Humanities & Social Sciences Communications

REVIEW ARTICLE

https://doi.org/10.1057/s41599-022-01147-y OPEN

Beyond safety: mapping the ethical debate on heritable genome editing interventions

Mara Almeida [1]✉ & Robert Ranisch [2,3]

Genetic engineering has provided humans the ability to transform organisms by direct manipulation of genomes within a broad range of applications including agriculture (e.g., GM crops), and the pharmaceutical industry (e.g., insulin production). Developments within the last 10 years have produced new tools for genome editing (e.g., CRISPR/Cas9) that can achieve much greater precision than previous forms of genetic engineering. Moreover, these tools could offer the potential for interventions on humans and for both clinical and non-clinical purposes, resulting in a broad scope of applicability. However, their promising abilities and potential uses (including their applicability in humans for either somatic or heritable genome editing interventions) greatly increase their potential societal impacts and, as such, have brought an urgency to ethical and regulatory discussions about the application of such technology in our society. In this article, we explore different arguments (pragmatic, socio-political and categorical) that have been made in support of or in opposition to the new technologies of genome editing and their impact on the debate of the permissibility or otherwise of human heritable genome editing interventions in the future. For this purpose, reference is made to discussions on genetic engineering that have taken place in the field of bioethics since the 1980s. Our analysis shows that the dominance of categorical arguments has been reversed in favour of pragmatic arguments such as safety concerns. However, when it comes to involving the public in ethical discourse, we consider it crucial widening the debate beyond such pragmatic considerations. In this article, we explore some of the key categorical as well sociopolitical considerations raised by the potential uses of heritable genome editing interventions, as these considerations underline many of the societal concerns and values crucial for public engagement. We also highlight how pragmatic considerations, despite their increasing importance in the work of recent authoritative sources, are unlikely to be the result of progress on outstanding categorical issues, but rather reflect the limited progress on these aspects and/or pressures in regulating the use of the technology.

[1] Centro de Filosofia das Ciências da Universidade de Lisboa, Campo Grande, 1749-016 Lisbon, Portugal. [2] Faculty of Health Sciences Brandenburg, University of Potsdam, Karl-Liebknecht-Str. 24-25, House 16, 14476 Potsdam, Golm, Germany. [3] Research Unit "Ethics of Genome Editing", Institute for Ethics and History of Medicine, University of Tübingen, Gartenstr. 47, 72074 Tübingen, Germany. ✉email: msalmeida@fc.ul.pt

Introduction

The ability to alter a sequence of genetic material was initially developed in microorganisms during the 1970s and 1980s (for an overview: Walters et al., 2021). Since then, technological advances have allowed researchers to alter DNA in different organisms by introducing a new gene or by modifying the sequence of bases in the genome. The manipulation of the genome of living organisms (typically plants) continues a course that science embraced more than 40 years ago, and may ultimately allow, if not deliberately curtailed by societal decisions, the possibility of manipulating and controlling genetic material of other living species, including humans.

Genetic engineering can be used in a diverse range of contexts, including research (e.g., to build model organisms), pharmacology (e.g., for insulin production) and agriculture (e.g., to improve crop resistance to environmental pressures such as diseases, or to increase yield). Beyond these applications, modern genetic engineering techniques such as genome editing technologies have the potential to be an innovative tool in clinical interventions but also outside the clinical realm. In the clinical context, genome editing techniques are expected to help in both disease prevention and in treatment (Porteus, 2019; Zhang, 2019). Nevertheless, genome editing technology raises several questions, including the implications of its use for human germline cells or embryos, since the technology's use could facilitate heritable genome editing interventions (Lea and Niakan, 2019). This possible use has fuelled a heated debate and fierce opposition, as illustrated by the moratoriums proposed by researchers and international institutions on the use of the technology (Lander et al., 2019; Baltimore et al., 2015; Lanphier et al., 2015). Heritable human germline modifications are currently prohibited under various legislations (Baylis et al., 2020; Ledford, 2015; Isasi et al., 2016; König, 2017) and surveys show public concerns about such applications, especially without clear medical justification (e.g., Gaskell et al., 2017; Jedwab et al., 2020; Scheufele et al., 2017; Blendon et al., 2016).

To analyse some implications of allowing heritable genome editing interventions in humans, it is relevant to explore underlying values and associated ethical considerations. Building on previous work by other authors (e.g., Coller, 2019; de Wert et al., 2018; van Dijke et al., 2018; Mulvihill et al., 2017; Ishii, 2015), this article aims to provide context to the debates taking place and critically analyse some of the major pragmatic, categorical and sociopolitical considerations raised to date in relation to human heritable genome editing. Specifically, we explore some key categorical and sociopolitical considerations to underline some of the possible barriers to societal acceptance, key outstanding questions requiring consideration, and possible implications at the individual and collective level. In doing so, we hope to highlight the predominance of pragmatic arguments in the scientific debate regarding the permissible use of heritable genome editing interventions compared to categorical arguments relevant to broader societal debate.

Box 1 | Difference associated with germline cells and somatic cells.

For the purposes of the analysis presented in this article, one of the main differences is the heritability of genes associated with either type of cell. Germline cells include spermatozoa, oocytes, and their progenitors (e.g., embryonic cells in early development), which can give rise to a new baby carrying a genetic heritage coming from the parents. Thus, germline are those cells in an organism which are involved in the transfer of genetic information from one generation to the next. Somatic cells, conversely, constitute many of the tissues that form the body of living organisms, and do not pass on genetic traits to their progeny.

Human genome editing: a brief history of CRISPR/Cas9

Human genome editing is an all-encompassing term for technologies that are aimed at making specific changes to the human genome. In humans, these technologies can be used in embryos or germline cells as well as somatic cells (Box 1). Concerning human embryos or germline cells, the intervention could introduce heritable changes to the human genome (Lea and Niakan, 2019; Vassena et al., 2016; Wolf et al., 2019). In contrast, an intervention in somatic cells is not intended to result in changes to the genome of subsequent generations. It is worth noting that intergenerational effects occur only when the modified cells are used to establish a pregnancy which is carried to term. Thus, a distinction has been made between germline genome editing (GGE), which may only affect in vitro embryos in research activity, and heritable genome editing (HGE), which is used in reproductive medicine (e.g., Baylis et al., 2020). HGE could be used to prevent the transmission of serious genetic disease; however, other applications could be imagined, e.g., creating genetic resistance or even augmenting human functions.

In the last decade, prominent technical advances in genome engineering methods have taken place, including the zinc-finger nucleases (ZFNs) and TAL effector nucleases (TALENs), making human genome modification a tangible possibility (Gaj et al., 2013; Li et al., 2020; Gupta and Musunuru, 2014). In 2012, a study showed that the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), combined with an enzyme called Cas9, could be used as a genome-editing tool in human cell culture (Jinek et al., 2012). In 2013, the use of CRISPR/Cas9 in mammalian cells was described, demonstrating the application of this tool in the genome of living human cells (Cong et al., 2013). In 2014, CRISPR/Cas9 germline modifications were first used in non-human primates, resulting in the birth of gene-edited cynomolgus monkeys (Niu et al., 2014). This was followed in 2015 by the first-ever public reported case of genome modification in non-viable human embryos (tripronuclear zygotes) (Liang et al., 2015). This study has caused broad concerns in the scientific community (Bosley et al., 2015) with leading journals rejecting publication for ethical reasons. Five years after these initial experiments were conducted, more than 10 papers have been published reporting the use of genome editing tools on human preimplantation embryos (for an overview: Niemiec and Howard, 2020).

Compared to counterpart genome technologies (e.g., ZFNs and TALENs), CRISPR/Cas9 is considered by many a revolutionary tool due to its efficiency and reduced cost. More specifically, CRISPR/Cas9 seems to provide the possibility of a more targeted and effective intervention in the genome involving the insertion, deletion, or replacement of genetic material (Dance, 2015). The potential applicability of CRISPR/Cas9 technique is considered immense, since it can be used on all type of organisms, from bacteria to plants, non-human cells, and human cells (Barrangou and Horvath, 2017; Hsu et al., 2014; Doudna and Charpentier, 2014; Zhang, 2019).

Germline interventions: the international debate

As a reaction to the 2015 study with CRISPR/Cas9, several commentaries by scientists were published regarding the future use of the technology (e.g., Bosley et al., 2015; Lanphier et al., 2015; Baltimore et al., 2015). Many of them focused on germline applications, due to the possibility of permanent, heritable changes to the human genome and its implications for both individuals and future generations. These commentaries included

position statements calling for great caution in the use of genome editing techniques for heritable interventions in humans and suggested a voluntary moratorium on clinical germline applications of CRISPR/Cas9, at least until a broad societal understanding and consensus on their use could be reached (Brokowski, 2018; Baltimore et al., 2015; Lander, 2015). Such calls for a temporary ban were often seen as reminiscent of the "Asilomar ban" on recombinant DNA technology in the mid-1970s (Guttinger, 2017). Other commentaries asked for research to be discouraged or halted all together (Lanphier et al., 2015). More firmly, the United States (US) National Institutes of Health (NIH) released a statement indicating that the NIH would not fund research using genome editing technologies on human embryos (Collins, 2015).

In December 2015, the first International Summit on Human Gene Editing took place, hosted by the US National Academy of Sciences, the US National Academy of Medicine, the UK Royal Society, and the Chinese Academy of Sciences (NASEM). The organizing committee issued a statement about appropriate uses of the technology that included the following: "It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application" (NASEM, 2015).

Following this meeting, initiatives from different national bodies were organized to promote debate on the ethical issues raised by the new genome editing technologies and to work towards a common framework governing the development and permissibility of their use in humans. This included an ethical review published in 2016 by the Nuffield Council on Bioethics, addressing conceptual and descriptive questions concerning genome editing, and considering key ethical questions arising from the use of the technology in both human health and other contexts (Nuffield Council on Bioethics, 2016). In 2017, a committee on human genome editing set up by the US National Academy of Sciences (NAS) and the National Academy of Medicine (NAM) carried out a so-called consensus study "Human Genome Editing: Science, Ethics, and Governance" (NASEM, 2017). This study put forward a series of recommendations on policies and procedures to govern human applications of genome editing. Specifically, the study concluded that HGE could be justified under specific conditions: "In some situations, heritable genome editing would provide the only or the most acceptable option for parents who desire to have genetically related children while minimizing the risk of serious disease or disability in a prospective child" (NASEM, 2017). The report stimulated much public debate and was met with support and opposition since it was seen as moving forward on the permissibility of germline editing in the clinical context (Ranisch and Ehni, 2020; Hyun and Osborn, 2017).

