷ or arguably better health. In a similar vein, de Wert et al recognised that the correction of disease-causing genes may promote justice, by “increasing the equality of opportunity of every person”⁴⁰. As such, the permissibility of HHGE would symbolise a “compensatory action”⁵⁷ to maximise the welfare of future generations. A similar rationale was presented by Doudna and Sternberg, “[i]f we have tools that can one day help doctors safely and effectively correct mutations, whether prior to or just after conception, it seems to me that we’d be justified in using them”⁵³.

The notion of dignity is also relevant to the principle of procreative beneficence. According to Savulescu, this principle advocates that “couples (or single reproducers) should select the child, of the possible children they could have, who is expected to have the best life, or at least as good a life as the others, based on the relevant, available information”⁵⁸. In supporting this utilitarian principle, Savulescu argued that prospective parents should use available information to choose an option that will most likely bring the best outcome⁵⁸. The notion of a best outcome translates to the selection of an embryo that will have the “best life”, which is understood as a life with “... the most wellbeing”⁵⁸. However, this is a very subjective outcome, which will be defined according to the context in which ethical principles apply. The impact of non-genomic factors on gene expression must also be considered when determining the potential for a best life.

Procreative beneficence may be appropriately applied to prospective parents who are faced with a decision to undergo HHGE to prevent a fatal genetic disease. If procreative beneficence is applied in this scenario, it so follows that the principle reinforces welfare and preserves the dignity of the future offspring. While Gyngell et al offer a deontological argument to pursue HHGE as a moral imperative, procreative beneficence is representative of a utilitarian position. Both a deontological and utilitarian argument strive to affirm an ethical basis to justify the use of HHGE exists in cases where a genetic disease can be prevented or corrected.

Support for the Principle of Welfare

Genetic exceptionalism and human dignity offer two examples whereby an argument for and against permissible uses of HHGE exists. Further,

they highlight the complexity in navigating the ethical terrain that accompanies HHGE. In applying these concepts to the ethical issue of intergenerational impact – it is argued that they support the principle of welfare, which should be a relevant factor in determining permissible uses of HHGE. As noted above, welfare refers to the social and health betterment of future offspring⁴⁷.

Similarly, the Nuffield Council on Bioethics defined the principle – “the welfare of the future person” as:

Gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be used only where the procedure is carried out in a manner and for a purpose that is intended to secure the welfare of and is consistent with the welfare of a person who may be born as a consequence of treatment using those cells⁴².

While this principle should be a compulsory factor to consider when determining the permissibility of HHGE, it is not sufficient in itself to render an application ethically permissible⁴². It is argued this proposition is reasonable and should be accepted. It represents a deontological approach. Any future decision to pursue HHGE should adhere to this principle. Compliance with this principle will maximise the welfare of future offspring. However, the means to achieve this goal remain important. This refers to the importance of the plethora of ethical issues invoked by HHGE, including, but not limited to safety, efficacy and equitable access. While the identification of guiding ethical principles has a deontological basis, the outcome of their application in practice, notably to maximise welfare, remains an important consideration.

The principle of welfare is also consistent with Article 13 of the *Oviedo Convention*, which states that “[a]n 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” (*Oviedo Convention*, 1999). Despite its prohibition on HHGE, it is arguable that, as the technology continues to mature, any application would be premised upon diagnostic, preventive and therapeutic aims to promote the welfare of future generations.

The benefits of HHGE on a population-level also support the principle of welfare. For example, Rubeis and Steger observed:

Correcting a pathogenic genetic mutation in the germ cells of an individual patient means that the genetic errors disappear from the germline. Thus, the mutation is prevented from spreading within the gene pool of a given population. Disease prevention would benefit future generations, in addition to the individual affected by the application of GGE [germline genome editing] ... this argument suggests that we are morally obliged to improve health outcomes for future generations. In addition, the implementation of a large-scale program would lead to an eventual decrease in healthcare costs. Taken in its totality, supporters of GGE claim that in the light of its public health benefits, this pursuit should be regarded as a moral imperative ³⁷.

This merely reinforces the need to comply with the welfare of the future person as a principle guiding the development of HHGE, with the intent to advance the welfare of future generations. It is clear that “any research involving germline genome editing should not be completely rejected on ethical grounds” ⁵⁹. This position was also endorsed by the World Health Organisation, where it was concluded “innovation in human genome editing should be driven by anticipated benefit to individuals and society in human health and collective well-being” ⁶⁰. However, this does not mean the process of attaining this goal is ethically insignificant. Developments must be achieved within an ethically acceptable framework of innovation and governance.

While intergenerational impact represents a significant recurring ethical issue in the literature, it is clear it does not completely preclude some applications of HHGE. Two such instances include the prevention, treatment or correction of genetic disease.

Conclusion

The literature concerning the ethics of HHGE is vast. As a result, this article sought to provide a discussion concerning one recurring ethical issue – intergenerational impact.

The way in which ethical issues are framed within the public domain is influenced by a number of factors. The reality of genotype is evidenced by the fear surrounding CRISPR technology and its potential capabilities – namely speculative claims of designer babies and superhumans. This reinforces the need to maintain neutrality when framing these ethical considerations.

This article has also highlighted the “*geography of ethics*”. Specifically, the context-specific nature of ethical principles, their social value, prioritisation and translation in practice. For this reason, it is difficult to achieve a global societal consensus concerning universal ethically permissible applications of HHGE. This was aptly noted by Ormond et al:

One of the challenges in moving forward is arriving at an ethical policy decision. To do so, we must bridge the chasm between descriptive ethics (i.e., what people believe should be done) and normative ethics (i.e., what ethical principles oblige), perspectives that are sometimes considered irreconcilable ²⁸.

In addition to these challenges, measures must be implemented to mitigate the risk of ethics being sidelined, when competing against prevailing factors such as the economy and political power.

Precedent shows us that uncertainty is not sufficient in itself to hinder or condemn uses of a new technology, despite the presence of ethical concerns. Rather, reassurance is offered when relying upon ethics as the necessary anchor to identify issues and provide a framework for a response that is substantiated.

Intergenerational impact represents a unique attribute of germline editing. The heritability of edits has ignited a global dialogue questioning the relevance of ethical principles including the interests of future offspring, genetic exceptionalism, human dignity and welfare. While arguments may be made regarding these principles as barriers to or initiators of HHGE, their prioritisation and operationalisation is context-specific. It is argued a deontological approach, advocating for compliance to these principles is necessary. Notably, when determining whether a proposed application of HHGE ought to be permissible, compliance with the principle of the welfare of the future person is essential.

Our increased capacity and access to genetic knowledge arguably harnesses individuals with a new tool to use when exercising reproductive autonomy. A robust argument can be made to support the application of HHGE to prevent, treat or correct a genetic disease, as a means to promote intergenerational justice, the welfare of future generations and the preservation of dignity. Further, the value and importance of ‘choice’ cannot be undermined. Exercising a choice to undergo HHGE promotes reproductive autonomy and liberty. It also enables ethical principles to be autonomously applied to an individual’s

circumstances, accommodating for the context-specific nature of ethics.

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