



Human germline editing: Legal-ethical guidelines for South Africa

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Human germline editing holds much promise for improving people's lives, but at the same time this novel biotechnology raises ethical and legal questions. The South African ethics regulatory environment is problematic, as it prohibits all research on, and the clinical application of, human germline editing. By contrast, the South African legal regulatory environment allows a regulatory path that would, in principle, permit research on human germline editing. However, the legal regulation of the clinical application of human germline editing is uncertain. As such, the current ethical and legal positions in South Africa are in need of reform. Five guiding principles – aligned with the values of the Constitution – are proposed to guide ethical and legal policy reform regarding human germline editing in South Africa: (1) Given its potential to improve the lives of the people of South Africa, human germline editing should be regulated, not banned. (2) Human germline editing clinical applications should only be made accessible to the public if they are proven to be safe and effective. (3) Non-therapeutic human germline editing may be permissible, and should be regulated in the same way as therapeutic human germline editing. (4) The decision on whether to use germline gene editing on a prospective child, should, subject to Principle 2, be left to the prospective parents. (5) Concerns about exacerbating social inequalities should be addressed by measures to increase access. In conclusion, recommendations are made to policymakers and scientists contemplating research in this field.

Significance:

The ethical and legal positions regarding human germline editing in South Africa are comprehensively analysed. Furthermore, five guiding principles – aligned with the values of the Constitution – are proposed to guide much needed ethical and legal policy reform regarding human germline editing in South Africa.

Introduction

Human germline editing holds the promise of significant benefit, but also harbours secrets of yet unknown possible genetic risks and consequences for future generations.¹ These risks and benefits considered, the germline editing reportedly performed by Chinese scientist He Jiankui on human in vitro embryos, resulting in the birth of two girls with edited genomes², ignited a flurry of global legal-ethical debate on whether germline editing should be permissible, and if so, under what circumstances³⁻⁷. What is South Africa's current position in terms of legal and ethical regulation of human germline editing? And what *should* South Africa's current position be in light of the values of the South African Constitution? These are the questions that we grapple with in this article.

Terminology

Genome editing⁸ (or gene editing) refers to the modification of the genome through targeted adding, replacing or removing one or more DNA base pairs in the genome, regardless of whether the modifications occur in a particular gene or a non-coding region of the genome⁹. Modern techniques used in genome editing are more precise than those that have in the past been used to genetically modify organisms, and include technologies such as CRISPR-CasX (where X is usually a digit e.g. 9), zinc finger nuclease (ZFN) transcription activator-like-effector based nucleases (TALEN) and meganucleases.^{10,11} Genome editing can be performed in both somatic cells and germline cells.⁹ Germline cells include early stage embryos, eggs, sperm and any cells that give rise to eggs and sperm.¹ Genome editing on germline cells (or germline editing in short) is usually more ethically and legally controversial, because the modification to the genome is intended to be heritable – in other words, the modification is likely to impact both the gene-edited individual and his or her genetic offspring. This article focuses exclusively on human germline editing.

Human germline editing is often divided into therapeutic and non-therapeutic germline editing. Typically, the term 'therapeutic' germline editing (or germline gene therapy) refers to the correction of a genetic defect in germ cells, with the aim of the gene-edited individual being born with a 'normal' genome; while the term 'non-therapeutic' germline editing refers to the modification of a normal genome in germ cells, with the aim of the gene-edited individual being born with an 'enhanced' genome.¹² Non-therapeutic germline editing therefore applies both to a modification that aims to bestow a health-related benefit to the gene-edited individual (such as immunity against contracting a certain illness) and to a modification that aims to bestow a non-health-related benefit to the gene-edited individual (such as higher intelligence – assuming it is possible).

For purposes of regulation, a further differentiation is relevant, namely between *research* on human germline editing and the *clinical application* of human germline editing. However, these terms, broadly understood, can overlap. With 'research' we refer to the production of generalisable knowledge about human germline editing through systematic investigation, including preclinical studies (such as in vitro human studies and animal trials)¹³ and clinical trials. With 'clinical application' we refer to the use of modified germ cells in human reproduction. This will include clinical trials and – if shown to be safe and effective – the provision of human germline editing as a service to the public.

Analysis of the current position

Ethics guidelines

In this section, we analyse the relevant provisions of the three most prominent ethics instruments in South Africa, namely the ethics guidelines of the South African Department of Health¹⁴, the Health Professions Council of South Africa (HPCSA)¹⁵ and the South African Medical Research Council (MRC)¹⁶.

The Department of Health's ethics guidelines have sections on genetics research and on genomics research that highlight general issues that are of ethical relevance with these types of research. However, the Department of Health's ethics guidelines are silent on the more specific topic of genome editing.

In 2008, the HPCSA published a code of ethical practice for medical biotechnology research in South Africa as Booklet 14 titled 'General ethical guidelines for biotechnology research in South Africa'.¹⁵ Subsequently, and at the time of finalising this article, a different version of Booklet 14, dated 2016, was available on the HPCSA website. However, this version is a verbatim duplicate of Booklet 13, titled 'General ethical guidelines for health researchers', which provides only general guidance on health research. Given the duplication, we assume that this is an administrative error and so rather rely on the 2008 version of Booklet 14 that specifically provides guidance on germline gene therapy and research.