Following the report in 2016, the Nuffield Council on Bioethics published a second report in 2018. Similar to the NASEM 2017 report, this report emphasizes the value of procreative freedom and stresses that in some cases HGE might be the only option for couples to conceive genetically related, healthy offspring. In this document, the Nuffield Council on Bioethics maintains that there are no categorical reasons to prohibit HGE. However, it highlights three kinds of interests that should be recognized when discussing prospective HGE. They are related to individuals directly affected by HGE (parents or children), other parts of society, and future generations of humanity. In this context, two ethical principles are highlighted as important to guide future evaluations of the HGE use in specific interventions: "(...) to influence the characteristics of future generations could be ethically acceptable, provided if, and only if, two principles are satisfied: first, that such interventions are intended to secure, and are consistent with, the welfare of a person who may be born as a consequence, and second, that any such interventions would uphold principles of social justice and solidarity (…)" (Nuffield Council on Bioethics, 2018). This report was met with criticism for (implicitly) advocating genetic heritable interventions might be acceptable even beyond the boundaries of therapeutic uses. This is particularly controversial and goes well beyond the position previously reached by the NASEM report (which limited permissible uses of genome editing at preventing the transmission of genetic variants associated to diseases) (Drabiak, 2020). On the other hand, others have welcomed the report and, within it, the identification of explicit guiding ethical principles helpful in moving forward the debate on HGE (Gyngell et al., 2019).

As a follow-up to the 2015 conference, a second International Summit on Human Gene Editing was scheduled for November 2018 in Hong Kong (National Academies of Sciences, Engineering, and Medicine, 2019). The event, convened by the Hong Kong Academy of Sciences, the UK Royal Society, the US National Academy of Sciences and the US National Academy of Medicine, was supposed to focus on the prospects of HGE. Just before the Summit began, news broke that He Jiankui, a Chinese researcher and invited speaker at the Summit, created the world's first genetically edited babies resulting from the use of CRISPR/Cas9 in embryos (Regalado, 2018; Lovell-Badge, 2019). Although an independent investigation of the case is still pending, his experiments have now been reviewed in detail by some scholars (e.g., Greely, 2019, 2021; Kirksey, 2020; Davies, 2020; Musunuru, 2019). These experiments were globally criticized, since they did not follow suitable safety procedures or ethical guidelines (Wang and Yang, 2019; Lovell-Badge, 2019; Krimsky, 2019), nor considered the recommendations previously put forward by international reports (NASEM, 2017; Nuffield Council on Bioethics, 2018) and legal frameworks (Araki and Ishii, 2014; Isasi et al., 2016). Different reactions were triggered, including another call by scientists for a global moratorium on clinical human genome editing, to allow time for international discussions to take place on its appropriate uses (Lander et al., 2019) or an outright ban on the technology (Botkin, 2019). There were also calls for a measured analysis of the possible clinical applications of human genome editing, without the imposition of a moratorium (Daley et al., 2019; Dzau et al., 2018).

Most countries currently have legal frameworks to ban or severely restrict the use of heritable genome editing technologies (Araki and Ishii, 2014; Isasi et al., 2016; Baylis et al., 2020). However, since He's experiment, the possibility that researchers might still attempt (with some likelihood of success) to use the technology in human embryos, became a growing concern, particularly since some scientists have already announced their interest in further clinical experiments (Cyranoski, 2019). For many, He's experiments highlighted the ongoing risks associated with the use of modern genome editing technology without proper safety protocols and regulatory frameworks at an international level (Ranisch et al., 2020). This has triggered the need to develop clear and strict regulations to be implemented if these tools are to be used in the future. This incident also led to the formation of several working groups, including the establishment of an international commission on the Clinical Use of Human Germline Genome Editing set up by the US National Academy of Medicine, the US National Academy of Sciences, and the UK's Royal Society. In 2020, the commission published a comprehensive report on HGE, proposing a translational pathway from research to clinical use (National Academy of Medicine, National Academy of Sciences, and the Royal Society, 2020). Likewise, a global expert Advisory Committee was established by the World

Health Organization (WHO) with the goal of developing recommendations on governance mechanisms for human genome editing. Although the committee insisted in an interim recommendation that "it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing" (WHO, 2019), it did not express fundamental concerns on the possibility that some forms of HGE will one day become a reality. In 2021, the WHO's Advisory Committee issued some publications, including a "Framework for governance" report and a "Recommendations" report (WHO, 2021). Building on a set of procedural and substantive values and principles, the "Framework for Governance" report discusses a variety of tools and institutions necessary for developing appropriate national, transnational, and international governance and oversight mechanisms for HGE. Specifically, the report considers the full spectrum of possible applications of human genome editing (including epigenetic editing and human enhancement) and addresses specific challenges associated with current, possible and speculative scenarios. These range from somatic gene therapy for the prevention of serious hereditary diseases to potentially more controversial applications reminiscent of the He Jiankui case (e.g., the use of HGE in reproductive medicine outside regulatory controls and oversight mechanisms). Additionally, the "Recommendations" report proposes among other things whistleblowing mechanisms to report illegal or unethical research. It also highlights the need for a global human genome editing registry, that should also cover basic and preclinical research on different applications of genetic manipulation, including HGE. The report also emphasises the need of making possible benefits of human genome editing widely accessible.

The idea of a human genome editing registry has also been supported by the European Group on Ethics in Science and New Technologies (EGE), an advisory board to the President of the European Commission. After an initial statement on genome editing published in 2016, still calling for a moratorium on editing of human embryos (EGE, 2016), the EGE published a comprehensive Opinion in 2021 (EGE, 2021). Although the focus of this report is on the moral issues surrounding genome editing in animals and plants, HGE is also discussed. Similar to the WHO Advisory Committee, the EGE recommends for HGE not to be introduced prematurely into clinical application and that measures should be taken to prevent HGE's use for human enhancement.

Overall, when reviewing reports and initiatives produced since 2015, common themes and trajectories can be identified. A key development is the observation that the acceptance of the fundamental permissibility of such interventions appears to be increasing. This constitutes an important change from previous positions, reflecting the fact that human germline interventions have long been considered a 'red line' or at least viewed with deep scepticism (Ranisch and Ehni, 2020). In particular, while there is agreement that it would be premature to bring HGE into a clinical context, key concerns expressed by authoritative international bodies and committees are now associated with acceptable uses of the technology, rather than its use per se. Consideration is now being given to the conditions and objectives under which germline interventions could be permissible, instead of addressing the fundamental question of whether HGE may be performed at all. The question of permissibility is often linked to the stage of technological development. These developments are remarkable, since the key ethical aspects of genome editing are now frequently confined to questions of safety or cost–benefit ratios, rather than categorical considerations.

Another common issue can also be found in recent reports: the question of involving society in the debate. There is consensus on the fact that the legitimacy and governance of HGE should not be left solely to scientists and other experts but should involve society more broadly. Since germline interventions could profoundly change the human condition, the need for a broad and inclusive public debate is frequently emphasized (Iltis et al., 2021; Scheufele et al., 2021). The most striking expression of the need for public engagement and a "broad societal consensus" can be found in the final statement by the 2015 International Summit on Human Gene Editing organizing committee, as previously quoted (NASEM, 2015). Furthermore, the EGE and others also stresses the need for an inclusive societal debate before HGE can be considered permissible.

The pleas for public engagement are, however, not free of tension. For example, the NASEM's 2017 report was criticised for supporting HGE bypassing the commitment for the broad societal consensus (Baylis, 2017). Regarding HGE, some argue that only a "small but vocal group of scientists and bioethicists now endorse moving forward" (Andorno et al., 2020). Serious efforts to engage the public on the permissibility and uses of HGE have yet to be made. This issue not only lacks elaboration on approaches to how successful public participation can occur, but also how stop short of presenting views on how to translate the public's views into ethical considerations and policy (Baylis, 2019).

Potential uses of heritable genome editing technology

HGE is expected to allow a range of critical interventions: (i) preventing the transmission of genetic variants associated with severe genetic conditions (mostly single gene disorders); (ii) reducing the risk of common diseases (mostly polygenic diseases), with the promise of improving human health; and (iii) enhancing human capabilities far beyond what is currently possible for human beings, thereby overcoming human limitations. The identification of different classes of potential interventions has shifted the debate to the applications considered morally permissible beyond the acceptable use of HGE (Dzau et al., 2018). Specifically, there are differences in the limits of applicability suggested by some of the key cornerstone publications discussed above. For example, the NASEM (2017) report suggests limiting the use of HGE to the transmission of genetic variants linked to severe conditions, although in a very regulated context. In a very similar way, the 2020 report from the International Commission on the Clinical Use of Human Germline Genome Editing suggests that the initial clinical use of HGE should be limited to the prevention of serious monogenic diseases. By contrast, the 2018 Nuffield Council on Bioethics Report does not seem to limit the uses of genome editing to specific applications, though suggests that applications should be aligned with fundamental guiding ethical principles and need to have followed public debate (Savulescu et al., 2015). The same report also discusses far-reaching and speculative uses of HGE that might achieve "other outcomes of positive value" (Nuffield Council on Bioethics, 2018). Some of these more speculative scenarios include "built-in genetic resistance or immunity to endemic disease"; "tolerance for adverse environmental conditions" and "supersenses or superabilities" (Nuffield Council on Bioethics, 2018, p. 47).

There have been different views on the value of HGE technology. Some consider that HGE should be permissible in the context of therapeutic applications, since it can provide the opportunity to treat and cure diseases (Gyngell et al., 2017). For example, intervention in severe genetic disorders is considered as therapeutic and hence morally permissible, or even obligatory. Others consider HGE to be more like a public health measure, which could be used to reduce the prevalence of a disease (Schaefer, 2020). However, others maintain that reproductive uses of HGE are not therapeutic because there is no individual in a

current state of disease which needs to be treated, rather a prospective individual to be born with a specific set of negative prospective traits (Rulli, 2019).

Below, HGE is discussed in the context of reproductive uses and conditions of clinical advantage over existent reproductive technologies. The HGE applications are explored regarding their potential for modifying one or more disease-related genes relevant to the clinical context. Other uses associated with enhancement of physical and mental characteristics, which are considered non-clinical (although the distinction is sometimes blurred), are also discussed.

Single gene disorders. An obvious application of HGE interventions is to prevent the inheritance of genetic variants known to be associated with a serious disease or condition. Its potential use for this purpose could be typically envisaged through assisted reproduction, i.e., as a process to provide reproductive options to couples or individuals at risk of transmitting genetic conditions to their offspring. Critics of this approach often argue that other assisted reproductive technologies (ARTs) and preimplantation screening technologies e.g., preimplantation genetic diagnosis (PGD), not involving the introduction of genetic modifications to germline cells, are already available for preventing the transmission of severe genetic conditions (Lander, 2015; Lanphier et al., 2015). These existent technologies aim to support prospective parents in conceiving genetically related children without the condition that affect them. In particular, PGD involves the creation of several embryos by in vitro fertilization (IVF) treatment that will be tested for genetic anomalies before being transferred to the uterine cavity (Sermon et al., 2004). In Europe, there is a range in the regulation of the PGD technology with most countries having restrictions of some sorts (Soini, 2007). The eligibility criteria for the use of PGD also vary across countries, depending on the range of heritable genetic diseases for which it can be used (Bayefsky, 2016).

When considering its effectiveness, PGD presents specific limitations, which include the rare cases in which either both prospective parents are homozygous carriers of a recessive genetic disease, or one of the parents is homozygous for a dominant genetic disease (Ranisch, 2020). In these cases, all embryos produced by the prospective parents will be affected by the genetic defect, and therefore it will not be possible to select an unaffected embryo after PGD. Currently, beyond adoption of course, the options available for these prospective parents include the use of a third-party egg or sperm donors.

Overall, given the rarity of cases in which it is not applicable, PGD is thought to provide a reliable option to most prospective parents for preventing severe genetic diseases to be transmitted to their offspring, except in very specific cases. HGE interventions have been suggested to be an alternative method to avoid single gene disorders in the rare cases in which selection techniques such as PGD cannot be used (Ranisch, 2020). It has also been proposed to use tools such as CRISPR/Cas9 to edit morphologically suitable but genetically affected embryos, and thus increase the number of embryos available for transfer (de Wert et al., 2018; Steffann et al., 2018). Moreover, HGE interventions are considered by some as a suitable alternative to PGD, even when the use of PGD could be possible. One argument in this respect is that, although not leading to the manifestation of the disease, the selected embryos can still be carriers of it. In this respect, differently from PGD, HGE interventions can be used to eliminate unwanted, potential future consequences of genetic diseases (i.e., by eliminating the critical mutation carried out in the selected embryo), with the advantage of reducing the risks of further propagation of the disease in subsequent future generations (Gyngell et al., 2017).

Overall, HGE interventions are thought to offer a benefit over PGD in some situations by providing a broader range of possible interventions, as well as by providing a larger number of suitable embryos. The latter effect is usually important in the cases where unaffected embryos are small in number, making PGD ineffective (Steffann et al., 2018). Whether these cases provide a reasonable ground to justify research and development on the clinical use of HGE remain potentially contentious. Some authors have suggested that the number of cases in which PGD cannot be effectively used to prevent transmission of genetic disorders is so marginal that clinical application of HGE could hardly be justified (Mertes and Pennings, 2015). Particularly when analyzing economic considerations (i.e., the allocation of already scarce resources towards clinical research involving expensive techniques with limited applicability) and additional risks associated with direct interventions. In either case of HGE being used as an alternative or a complementary tool to PGD, PGD will most likely still be used to identify those embryos that would manifest the disease and would hence require subsequent HGE.

The PGD technique, however, is not itself free of criticism and possible moral advantages of HGE over PGD have also been explored (Hammerstein et al., 2019; Ranisch, 2020). PGD remains ethically controversial since, identifying an unaffected embryo from the remaining embryos (which will not be used and ultimately discarded) amounts to the selection of 'healthy' embryos rather than 'curing' embryos affected by the genetic conditions. On the other hand, given a safe and effective application of the technology, the use of HGE is considered by many morally permissible to prevent the transmission of genetic variants known to be associated with serious illness or disability (de Miguel Beriain, 2020). One question that remains is whether HGE and PGD have a differing or equal moral permissibility or, at least, comparable. On issues including human dignity and autonomy, it was argued that HGE and PGD interventions can be considered as equally morally acceptable (Hammerstein et al., 2019). This equal moral status was, however, only valid if HGE is used under the conditions of existent gene variants in the human gene pool and to promote the child health's best interest in the context of severe genetic diseases (Hammerstein et al., 2019). Because of selection and 'therapy', moral assessments resulted in HGE interventions being considered to some extent preferable to PGD, once safety is carefully assessed (Gyngell et al., 2017; Cavaliere, 2018). Specifically, PGD's aim is selective and not 'therapeutic', which could be said to contradict the aims of traditional medicine (MacKellar and Bechtel, 2014). In contrast to PGD's selectivity, HGE interventions are seen as 'pre-emptively therapeutic', and therefore closer to therapy than PGD (Cavaliere, 2018). However, it is also argued that HGE does not have curative aims, and thus it is not a therapeutic application, as there is no patient involved in the procedure to be cured (Rulli, 2019). On balance, there appears to be no consensus on which of the approaches, HGE and PGD, is morally a better strategy to prevent the transmission of single gene disorders, with a vast amount of literature expressing diverse positions when considering different scenarios (Delaney, 2011; Gyngell et al., 2017; Cavaliere, 2018; Ranisch, 2020; Rehmann-Sutter, 2018; Sparrow, 2021).

Polygenetic conditions. HGE is also argued to have the potential to be used in other disorders which have a polygenic disposition and operate in combination with environmental influences (Gyngell et al., 2017, 2019). Many common diseases, which result from the involvement of several genes and environmental factors, fall into this category. Examples of common diseases of this type includes diabetes, coronary artery disease and different types of cancers, for which many of the genes involved were identified by

studies of genome wide association (e.g., Wheeler and Barroso, 2011; Peden and Farral, 2011). These diseases affect the lives of millions of people globally, severely impacting health and often leading to death. Furthermore, these diseases have a considerable burden on national health systems. Currently, many of these diseases are controlled through pharmaceutical products, although making healthier life choices about diet and exercise can also contribute to preventing and managing some of them. Despite the interest, the use of PGD in polygenic conditions would hardly be feasible, due to the number of embryos needed to select the preferred genotype and available polygenic predictors (Karavani et al., 2019; Shulman and Bostrom, 2014).

In theory, HGE could be a potentially useful tool to target different genes and decrease the susceptibility to multifactorial conditions in current and future generations. The application of HGE to polygenic conditions is often argued by noting that the range of applicability of the technique (well beyond single gene disorders) would justify and outweigh the cost needed to develop it. However, to do so, a more profound knowledge of genetic interactions, of the role of genes and environmental factors in diverse processes would be needed to be able to modify such interconnected systems with limited risk to the individual (Lander, 2015). Besides, it is now understood that, depending on the genetic background, individuals will have different risks of developing polygenetic diseases (risk-associated variants), but hardly any certainty of it. In other words, although at the population level there would most likely be an incidence of the disease, it is not possible to be certain of the manifestation of the disease in any specific individual. As a result, the benefits of targeting a group of genes associated to a disease in a specific individual would have to be assessed in respect to the probability of incidence of the disease. The risk-benefit ratio for HGE is considerably increased for polygenic conditions compared to monogenic disorders. Additionally, the risks of adverse effects, e.g., off-target effects, increases with the number of genes targeted for editing. The latter effects make the potential benefits of HGE in polygenic diseases more uncertain than in single gene disorders.

Genetic enhancement. A widespread concern regarding the use of HGE is that such interventions could be used not only to prevent serious diseases, but also to enhance desirable genetic traits. Currently, our knowledge on how to genetically translate information into specific phenotypes is very limited and some argue that it might never be technically feasible to achieve comprehensive genetic enhancements using current gene editing technologies (Janssens, 2016; Ranisch, 2021). Similar to many diseases, in which different genetic and other factors are involved, many of the desirable traits to be targeted by any enhancement will most likely be the result of a combination of several different genes influenced by environment and context. Moreover, the implications for future generations of widespread genetic interventions in the human population and its potential impact on our evolutionary path are difficult to assess (Almeida and Diogo, 2019). Nevertheless, others argue that genetic enhancement through HGE could be possible in the near future (de Araujo, 2017).

There has been much discussion regarding the meaning of the terms and the conceptual or normative difference between 'therapy' and 'enhancement' (for an early discussion: Juengst, 1997; Parens, 1998). There are mainly three different meanings of 'enhancement' used in the literature. First, 'enhancement' is sometimes used to refer to measures that go beyond therapy or prevention of diseases, i.e., that transcend goals of medicine. Second, 'enhancement' is used to refer to measures that equip a human with traits or capacities that they typically do not possess. In both cases, the term points to equally controversial and contrasting concepts: on the one hand, those of 'health', 'disease' or 'therapy', and on the other, those of 'normality' or 'naturalness'. Third, 'enhancement' is sometimes also used as an umbrella-term describing all measures that have a positive effect on a person's well-being. According to this definition, the cure, or prevention of a disease is then also not opposed to an enhancement. Here again, this use refers to the controversial concept of 'well-being' or a 'good life'.

It is beyond the scope of this article to provide a detailed review of the complex debate about enhancement (for an overview: Juengst and Moseley, 2019). However, three important remarks can be made: first, although drawing a clear line between 'enhancement' and 'therapy' (or 'normality', etc.) will always be controversial, some cases can be clearly seen as human enhancement. This could include modifications to augment human cognition, like having a greater memory, or increasing muscle mass to increase strength, which are not considered essential for human health (de Araujo, 2017).

Second, it is far from clear whether a plausible account of human enhancement would, in fact, be an objectivist account. While authors suggest that there is some objectivity regarding the conditions that constitute a serious disease (Habermas, 2003), the same might not be true for what constitutes an improvement of human functioning. It may rather turn out that an enhancement for some might be seen as a dis-enhancement for others. Furthermore, the use of the HGE for enhancement purposes can be considered at both an individual and a collective level (Gyngell and Douglas, 2015; Almeida and Diogo, 2019), with a range of ethical and biological implications. If HGE is to be used for human enhancement, this use will be in constant dependence on what we perceive as 'normal' functioning or as 'health'. Therefore, factors such as cultural and societal norms will have an impact on where such boundaries are drawn (Almeida and Diogo, 2019).

Third, it should be noted that from an ethical perspective the conceptual question of what enhancement is, and what distinguishes it from therapy, is less important than whether this distinction is ethically significant in the first place. In this context, it was pointed out that liberal positions in bioethics often doubt that the distinction between therapy and enhancement could play a meaningful role in determining the limits of HGE (Agar, 1998). The consideration of genetic intervention for improving or adding traits considered positive by individuals have raised extreme positions. Some welcome the possibility to ameliorate the human condition, whilst others consider it an alarming attempt to erase aspects of our common human 'nature'. More specifically, some authors consider HGE a positive step towards allowing humans the opportunity to obtain beneficial traits that otherwise would not be achievable through human reproduction, thus providing a more radical interference in human life to overcome human limitations (de Araujo, 2017; Sorgner, 2018). The advocates of this position are referred to as 'bioliberals' or 'transhumanists' (Ranisch and Sorgner, 2014), and its opponents are referred to as 'bioconservatives' (Fukuyama, 2002; Leon, 2003; Sandel, 2007). Transhumanism supports the possibility of humans taking control of their biology and interfering in their evolution with the use of technology. Bioconservatism defends the preservation and protection of 'human essence' and expresses strong concerns about the impact of advanced technologies on the human condition (Ranisch and Sorgner, 2014).