The HPCSA states (under heading '13.3 Gene Therapy Research') that 'no attempts should be made through the use of gene modification, to change human traits not associated with disease'. The HPCSA does not provide any indication as to its reasons for this position. The HPCSA further argues (under heading '13.3.2 Germ line gene therapy research') that because of the heritable nature of germline gene therapy, research relating to germline gene therapy is 'not acceptable'. Although the HPCSA does not define exactly what it means by 'therapy' (e.g. does it include health-related enhancements to the genome?), it appears from the reasoning (based on heritability) that the intention is to ban all forms of human germline editing research – and per implication the clinical application thereof. This we view as problematic. As we discuss below, heritability per se is certainly a factor to consider, but it is not necessarily a negative factor, or sufficient reason for a ban.

The ethics guidelines of the MRC appear to have contradictory positions. First, in paragraph 3.2.3 of Book 2 of its ethics guidelines, the MRC states in categorical terms that 'germline therapy should not be contemplated'. This is an unhappy choice of words, given that this ethics guideline would ostensibly render this present article – and the reader's act of reading it – unethical, merely because the content of this article *contemplates* germline therapy. Then, in paragraph 3.2.3.1, the MRC takes a less categorical position, by stating that 'gene modification of the human germline should not yet be attempted until such time that it is clearly sanctioned in South Africa'. This statement is comprehensively vague: Who must sanction human germline editing before it should be attempted, and when will such sanction be sufficiently clear? These positions stand in contrast with paragraph 2.17 of the same document, where the MRC takes a significantly more permissive approach to the genetic manipulation of embryos – which would include genome editing of embryos – when it states: 'Pre-embryo manipulation and research may yield valuable medical information ... [T]he embryos should not be transferred to the uterus unless there is reasonable certainty that the manipulation carries no potential risks for the fetus'. The MRC is silent on risks to the prospective person (after birth) whose genome is to be edited.

We suggest that the antipathy towards human germline editing by the HPCSA and seemingly the MRC is problematic. There is no ostensible justification for placing an absolute prohibition on human germline editing. At best, considerations of safety and efficacy are good reasons for a temporary ban on clinical application, but not on research.¹⁷ Also, safety and efficacy concerns may be of a transient nature, emphasising why any ban on clinical application should be temporary, and allow the opportunity for further research and clinical trials. Furthermore, the MRC's focus on the foetus – with no mention of the prospective

person whose genome is to be edited, or his or her progeny – seems misplaced. Importantly, the MRC's requirement of 'no potential risks' is an unrealistic benchmark for when human reproduction is appropriate. Consider the 'potential risks' in normal conception: a recent study in the USA found that the frequency of fetuses potentially affected by a profound or severe genetic condition ranged from 94.5 to 392.2 per 100 000, depending on the ethnic group.¹⁸ Accordingly, the standard of 'no potential risks' would necessitate the banning of all unprotected heterosexual sex.

Legislation

As a general rule, the relevant legislative instruments focus either on research, or on clinical application, allowing us to analyse these two regulatory spaces separately. We start with research, followed by clinical application.

Research on human germline editing

Ethics committee oversight of scientific research has become best practice globally. Section 73 of the *National Health Act (NHA)*¹⁹ provides that every organisation that conducts 'health research' must have a health research ethics committee (HREC), and that this HREC must review research proposals and protocols, and grant approval where research proposals and protocols meet its ethical standards. Although not all human germline editing research would necessarily be health related, the NHA's broad definition of 'health research' is likely to include all human germline editing research within its ambit, and hence make HREC approval legally compulsory.

Given that research on human germline cells would require human research participants to donate germline cells, human germline editing research will trigger the application of the Regulations Relating to Research with Human Participants.²⁰ These Regulations provide that research involving human participants must: (a) comply with the Department of Health Ethics Guidelines at a minimum; (b) be responsive to health needs or priorities of the population, participating community or proposed participants; (c) have a valid scientific methodology and be likely to provide answers for the specific research questions posed; (d) include a favourable risk–benefit analysis; (e) ensure that the recruitment and selection process is just and fair; (f) be undertaken with appropriate consent processes; (g) undergo independent review by a registered HREC; (h) respect participants' rights, including but not limited to the rights to dignity, privacy, bodily integrity and equality; (i) make provision for compensation for research-related injury, for more than minimal risk research; and (j) be managed by a lead researcher, or person with similar standing or title, with suitable experience and qualifications. The Regulations also impose a wide array of further legal duties on researchers.