For the general public, HGE used in a clinical context seems to be less contentious compared when used as a possible human enhancement tool. Specifically, some surveys indicate that the general-public typically exhibits a reduced support for the use of genome editing interventions for enhancement purposes

compared to therapeutic purposes (Gaskell et al., 2017; Scheufele et al., 2017). In contrast, many technologies and pharmaceutical products developed in the medical context to treat patients are already being used by individuals to 'enhance' some aspect of their bodies. Some examples include drugs to boost brain power, nutritional supplements, and brain-stimulating technologies to control mood, even though their efficiency and safety is not clear. This could suggest that views on enhancement may vary depending on the context and on what is perceived as an enhancement by individuals. It may be informative to carry out detailed population studies to explore whether real ethical boundaries and concerns exist, or whether these are purely the result of the way information is processed and perceived.

Heritable genome editing: Mapping the ethical debate

Even though genome editing methods have only been developed in the last decade, the normative implication of interventions into the human germline have been discussed since the second half of the 20th century (Walters et al., 2021). Some even argue that, virtually, all the ethical issues raised by genetic engineering were already being debated at that time (Paul, 2005). This includes questions about the distinction between somatic and germline interventions, as well as between therapy and enhancement (e.g., Anderson, 1985). Nevertheless, as it has been widely noted, it is difficult to draw clear lines between these two categories (e.g., McGee, 2020; Juengst, 1997), and alternative frameworks have been proposed, particularly in the context of HGE (Cwik, 2020). Other questions include the normative status of human nature (e.g., Ramsey, 1970), the impossibility of consent from future generations (e.g., Lappe, 1991), possible slippery slopes towards eugenics (e.g., Howard and Rifkin, 1977), or implications for justice and equality (e.g., Resnik, 1994).

When discussing the ethics of HGE, roughly three types of considerations can be distinguished: (i) pragmatic, (ii) sociopolitical, and iii) categorical (Richter and Bacchetta, 1998; cf. Carter, 2002). *Pragmatic* considerations focus on medical or technological aspects of HGE, such as the safety or efficacy of interventions, risk–benefit ratio, possible alternatives or the feasibility of responsible translational research. Such considerations largely depend on the state of science and are thus always provisional. For example, if high-risk technologies one day evolve into safe and reliable technologies, some former pragmatic considerations may become obsolete. *Sociopolitical* aspects, on the other hand, are concerned with the possible societal impact of technologies, e.g., how they can promote or reduce inequalities, support or undermine power asymmetries, strengthen, or threaten democracy. Similar to pragmatic considerations, sociopolitical reasons depend on specific contexts and empirical factors. However, these are in a certain sense 'outside' the technology—even though technologies and social realities often have a symbiotic relationship. While sociopolitical considerations can generate strong reasons against (or in favour of) implementing certain technologies, most often these concerns could be mitigated by policies or good governance. *Categorical* considerations are different and more akin to deontic reasons. They emphasise categorical barriers to conduct certain deeds. It could be argued, for instance, that the integrity of the human genome or the impossibility to obtain consent from future generation simply rule out certain options to modify human nature. Such categorical considerations may persist despite technological advances or changing sociopolitical conditions.

Comparing the bioethical literature on genetic engineering from the last century with the ongoing discussions shows a remarkable shift in the ethical deliberation. In the past, scholars from the field of medical ethics, as well as policy reports, used to focus on possible categorical boundaries for germline interventions and on possible sociopolitical consequences of such scenarios. For instance, the influential 1982 report "Splicing Life" from the US President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research prominently discussed concerns about 'playing God' against the prospects of genetically engineering human beings, as well as possible adverse consequences of such interventions. Although this study addresses potential harms, pragmatic arguments played only a minor role, possibly due to the technical limitations at the time.

With the upcoming availability of effective genome editing techniques, the focus on the moral perspective seems to have been reversed. Increasingly, the analysis of the permissibility of germline interventions is confined to questions of safety and efficacy. This is demonstrated by the 2020 consensus study report produced by an international commission convened by the US National Academy of Medicine, the US National Academy of Sciences, and the UK's Royal Society, which aimed at defining a translational pathway for HGE. Although the report recognizes that HGE interventions does not only raise pragmatic questions, ethical aspects were not explicitly addressed (National Academy of Medicine, National Academy of Sciences, and the Royal Society, 2020).

Similarly, in 2019, a report on germline interventions published by the German Ethics Council (an advisory body to the German government and parliament) emphasizes that the "previous categorical rejection of germline interventions" could not be maintained (Deutscher Ethikrat, 2019, p. 5). The German Ethics Council continues to address ethical values and societal consequences of HGE. However, technical progress and the development of CRISPR/Cas9 tools seem to have changed the moral compass in the discussion about germline interventions.

For a comprehensive analysis of HGE to focus primarily on pragmatic arguments such as safety or efficacy would be inadequate. In recent years, developments in the field of genome editing have occurred at an incredibly fast pace. At the same time, there are still many uncertainties about the efficacy of the various gene editing methods and unexpected effects in embryo editing persist (Ledford, 2015). Social and political implication also remain largely unknown. To date, it has been virtually impossible to estimate how deliberate interventions into the human germline could shape future societies and to conduct a complete analysis of the safety aspects of germline interventions.

Moreover, as the EGE notes, we should be cautious not to limit the complex process of ethical decision-making to pragmatic aspects such as safety. The "'safe enough' narrative purports that it is enough for a given level of safety to be reached in order for a technology to be rolled out unhindered, and limits reflections on ethics and governance to considerations about safety" (EGE, 2021, p. 20). Consequently, the EGE has highlighted the need to engage with value-laden concepts such as 'humanness', 'naturalness' or 'human diversity' when determining the conditions under which HGE could be justified. Even if a technology has a high level of safety, its application may still contradict ethical values or lead to undesirable societal consequences. Efficacy does not guarantee compatibility with well-established ethical values or cultural norms.

While concepts such as 'safety' or 'risk' are often defined in scientific terms, this does not take away the decision of what is ethically desirable given the technical possibilities. As Hurlbut and colleagues put it in the context of genome editing: "Limiting early deliberation to narrowly technical constructions of risk permits science to define the harms and benefits of interest, leaving little opportunity for publics to deliberate on which imaginations need widening, and which patterns of winning and

losing must be brought into view" (Hurlbut et al., 2015). Therefore, if public engagement is to be taken seriously, cultural norms and values of those affected by technologies must also be considered (Klingler et al., 2022). This, however, means broadening the narrow focus on pragmatic reasons and allowing categorical as well as sociopolitical concerns in the discourse. Given the current attention on pragmatic reasons in current debates on HGE, it is therefore beneficial to revisit the categorical and sociopolitical concerns that remain unresolved. The following sections provide an overview of relevant considerations that can arise in the context of HGE and that underline many of the societal concerns and values crucial for public engagement.

Human genome 'integrity'. Heritability seems to be one of the foremost considerations regarding germline genome editing, as it raises relevant questions on a 'natural' human genome and its role in 'human nature' (Bayertz, 2003). This follows an ongoing philosophical debate on 'human nature', at least as defined by the human genome. This has ensued a long debate on the value of the human genome and normative implications associated with its modification (e.g., Habermas, 2003). Although a comprehensive discussion of these topics goes beyond the scope of this paper, the human genome is viewed by many as playing an important role in defining 'human nature' and providing a basis for the unity of the human species (for discussion: Primc, 2019). Considering the implications for the individual and the collective, some affirm the right of all humans to inherit an unmodified human genome. For some authors, germline modification is considered unethical, e.g., a "line that should not be crossed" (Collins, 2015) or a "crime against humanity" (Annas et al., 2002).

The Universal Declaration on the Human Genome and Human Rights (UDHGHR) states 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" (Article 1, UNESCO, 1997). The human genome is viewed as our uniquely human collective 'heritage' that needs to be preserved and protected. Critics of heritable genetic interventions argue that germline manipulation would disrupt this natural heritage and therefore would threaten human rights and human equality (Annas, 2005). Heritable human genome editing creates changes that can be heritable to future generations. For many, this can represent a threat to the unity and identity of the human species, as these modifications could have an impact on the human's gene pool. Any alterations would then affect the evolutionary trajectory of the human species and, thus, its unity and identity.

However, the view of the human genome as a common heritage is confronted with observations of the intrinsic dynamism of the genome (Scally, 2016). Preservation of the human genome, at least in its current form, would imply that the genome is static. However, the human genome is dynamic and, at least in specific periods of environmental pressure, must have naturally undergone change, as illustrated by human evolution (Fu and Akey, 2013). The genome of any individual includes mutations that have occurred naturally. Most of them seem to be neither beneficial nor detrimental to the ability of an individual to live or to his/her health. Others can be detrimental and limiting to their wellbeing. It has been shown that, on average, each human genome has 60 new mutations compared to their parents (Conrad et al., 2011). At the human population level, a human genome can have in average 4.1–5 million variants compared to the 'reference' genome (Li and Sadler, 1991; Genomes Project C, 2015). The reference genome itself is thus a statistical entity, representing the statistic distribution of the probability of different gene variants in the whole genome. Human genomic variation is at the basis of the differences in the various physical traits present in humans (e.g., eye colour, height, etc.), as well as specific genetic diseases. Thus, the human population is comprised of genomes with a pattern of variants and not of 'one' human genome that needs to be preserved (Venter et al. 2001). The human genome has naturally been undergoing changes throughout human history. An essentialist view of nature seems to be the basis for calling for the preservation of genome integrity. However, in many ways, this view is intrinsically challenged by the interpretation portrayed by evolutionary biology of our genetic history already more than a century ago. Nevertheless, despite the dynamic state of the human genome, this in itself cannot justify the possibility of modifying the human genome. It is also worth considering that the integrity of the human genome could also be perceived in a 'symbolic' rather than biological literal meaning. Such an interpretation would not require a literally static genome over time, but instead suggest a boundary between 'naturally' occurring variation and 'artificially' induced change. This is rather a version of the 'natural'/unnatural argument, rather than an argument for a literally unchanged genetic sequence.

The modification of the human genome raises complex questions about the characterization of the human species genome and if there should be limits on interfering with it. The options to modify the human genome could range from modifying only the genes that are part of the human gene pool (e.g., those genes involved in severe genetic diseases such as Huntington's disease) to adding new variants to the human genome. Regarding variants which are part of the common range of variation found in the human population (although it is not possible to know all the existent variations), the question becomes whether HGE could also be used in any of them (e.g., even the ones providing some form of enhancement) or only in disease-associated variants and thus be restricted to the prevention of severe genetic diseases. In both cases, the integrity of the human genome is expected to be maintained with no disruption to human lineage. However, it could be argued that this type of modification is defending a somewhat conservative human nature argument, since it is considering that a particular genetic make-up is 'safe' or would not involve any relevant trade-offs. In contrast, a different conclusion could be drawn on the integrity of the human genome when introducing genotypical and phenotypical traits that do not lie within the common range of variation found in the population (Cwik, 2020). In all cases, since the implications of the technology are intergenerational and consequently, it will be important to carry out an assessment of the risks that we, as a species, are willing to take when dealing with disease and promoting health. For this, we will need to explore societal views, values and cultural norms associated with the human genome, as well as possibly existing perceptions of technology tampering with 'nature'. To support such an assessment, it would be useful to draw on a firm concept of human nature and the values it implies, beyond what is implied by genetic aspects.

Human dignity. In several of the legally binding and non-binding documents addressing human rights in the biomedical field, human dignity is one of the key values emphasized. There are concerns that heritable genome interventions might conflict with the value of human dignity (Calo, 2012; Melillo, 2017). The concerns are considered in the context of preserving the human genome (Nordberg et al. 2020). More specifically, the recommendation on Genetic Engineering by the Council of Europe (1982) states that "the rights to life and to human dignity protected by Articles 2 and 3 of the European Convention on Human Rights imply the right to inherit a genetic pattern which has not

been artificially changed" (Assembly, 1982). This is supported by the Oviedo Convention on Human Rights and Biomedicine (1997), where Article 13 prohibits any genetic intervention with the aim of introducing a modification in the genome of any descendants. The Convention is the only international legally binding instrument that covers human germline modifications among the countries which have ratified it (Council of Europe, 1997). However, there have been some authors disputing the continued ban proposed by the Oviedo Convention (Nordberg et al. 2020). Such authors have focused on the improvements of safety and efficacy of the technology in contrast to authors focusing on its value for human dignity (Baylis and Ikemoto, 2017; Sykora and Caplan, 2017). The latter authors seem to highlight the concept of human dignity to challenge heritable interventions to the human genome.

But a question in debate has been to demonstrate how 'human dignity', described in such norms, relates to heritable genome interventions. The concept of the human genome as common genetic heritage, distinguishing humans from other species seems one of the main principles implied by such norms. In this view, the human genome determines who belongs to the human species and who does not, and thus confers an individual the dignity of being a human by association. This creates an inherent and strong link between the concept of human genome and the concept of human dignity and its associated legal rights (Annas, 2005). It could be argued that a genetic modification to an individual may make it difficult for him/her to be recognized as a human being and therefore, preservation of the human genome being important for human dignity to be maintained. This simple approach, or at least interpretation, however, ignores the fact that the human genome is not a fixed or immutable entity, as exemplified by human evolution (as discussed in the previous section). As a result, the view that HGE interventions are inherently inadmissible based on the need to preserve human dignity is contested (Beriain, 2018; Raposo, 2019). More broadly, the idea that biological traits are the basis for equality and dignity, supporting the need for the human genome to be preserved, is often challenged (Fenton, 2008).

It is argued that to fully assess the impact of the HGE interventions on human dignity, it will be necessary to have a better understanding of the concept of human dignity in the first place (Häyry, 2003; Cutas, 2005). For some, however, human dignity is a value that underlies questions of equality and justice. Thus, the dignity-based arguments could uncover relevant questions in the discussion of ethical implications on modifying the human genome (Segers and Mertes, 2020). In the Nuffield Council on Bioethics Report (2018) principles of social justice and solidarity, as well as welfare, are used to guide the debate on managing HGE interventions. Similarly, the concept of human dignity could, therefore, provide the platform upon which consideration of specific values could be discussed, broaden the debate on HGE to values shared by society.

Right of the child: informed consent. In many modern societies, every individual, including children, have the rights to autonomy and self-determination. Therefore, each person is entitled to decide for themselves in decisions relating to their body. These rights are important for protecting the physical integrity of a person. When assessing the implication of allowing individuals to take (informed) decisions relative to the use of heritable genetic interventions on someone else's body, it is useful to reflect on the maturity of existing medical practices and, more broadly, on the additional complexities associated with the heritability of any such intervention.

In modern health-care systems, informed consent provides the opportunity for an individual to exercise autonomy and make an informed decision about a medical procedure, based on their understanding of the benefits and risks of such procedure. Informed consent is thus a fundamental principle in medical (research) ethics when dealing with human subjects (Beauchamp and Childress, 2019).

Heritable genome interventions present an ethical constraint on the impossibility of future generations of providing consent to an intervention on their genome (Smolenski, 2015). In other words, future generations cannot be involved in a decision which could limit their autonomy, since medical or health-related decisions affecting them are placed on the present generation (and, in the case of a child to be born, more specifically, on his/her parents). However, many other actions taken by parents of young children also intentionally influence the lives of those children and have been doing so for millennia (Ranisch, 2017). Although these actions may not involve altering their genes, many of such actions can have a long-lasting impact on a child's life (e.g., education and diet). However, it could be argued that they do not have the irreversible effect that HGE will have in the child and future generations. In cases where parents act to expand the life choices of their children by eliminating disease (e.g., severe genetic diseases), this would normally be thought to outweigh any possible restriction on autonomy. In these cases, if assuming HGE benefits will outweigh risks regarding safety and efficacy, the use of HGE could be expected to contribute to the autonomy of the child, as him/her would be able in the future to have a better life, not constrained by the limitations of the disease. As a result, even if it is accepted that these technologies may in one way reduce the autonomy of future generations, some believe that this will often be outweighed by other effects increasing autonomy (Gyngell et al., 2017). In other words, it is reasonable to suppose that, when taken by parents based on good information and understanding of risks and impacts, the limitation in the autonomy of unborn children associated with heritable genetic interventions would be compensated by the beneficial effects of increasing their autonomy when born (Gyngell et al., 2017).

It has often been emphasized that possible genetic interventions must not curtail the future possibilities of offspring to live their lives according to their own idea of a good life. This view originated in the liberal tradition and is associated with the "right to an open future", defended by Joel Feinberg (1992). That is an anticipatory autonomy right that parents can violate, even though the offspring could exercise it only in the future. Feinberg has discussed the right to an open future in the context of religious education. However, various authors have applied this argument to the question of permissible and desirable genetic interventions (Buchanan et al., 2000; Glover, 2006; Agar, 1998). Accordingly, germline modifications or selection would have to allow the offspring to have a self-determined choice of life plans. It would therefore be necessary to provide offspring with genetic endowments that represent the so-called all-purpose goods. These goods are "useful and valuable in carrying out nearly any plan of life or set of aims that humans typically have" (Buchanan et al., 2000, p. 167). While this claim is certainly appealing, in reality it will be difficult to identify phenotypes that will only broaden and do not narrow the spectrum of life plans. Take, for example, body size: a physique favourable for a basketball player would at the same time be less favourable in successfully riding horses as a professional jockey and vice versa. Increasing some opportunities often means reducing other ones.

The arguments of informed consent and open future need to be explored outside the realm of severe genetic diseases by considering other scenarios (including scenarios of genetic enhancement). Hereby, the effects of the interventions on the autonomy of future generations can be assessed more

comprehensively. As for enhancement, decisions outside the realm of health can be more controversial, as the traits that parents see fit to generate enhancement may inadvertently condition a child's choices in the future in an undesirable way.

If HGE is to be used, questions on how the consent and information should be provided to parents to fully equip them to decide in the best interests of the child will need to be assessed (Evitt et al., 2015). This is evident if considering the informed consent used in the study conducted by He Jiankui. One of the many criticisms of the study was the inadequacy of the informed consent process provided to the parents, which did not meet regulatory or ethical standards (Krimsky, 2019; Kirksey, 2020). This raises questions on how best to achieve ethical and regulatory compliance regarding informed consent in applications of HGE (Jonlin, 2020).

Discrimination of people with disabilities. For many years, there has been an effort to develop selective reproduction technologies to prevent genetic diseases or conditions leading to severe disabilities. These forms of reproductive genetic disease prevention are based on effectively filtering and eradicating embryos or foetuses affected by genetic diseases. There are divergent views regarding the use of these technologies. For example, the disability rights movement argues that the use of technologies such as prenatal testing (PNT) and PGD discriminates against people living with a disability (Scully, 2008; Asch and Barlevy, 2012). The key arguments presented supporting this view are: (i) the limited value of a genetic trait in respect to the life of an embryo (Parens and Asch, 2000) and (ii) the 'expressivist' argument (Buchanan, 1996; Shakespeare, 2006). The first argument is based on the critique that a disabling trait is viewed as being more significant than the life of an embryo/foetus. This argument was initially used in the context of prenatal testing and selective termination, and has also been applied in the context of new technologies like PGD (Parens and Asch, 2000). The second, the 'expressivist' argument, argues that the use of these technologies expresses negative or discriminatory views on the disabling conditions they are targeting and subsequently on the people living with these conditions (Asch and Wasserman, 2015). The expressivist argument, however, has been challenged by stressing the importance of differentiating between the disability itself and the people living with disability (Savulescu, 2001). The technology's use is aimed at reducing the incidence of disability, and it does not have a position of value on the people that have a specific condition.

When applying the same arguments to the use of HGE in comparison with other forms of preventing heritable genetic diseases, some important considerations can be made. Regarding the first argument, in contrast to selective reproduction technologies, HGE may allow the removal of the disabled trait with the aim of ensuring survival of the affected embryo. However, most likely, PGD would be used before and after the editing of the embryos to help the identification of the ones requiring intervention and verifying the efficiency of the genetic intervention (de Miguel Beriain, 2018; Ranisch, 2020). Similarly, the expressivist argument continues to be challenged if the application of human HGE is envisaged in the context of severe genetic diseases (e.g., Tay-Sachs and Huntington's disease). It has been argued that the choice to live without a specific genotype neither implies discriminating people living with a respective condition nor considering the life of people living with the disease not worth living or less valuable (Savulescu, 2001). In other words, the expressivist argument is not a valid or a sufficiently strong ethical argument for prospective parents not to have the option to have a future child without a genetic disease.

It is worth noting that the debate on the use of reproduction technologies for the prevention of genetic diseases is not at all new, and that modern HGE techniques only serve to highlight ethical concerns that have been expressed for a long time. In the case of preventing genetic diseases, the application of both arguments to HGE intervention could be considered not to provide sufficiently strong ethical arguments to limit the use of the technology in the future. However, it is worth exploring whether scientific innovations like HGE are either ameliorating or reinvigorating ethical concerns expressed so far, for example in creating a future that respects or devalues disability as a part of the human condition. Perhaps even more importantly, given their potential spectrum of possible intervention and efficacy, it is important to reflect on whether the broad use of HGE could have an impact on concepts of disability and 'normality' as a whole distorting an already unclear ethical line between clinical and non-clinical interventions. Moreover, research work exploring the relationship between disability and identity indicated that personhood with disability can be an important component to people's identity and interaction with the world. In the case of heritable human genome editing, it is not yet known how this technology will impact the notions of identity and personhood in people who had their germline genome modified (Boardman and Hale, 2018). For further progress on these issues public engagement might be important to gather different views and perceptions on the issue.

Justice and equality. Beside the limits of applicability, another common ethical concern associated with the use of genome editing technologies, as with many new technologies, is the question of accessibility (Baumann, 2016). Due to the large investments that will need to be made for continuing development of the technology, there is a (perceived) risk of it becoming an expensive technology that only a few wealthy individuals in any population (and/or only citizens in comparatively rich countries) can access. In addition, there is concern that patenting of genome editing technologies will delay widespread access or lead to unequal distribution of corresponding benefits (Feeney et al., 2018). This may, consequently, contribute to further increases in existing disparities, since individuals or countries with the means of accessing better health treatments may have economic advantages (Bosley et al., 2015). This could enhance inequality at different levels, depending on the limits of applicability of the technology. Taken to its extreme, the use of the technology could allow germline editing to create and distinguish classes of individuals that could be defined by the quality of their manipulated genome.

The concern that the possibility of germline interventions in humans could entrench or even increase inequalities has accompanied the discussion about ethics of genetic interventions from the very beginning until today (e.g. Resnik, 1994). In 'Remaking Eden' Lee Silver envisioned a divided future society, consisting of a genetically enhanced class, the "genRich", and a genetic underclass, the "naturals" (Silver, 1997). Françoise Baylis recently echoed such concerns regarding future HGE interventions, namely that "unequal access to genome-editing technologies will both accentuate the vagaries of the natural lottery and introduce an unjust genetic divide that mirrors the current unjust economic and social divide between rich and poor individuals" (Baylis, 2019, p. 67). At the same time, the possibility to genetically intervene in the 'natural lottery' has also been associated with the hope of countering natural inequalities and increase equality of opportunities. Robert Sinsheimer may be among the first to envision such a 'new' individualistic type of 'eugenics' that "would permit in principle the conversion of all of

the unfit to the highest genetic level" (Sinsheimer, 1969, p. 13). More recently, in the book 'From chance to choice: Genetics and justice' (2000) it is argued that "equality of opportunity will sometimes require genetic interventions and that the required interventions may not always be limited to the cure or prevention of disease" (Buchanan et al., 2000, p. 102). When discussing issues related to justice and equality, it will be important to involve a broad spectrum of stakeholders to better evaluate the economic effects of the commercialization of the technology.

Conclusions

With ongoing technological developments and progress with guiding and regulating its acceptable use, the possibility of HGE interventions in the human genome is closer than ever to becoming a reality. The range of HGE applicability can go from preventing the transmission of genetic variants associated with severe genetic conditions (mostly single gene disorders but also, to a lesser extent, polygenic diseases) to genetic enhancements. The permissibility of HGE has often been considered on the basis of possible uses, with therapeutic uses generally considered more acceptable than non-therapeutic ones (including human enhancement). When compared with other technologies with similar therapeutic uses (e.g., PGD) already in use, HGE presents similarities and differences. However, from an ethical acceptability perspective, there is currently no consensus on whether HGE is more or less acceptable than PGD.

An important conclusion of this study is that, along with the technological development of genome germline editing techniques, a shift in the focus of analyses on its applicability has been observed. More specifically, the emphasis on pragmatic considerations seems to have increased substantially compared with the previous emphasis on categorical and sociopolitical arguments. Many of the most recent publications from authoritative advisory committees and institutions discuss the permissibility of HGE interventions primarily on the basis of pragmatic arguments, in which safety and efficacy are the main focus. Since germline interventions could profoundly change the human condition, the need for a broad and inclusive public debate on this topic has also been frequently emphasized. However, limited consideration has been given to approaches to carry out such action effectively, and on how to consider their outcomes in relevant policies and regulations.

It is currently not entirely clear whether: (i) the pragmatic position championed by such authoritative sources builds on the premise that the ethical debate has reached sufficient maturity to allow a turning point; (ii) the lack of progress has somewhat hampered further consideration of issues still considered controversial; (iii) regulatory pressure is somewhat de facto pushing forward the introduction of such technologies despite critical, unresolved ethical issues. Based on the analysis presented in this paper, a combination of the latter factors (ii and iii) seems more likely. In engaging the public in societal debates on the acceptability of such technologies, unresolved questions are likely to re-emerge. Specifically, it is possible that categorical and sociopolitical considerations will gain renewed focus during public engagement. In other words, when involving the public in discussions on HGE, it is possible that cultural values and norms, not only questions of safety and efficacy, will re-emerge as crucial to the acceptance of the technology (What is meant by natural? What is understood by humanity? etc.).

HGE interventions put into question specific biological and moral views of individuals, including views on the value of the human genome, on human dignity, on informed consent, on disability and on societal equality and justice. The range of ethical issues affected by the introduction of such technology, often still characterised by non-convergent, and at times conflicting, positions, illustrate the importance of further consideration of these issues in future studies and public engagement activities. As a result, society's moral uncertainties will need to be assessed further to support the regulation of HGE technologies and form a well-informed and holistic view on how they can serve society's common goals and values.

Data availability

This statement is not applicable.

Received: 6 August 2021; Accepted: 28 March 2022;
Published online: 20 April 2022

References

Agar N (1998) Liberal eugenics. Public Aff Q 12(2):137–155
Almeida M, Diogo R (2019) Human enhancement: genetic engineering and evolution. Evol Med Public Health 1:183–189. https://doi.org/10.1093/emph/eoz026
Anderson WF (1985) Human Gene Therapy: scientific and ethical considerations. J Med Philos 10(3):275–291. https://doi.org/10.1093/jmp/10.3.275
Andorno R, Baylis F, Darnovsky M, Dickenson D, Haker H, Hasson K et al. (2020) Geneva statement on heritable human genome editing: the need for course correction. Trends Biotechnol 38(4):351–354
Annas GJ (2005) Bioethics: crossing human rights and health law boundaries. Oxford University Press, New York, NY
Annas GJ, Andrews LB, Isasi RM (2002) Protecting the endangered human: toward an international treaty prohibiting cloning and inheritable alterations. Am J Law Med 28(2–3):151–178
Araki M, Ishii T (2014) International regulatory landscape and integration of corrective genome editing into in vitro fertilization. Reprod Biol Endocrinol 12(1):108–120
Asch A, Barlevy D (2012) Disability and genetics: a disability critique of pre-natal testing and pre-implantation genetic diagnosis. eLS. Wiley, Chichester
Asch A, Wasserman D (2015) Reproductive testing for disability. In: Arras JD, Fenton E, Kukla R (eds.) Routledge companion to bioethics. Routledge, London
Baltimore D, Berg P, Botchan M, Carroll D, Charo RA, Church G et al. (2015) A prudent path forward for genomic engineering and germline gene modification. Science 348(6230):36. https://doi.org/10.1126/science.aab1028
Baltimore D, Baylis F, Berg P et al. (2015) On human gene editing: international summit statement. News release, December 3, International summit on human gene editing. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a
Barrangou R, Horvath P (2017) A decade of discovery: CRISPR functions and applications. Nat Microbiol 2(17092):1–9. https://doi.org/10.1038/nmicrobiol.2017.92
Baumann M (2016) CRISPR/Cas9 genome editing: new and old ethical issues arising from a revolutionary technology. Nanoethics 10:139–59
Bayefsky MJ (2016) Comparative preimplantation genetic diagnosis policy in Europe and the USA and its implications for reproductive tourism. Reprod Biomed Soc Online 3:41–47
Bayertz K (2003) Human nature: how normative might it be? J Med Philos 28(2):131–150. https://doi.org/10.1076/jmep.28.2.131.14210
Baylis F (2017) Human germline genome editing and broad societal consensus. Nat Hum Behav 1:0103
Baylis F (2019) Human genome editing: our future belongs to all of us. Issues Sci Technol 35:42–44
Baylis F, Ikemoto L (2017) The Council of Europe and the prohibition on human germline genome editing. EMBO Rep 8(12):2084–2085. https://doi.org/10.15252/embr.201745343
Baylis F, Darnovsky M, Hasson K, Krahn TM (2020) Human Germ Line and Heritable Genome Editing: the global policy landscape. CRISPR J 3(5):365–377. https://doi.org/10.1089/crispr.2020.0082. PMID: 33095042
Beauchamp TL, Childress JF (2019) Principles of biomedical ethics. Oxford University Press, USA
Blendon RJ, Gorski MT, Benson JM (2016) The public and the gene-editing revolution. New Engl J Med 374(15):1406–1411. https://doi.org/10.1056/NEJMp1602010
Boardman FK, Hale R (2018) How do genetically disabled adults view selective reproduction? Impairment, identity, and genetic screening. Mol Genet Genom Med 6(6):941–956
Bosley KS, Botchan M, Bredenoord AL, Carroll D, Charo RA, Charpentier E et al. (2015) CRISPR germline engineering: the community speaks. Nat Biotechnol 33(5):478–486. https://doi.org/10.1038/nbt.3227

Botkin JR (2019) The case for banning heritable genome editing. Genet Med 22:487–489
Brokowski C (2018) Do CRISPR germline ethics statements cut it? CRISPR J 1(2):115–125. https://doi.org/10.1089/crispr.2017.0024
Buchanan A (1996) Choosing who will be disabled: genetic intervention and the morality of inclusion. Soc Philos Policy 13:18–46
Buchanan A, Brock DW, Daniels N, Wikler D (2000) From chance to choice: genetics and justice. Cambridge University Press
Calo Z (2012) Human dignity and health law: personhood in recent bioethical debates. Notre Dame J Law Ethics Public Policy 26:473–499
Carter L (2002) The ethics of germ line gene manipulation—a five dimensional debate. Monash Bioeth Rev 21(4):S66–S81. https://doi.org/10.1007/BF03351288
Cavaliere G (2018) Genome editing and assisted reproduction: curing embryos, society or prospective parents? Med Health Care Phil 21(2):215–25
Coller BS (2019) Ethics of human genome editing. Annu Rev Med 27(70):289–305. https://doi.org/10.1146/annurev-med-112717-094629
Council of Europe (1997) 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. COE, Oviedo
Collins, F. (2015) Director, National Institutes of Health, https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologieshuman-embryos
Cong L, Ran FA, Cox D, Lin S, Barretto R, Habib N et al. (2013) Multiplex genome engineering using CRISPR/Cas systems. Science 339:819–823
Conrad DF, Keebler JE, DePristo MA, Lindsay SJ, Zhang Y, Casals F et al. (2011) Variation in genome-wide mutation rates within and between human families. Nat Genet 43(7):712–4. https://doi.org/10.1038/ng.862
Cutas DE (2005) Looking for the meaning of dignity in the bioethics convention and the cloning protocol. Health Care Anal 13(4):303–313
Cwik B (2020) Revising, correcting, and transferring genes. Am J Bioeth 20(8):7–18
Cyranoski D (2019) Russian biologist plans more CRISPR-edited babies. Nature 570(7760):145–147
Daley GQ, Lovell-Badge R, Steffann J (2019) After the storm—a responsible path for genome editing. N Engl J Med 380:897–899
de Araujo M (2017) Editing the genome of human beings: CRISPR-Cas9 and the ethics of genetic enhancement. J Evol Technol 27(1):24–42. http://jetpress.org/v27.1/araujo.pdf
Dance A (2015) Core concept: CRISPR gene editing. Proc Natl Acad Sci USA 112:6245–6246
Davies K (2020) Editing humanity: the CRISPR revolution and the new era of genome editing. Pegasus Books, New York, NY
Delaney JJ (2011) Possible people, complaints, and the distinction between genetic planning and genetic engineering. J Med Ethics 37(7):410–414
Deutscher Ethikrat, (2019) Intervening in the Human Germline. https://www.ethikrat.org/en/publications/publication-details/?tx_wwt3shop_detail%5Bproduct%5D=119&tx_wwt3shop_detail%5Baction%5D=index&tx_wwt3shop_detail%5Bcontroller%5D=Products&cHash=25e88ad52f8b75d311510a9bf7a8dc86
Doudna JA, Charpentier E (2014) Genome editing. The new frontier of genome engineering with CRISPR-Cas9. Science 346(6213):1258096. https://doi.org/10.1126/science.1258096
Drabiak K (2020) The Nuffield Council's green light for genome editing human embryos defies fundamental human rights law. Bioethics 34:223–227
Dzau VJ, McNutt M, Bai C (2018) Wake-up call from Hong Kong. Science 362(6420):1215. https://doi.org/10.1126/science.aaw3127
de Miguel Beriain I (2020) Gene editing and disabled people: a response to Felicity Boardman. J Community Genet 11(3):241–243
de Miguel Beriain I (2018) Human dignity and gene editing. EMBO Rep 19:e46789
de Wert G, Heindryckx B, Pennings G, Clarke A, Eichenlaub-Ritter U, van El CG (2018) Responsible innovation in human germline gene editing: background document to the recommendations of ESHG and ESHRE. Eur J Hum Genet 26(4):450–470. https://doi.org/10.1038/s41431-017-0077-z
EGE (2016) Statement on gene editing. https://ec.europa.eu/info/sites/default/files/research_and_innovation/ege/gene_editing_ege_statement.pdf
EGE (2021) Ethics of genome editing. https://ec.europa.eu/info/sites/default/files/research_and_innovation/ege/ege_ethics_of_genome_editing-opinion_publication.pdf
Evitt NH, Mascharak S, Altman RB (2015) Human germline crispr-cas modification: toward a regulatory framework. Am J Bioeth 15(12):25–29
Feeney O, Cockbain J, Morrison M, Diependaele L, Van Assche K, Sterckx S (2018) Patenting foundational technologies: lessons from CRISPR and other core biotechnologies. Am J Bioeth 18(12):36–48
Fenton E (2008) Genetic enhancement – a threat to human rights? Bioethics 22(1):1–7 https://doi.org/10.1111/j.1467-8519.2007.00564.x
Feinberg J (1992) The child's right to an open future. In: Feinberg J (ed.) Freedom and fulfillment: philosophical essays. Princeton University Press, Princeton, pp. 6–97
Fu W, Akey JM (2013) Selection and adaptation in the human genome. Annu Rev Genom Hum Genet 14:467–89
Fukuyama F (2002) Our posthuman future: consequences of the biotechnology revolution. Picador, New York, NY
Gaj T, Gersbach CA, Barbas III CF (2013) ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering. Trends Biotechnol 31(7):397–405
Gaskell G, Bard I, Allansdottir A, da Cunha RV, Eduard P, Hampel J et al. (2017) Public views on gene editing and its uses. Nat Biotechnol 35(11):1021–1023. https://doi.org/10.1038/nbt.3958
Genomes Project C et al. (2015) A global reference for human genetic variation. Nature 526(7571):68–74
Greely HT (2019) Human germline genome editing: an assessment. CRISPR J 2(5):253–265. https://doi.org/10.1089/crispr.2019.0038
Glover J (2006) Choosing children: genes, disability, and design. Oxford University Press, Oxford
Greely HT (2021) CRISPR people: the science and ethics of editing humans. MIT Press, Cambridge, MA; London, UK
Gupta RM, Musunuru K (2014) Expanding the genetic editing tool kit: ZFNs, TALENs, and CRISPR-Cas9. J Clin Investig 124(10):4154–4161. https://doi.org/10.1172/JCI72992
Gyngell C, Douglas T, Savulescu J (2017) The ethics of germline gene editing. J Appl Philosy 34(4):498–513
Gyngell C, Bowman-Smart H, Savulescu J (2019) Moral reasons to edit the human genome: picking up from the Nuffield report. J Med Ethics 0:1–10. https://doi.org/10.1136/medethics-2018-105084
Gyngell C, Douglas T (2015) Stocking the genetic supermarket: reproductive genetic technologies and collective action problems. Bioethics 29(4):241–250
Guttinger S (2017) Trust in science: CRISPR-Cas9 and the ban on human germline editing. Sci Eng Eth 1–20. https://doi.org/10.1007/s11948-017-9931-1
Habermas J (2003) The future of human nature. Polity Press, Cambridge
Hammerstein AL, Eggel M, Biller-Andorno N (2019) Is selecting better than modifying? An investigation of arguments against germline gene editing as compared to preimplantation genetic diagnosis. BMC Med Eth 83:20
Häyry M (2003) Philosophical arguments for and against human reproductive cloning. Bioethics 17(5–6):447–460
Howard T, Rifkin J (1977) Who should play God? The artificial creation of life and what it means for the future of the human race. Dell Publ. Co
Hsu PD, Lander ES, Zhang F (2014) Development and applications of CRISPR-Cas9 for genome engineering. Cell 157(6):1262–1278. https://doi.org/10.1016/j.cell.2014.05.010
Hurlbut JB, Saha K, Jasanoff S (2015) CRISPR democracy: gene editing and the need for inclusive deliberation. Issues Sci Technol 32(1):25–32
Hyun I, Osborn C (2017) Query the merits of embryo editing for reproductive research now. Nat Biotechnol 35(11):1023–1025. https://doi.org/10.1038/nbt.4000. PMID: 29121025
Iltis AS, Hoover S, Matthews KRW (2021) Public and stakeholder engagement in developing human heritable genome editing policies: what does it mean and what should it mean? Front Political Sci 3. https://www.frontiersin.org/article/10.3389/fpos.2021.730869
Isasi R, Kleiderman E, Knoppers BM (2016) Genetic technology regulation: editing policy to fit the genome? Science 351(6271):337–339. https://doi.org/10.1126/science.aad6778
Ishii T (2015) Germline genome-editing research and its socio-ethical implications. Trends Mol Med 21(8):473–481. https://doi.org/10.1016/j.molmed.2015.05.006
Janssens AC (2016) Designing babies through gene editing: science or science fiction? Genet Med 18(12):1186–1187. https://doi.org/10.1038/gim.2016.28
Jedwab A, Vears DF, Tse C, Gyngell C (2020) Genetics experience impacts attitudes towards germline gene editing: a survey of over 1500 members of the public. J Hum Genetics65(12):1055–1065
Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E (2012) Programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 337:816–821
Jonlin EC (2020) Informed consent for human embryo genome editing. Stem Cell Rep 14(4):530–537. https://doi.org/10.1016/j.stemcr.2020.03.010
Juengst ET (1997) Can enhancement be distinguished from prevention in genetic medicine? J Med Philos 22(2):125–142
Juengst, ET, Moseley D (2019) Human enhancement. In: Zalta EN (ed.) The Stanford encyclopedia of philosophy (Summer 2019 Edition), Metaphysics Research Lab, Philosophy Department, Stanford University, Stanford
Karavani E, Zuk O, Zeevi D, Barzilai N, Stefanis NC, Hatzimanolis A et al. (2019) Screening human embryos for polygenic traits has limited utility. Cell 179(6):1424–1435
Kirksey E (2020) The Mutant Project: inside the global race to genetically modify humans. St. Martin's Press
Klingler C, Wiese L, Arnason G, Ranisch R (2022) Public engagement with brain organoid research and application: lessons from genome editing. Am J Bioeth Neurosci 13(2):98–100. https://doi.org/10.1080/21507740.2022.2048733

König H (2017) The illusion of control in germline-engineering policy. Nat Biotechnol 35(6):502–506. https://doi.org/10.1038/nbt.3884
Krimsky S (2019) Ten ways in which He Jiankui violated ethics. Nat Biotechnol 37(1):19–20. https://doi.org/10.1038/nbt.4337
Lander ES (2015) Brave new genome. N Engl J Med 373(1):5–8
Lander ES, Baylis F, Zhang F, Charpentier E, Berg P, Bourgain C et al. (2019) Adopt a moratorium on heritable genome editing. Nature 567(7747):165–168. https://doi.org/10.1038/d41586-019-00726-5
Lanphier E, Urnov F, Haecker SE, Werner M, Smolenski J (2015) Don't edit the human germ line. Nature 519(7544):410–1. https://doi.org/10.1038/519410a
Lappe M (1991) Ethical issues in manipulating the human germ line. J Med Philos 16(6):621–639. https://doi.org/10.1093/jmp/16.6.621
Lea RA, Niakan KK (2019) Human germline genome editing. Nat Cell Biol 21(12):1479–1489. https://doi.org/10.1038/s41556-019-0424-0
Ledford H (2015) The landscape for human genome editing. Nature 526(7573):310–311
Leon K (2003) Ageless bodies, happy souls: biotechnology and the pursuit of perfection. New Atlantis 1:9–28
Li H, Yang Y, Hong W, Huang M, Wu M, Zhao X (2020) Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects. Signal Transduct Target Ther 5(1):1–23
Li WH, Sadler LA (1991) Low nucleotide diversity in man. Genetics 129(2):513–23
Liang P, Xu Y, Zhang X et al. (2015) CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. Protein Cell 6(5):363–372
Lovell-Badge R (2019) CRISPR babies: a view from the centre of the storm. Development 146(3):dev175778
MacKellar C, Bechtel C eds. (2014) The ethics of the new eugenics. Berghahn Books, New York, Oxford
McGee A (2020) Using the therapy and enhancement distinction in law and policy. Bioethics 34(1):70–80
Melillo TR (2017) Gene editing and the rise of designer babies. Vand J Trans Law 50:757–790
Mertes H, Pennings G (2015) Modification of the embryo's genome: more useful in research than in the clinic. Am J Bioeth 15(12):52–53. https://doi.org/10.1080/15265161.2015.1103813
Mulvihill JJ, Capps B, Joly Y, Lysaght T, Zwart HAE, Chadwick R, International Human Genome Organisation Committee of Ethics Law and Society (2017) Ethical issues of CRISPR technology and gene editing through the lens of solidarity. Br Med Bull 122(1):17–29. https://doi.org/10.1093/bmb/ldx002
Musunuru K (2019) The CRISPR generation: the story of the world's first gene-edited babies. BookBaby.
National Academies of Sciences, Engineering, and Medicine (2015) International summit on human gene editing: a global discussion. The National Academies Press, Washington
National Academy of Sciences, National Academy of Medicine (2017) Human genome editing: science, ethics and governance. The National Academies Press, Washington, DC
National Academy of Medicine, National Academy of Sciences, and the Royal Society (2020) Heritable human genome editing. The National Academies Press, Washington, DC
Niemiec E, Howard HC (2020) Ethical issues related to research on genome editing in human embryos. Comput Struct Biotechnol J 18:887–896
National Academies of Sciences, Engineering, and Medicine (2019) Second International Summit on human genome editing: continuing the global discussion: proceedings of a workshop in brief. The National Academies Press, Washington
Niu Y, Shen B, Cui Y, Chen Y, Wang J, Wang L et al. (2014) Generation of gene-modified cynomolgus monkey via Cas9/RNA-mediated gene targeting in one-cell embryos. Cell 156(4):836–843
Nordberg A, Minssen T, Feeney O, de Miguel Beriain I, Galvagni L, Wartiovaara K (2020) Regulating germline editing in assisted reproductive technology: an EU cross-disciplinary perspective. Bioethics 34(1):16–32
Nuffield Council on Bioethics (2016) Genome Editing: an ethical review. https://www.nuffieldbioethics.org/publications/genome-editing-an-ethical-review
Nuffield Council on Bioethics (2018) Genome editing and human reproduction: social and ethical issues. http://nuffieldbioethics.org/project/genome-editing-human-reproduction
Parens E, Asch A (2000) The disability rights critique of prenatal testing: reflections and recommendations. In: Parens E, Asch A (eds.) Prenatal testing and disability rights. Georgetown University Press, Washington
Parliamentary Assembly (1982) Recommendation on genetic engineering. In Recommendation 934. Council of Europe
Paul D (2005) Genetic engineering and eugenics: the uses of history. In: Baillie HW, Casey TK (eds.) Is human nature obsolete? Genetics, bioengineering, and the future of the human condition. MIT Press, Cambridge Mass
Peden JF, Farrall M (2011) Thirty-five common variants for coronary artery disease: the fruits of much collaborative labour. Hum Mol Genet 20:R198–205
Porteus MH (2019) A new class of medicines through DNA editing. New Engl J Med 380(10):947–959. https://doi.org/10.1056/NEJMra1800729
Parens ET (Ed.) (1998) Enhancing human traits: ethical and social implications. Georgetown University Press, Washington, DC
Primc N (2020) Do we have a right to an unmanipulated genome? The human genome as the common heritage of mankind Bioethics 34(1):41–48
Ramsey P (1970) Fabricated man: the ethics of genetic control. Yale University Press, New Haven
Ranisch R (2017) Germline genome editing and the functions of consent. Am J Bioeth 17(12):27–29
Ranisch R (2020) Germline genome editing versus preimplantation genetic diagnosis: Is there a case in favour of germline interventions? Bioethics 34:60–69. https://doi.org/10.1111/bioe.12635
Ranisch R, Ehni HJ (2020) Fading red lines? Bioethics of germline genome editing. Bioethics 34(1):3–6. https://doi.org/10.1111/bioe.12709
Ranisch R, Rudolph T, Cremer HJ, Knoepffler N (2020) Ordo-responsibility for germline gene editing. CRISPR J 3(1):37–43
Ranisch R (2021) When CRISPR meets fantasy: transhumanism and the military in the age of gene editing. In: Transhumanism: the proper guide to a posthuman condition or a dangerous idea?. Springer, Cham, pp. 111–120
Ranisch R, Sorgner SL (2014) Introducing post-and transhumanism. In: Ranisch & Sorgner (eds.) Post-and transhumanism: an introduction. pp. 7–27. Peter Lang Group AG, Switzerland
Raposo VL (2019) Gene editing, the mystic threat to human dignity. Bioeth Inq 16:249–257. https://doi.org/10.1007/s11673-019-09906-4
Regalado A (2018) EXCLUSIVE: Chinese scientists are creating CRISPR babies. MIT Technol Rev. https://www.technologyreview.com/s/612458/exclusive-chinese-scientists-are-creating-crispr-babies/. Accessed 4 Aug 2021
Rehmann-Sutter C (2018) Why human germline editing is more problematic than selecting between embryos: ethically considering intergenerational relationships. New Bioeth 24(1):9–25. https://doi.org/10.1080/20502877.2018.1441669
Resnik D (1994) Debunking the slippery slope argument against human germ-line gene therapy. J Med Philos 19(1):23–40. https://doi.org/10.1093/jmp/19.1.23
Richter G, Bacchetta MD (1998) Interventions in the human genome: some moral and ethical considerations. J Med Philos 23(3):303–317. https://doi.org/10.1076/jmep.23.3.303.2581
Rulli T (2019) Reproductive CRISPR does not cure disease. Bioethics 33:1072–1082
Sandel M (2007) The case against perfection: ethics in the age of genetic engineering. The Belknap Press of Harvard University Press, Cambridge
Savulescu J (2001) Procreative beneficence: why we should select the best children. Bioethics 15(5–6):413–26
Savulescu J, Pugh J, Douglas T, Gyngell C (2015) The moral imperative to continue gene editing research on human embryos. Protein Cell 6:476–479
Scally A (2016) The mutation rate in human evolution and demographic inference. Curr Opin Genet Dev 41:36–43
Schaefer GO (2020) Can reproductive genetic manipulation save lives? Med Health Care Philos 23(3):381–386
Scheufele DA, Xenos MA, Howell EL, Rose KM, Brossard D, Hardy BW (2017) U.S. attitudes on human genome editing. Science 357(6351):553–554. https://doi.org/10.1126/science.aan3708
Scheufele DA, Krause NM, Freiling I, Brossard D (2021) What we know about effective public engagement on CRISPR and beyond. Proc Natl Acad Sci USA 118(22). https://doi.org/10.1073/pnas.2004835117
Scully JL (2008) Disability and genetics in the era of genomic medicine. Nat Rev Genet 9(10):797–802
Segers S, Mertes H (2020) Does human genome editing reinforce or violate human dignity? Bioethics 34(1):33–40
Sermon K, Van Steirteghem A, Liebaers I (2004) Preimplantation genetic diagnosis. Lancet 363(9421):1633–1641. https://doi.org/10.1016/S0140-6736(04)16209-0
Shakespeare T (2006) Disability rights and wrongs. Routledge, London
Shulman C, Bostrom N (2014) Embryo selection for cognitive enhancement: curiosity or game-changer? Glob Policy 5(1):85–92. https://doi.org/10.1111/1758-5899.12123
Silver LM (1997) Remaking Eden: cloning and beyond in a brave new world. William Morrow, New York, NY
Sinsheimer RL (1969). The prospect for designed genetic change. Am Sci, 57(1):134–142. http://www.jstor.org/stable/27828443
Smolenski J (2015) Crispr/cas9 and germline modification: new difficulties in obtaining informed consent. Am J Bioeth 15(12):35–37
Soini S (2007) Preimplantation genetic diagnosis (PGD) in Europe: diversity of legislation a challenge to the community and its citizens. Med Law 26(2):309–323
Sorgner SL (2018) Genes, CRISPR/Cas 9, and posthumans. In: Sinaci M and Sorgner SL (eds.) Ethics of emerging biotechnologies, pp. 5–17. Trivent Publishing
Sparrow R (2021) Human germline genome editing: on the nature of our reasons to genome edit Am J Bioeth 19:1–12

Steffann J, Jouannet P, Bonnefont JP, Chneiweiss H, Frydman N (2018) Could failure in preimplantation genetic diagnosis justify editing the human embryo genome? Cell Stem Cell 22(4):481–482. https://doi.org/10.1016/j.stem.2018.01.004
Sykora P, Caplan A (2017) The Council of Europe should not reaffirm the ban on germline genome editing in humans. EMBO Rep 18:1871–1872. https://doi.org/10.15252/embr.201745246
UNESCO (1997) Universal declaration on the human genome and human rights. UNESCO, Paris
van Dijke I, Bosch L, Bredenoord AL, Cornel M, Repping S, Hendriks S (2018) The ethics of clinical applications of germline genome modification: a systematic review of reasons Hum Reprod 33(9):1777–1796
Vassena R, Heindryckx B, Peco R, Pennings G, Raya A, Sermon K, Veiga A (2016) Genome engineering through CRISPR/Cas9 technology in the human germline and pluripotent stem cells. Hum Reprod Update 22(4):411–419. https://doi.org/10.1093/humupd/dmw005
Venter JC et al. (2001) The sequence of the human genome. Science 291(5507):1304–51
Walters L, Cook-Deegan RM, Adashi EY (2021) Governing heritable human genome editing: a textual history and a proposal for the future. CRISPR J 4(4):469–476
Wang H, Yang H (2019) Gene-edited babies: what went wrong and what could go wrong. PLoS Biol 17(4). https://doi.org/10.1371/journal.pbio.3000224
Wheeler E, Barroso I (2011) Genome-wide association studies and type 2 diabetes. Brief Funct Genom 10:52–60
WHO (2019) Statement on governance and oversight of human genome editing. https://www.who.int/news/item/26-07-2019-statement-on-governance-and-oversight-of-human-genome-editing
WHO (2021) Human genome editing: position paper. https://www.who.int/publications/i/item/9789240030404
Wolf DP, Mitalipov PA, Mitalipov SM (2019) Principles of and strategies for germline gene therapy. Nat Med 25(6):890–897
Zhang F (2019) Development of CRISPR-Cas systems for genome editing and beyond. Q Rev Biophys 52. https://doi.org/10.1017/s0033583519000052

Acknowledgements

This work was supported by Fundação para Ciência e a Tecnologia (FCT) of Portugal [UIDP/00678/2020 to M.A]. We thank Dr. Michael Morrison for his comments and Dr. Gustav Preller for his proofreading of this manuscript.

Competing interests

The authors declare no competing interests.

Ethical approval

An ethical approval is not applicable.

Informed consent

This article does not contain any studies with human participants performed by any of the authors.

Additional information

Correspondence and requests for materials should be addressed to Mara Almeida.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.