Research on human germline editing would also trigger the application of a second set of regulations made in terms of the NHA, namely the Regulations Relating to the Use of Human Biological Material.²¹ These Regulations prescribe various legal requirements for 'genetic health research'. Given the broad definition of 'health research' in the NHA, and given that germline editing is undoubtedly genetic in nature, research on human germline editing is likely to qualify as 'genetic health research'. The legal requirements for genetic health research prescribed by these Regulations include, inter alia, that such research must be done at an institution authorised as such in terms of the NHA, and that the institution must keep separate registers to record the genetic health research it conducts, and submit these registers to the Minister of Health by the end of March each year.

In addition, embryos would also be regulated by another provision of the NHA, namely section 57(4). This section provides that research on embryos within the first 14 days of embryonic development is permissible, subject to: (a) ministerial consent, (b) donor consent, and (c) an undertaking by the researcher to keep records of the research.

In the event that the research reaches a point, after properly designed preclinical studies,¹³ where it is ready for human clinical trials – for an embryo with an edited genome to be transferred in utero for reproductive

purposes – section 71 of the NHA will apply. Although editing takes place on a germ cell prior to the prospective child's existence, the research does not stop with that act, but continues through the gestation and into the child's life. If the particular genome edit holds out the prospect of direct benefit to the child,²⁰ the research may only be conducted: (a) if it is in the best interests of the child; (b) in such manner and on such conditions as may be prescribed in regulations; and (c) with the consent of the parent or guardian of the child. Similar to a minor, the prospective child cannot consent. If the particular genome edit does not hold out the prospect of direct benefit to the child, but holds out the prospect of generalisable knowledge,²⁰ the consent of the Minister is required in addition to requirements (a) to (c) above. The NHA provides that the Minister may not give consent in circumstances where, *inter alia*, (i) the reasons for the consent to the research or experimentation by the parent or guardian are contrary to public policy; (ii) the research or experimentation poses a significant risk to the health of the minor; or (iii) there is some risk to the health or well-being of the minor and the potential benefit of the research does not significantly outweigh that risk.

Given our brief analysis above, we suggest that there is a robust formal legal regulatory environment for human germline editing research in South Africa. In addition, the Regulations Relating to Research with Human Participants also provide important substantive legal rules to determine whether to permit germline editing research, such as responsiveness to the health needs of the South African population, and a valid scientific methodology. However, a potential problem arises whenever there is deference to HRECs, as these bodies would be guided by the ethical rules contained in the leading South African ethics guidelines, which we suggest are problematic (as discussed above).

Clinical application of human germline editing

We now move to the clinical application of human germline editing, and first consider the *Medicines and Related Substances Control Act* (MRSCA).²² If germline editing clinical applications fall within the regulatory ambit of the MRSCA, the South African Health Products Regulatory Authority (SAHPRA) can call on such applications to be registered. SAHPRA will review registration applications based on the criteria of safety, efficacy and quality – as determined by clinical trials. To fall within the regulatory ambit of the MRSCA, a germline editing application must qualify as either a 'medicine', or a 'medical device'. In brief, a medicine is a *substance* that is used for a medical purpose in humans, while a medical device is an *instrument* that is used for a medical purpose, but that does not achieve its primary intended action by pharmacological, immunological or metabolic means in the human body. Given that the court held that a bacterium qualifies as a *substance*,²³ it is not unrealistic that the biological components used in genome editing, such as guide RNA, enzymes and viral vectors, may qualify as substances. Similarly, given that a genome editing technology such as CRISPR-Cas9 and the viral vectors used to deliver it to target cells can be described as biological tools for precision work (and hence as instruments), it is not unrealistic that these biological tools may qualify as medical devices. However, it is uncertain whether germline editing applications would qualify as something that is used *in humans*, given that germline editing is performed on human germ cells, and not on human organisms – although germline editing will have an *effect* on human organisms. Lastly, while some potential clinical applications of human germline editing will have a medical purpose (which is broader than therapy, and includes prevention as well), other potential clinical applications of human germline editing will not have a medical purpose (such as increasing an individual's intelligence quotient or athleticism), and will therefore clearly fall outside the regulatory scope of the MRSCA. In sum, therefore: SAHPRA's legal mandate to regulate clinical applications of human germline editing (i) does not include non-medical applications, and (ii) is uncertain even in the case of applications with a medical purpose.

Let us now consider the NHA. A concept used in the NHA that can conceivably include the clinical application of human germline editing is 'reproductive cloning of a human being', which is defined in section 57(6)(a) of the NHA as:

'reproductive cloning of a human being' means the manipulation of genetic material in order to achieve the reproduction of a human being and includes nuclear transfer or embryo splitting for such purpose;

The 'reproductive cloning of a human being' is declared illegal in section 57(1) of the NHA, and in section 57(5) is made a criminal offence punishable by a fine and up to 5 years' imprisonment.

Although the clinical application of human germline editing is not cloning as the term is generally understood, one can argue that because germline editing is a form of 'manipulation of genetic material', it falls within the NHA's definition of 'reproductive cloning of a human being'. If this argument is accepted, the clinical application of human germline editing would be illegal and a punishable criminal offence in South Africa.

On the other hand, applying the principles of statutory interpretation to section 57 leads to the conclusion that germline editing should *not* be included within the ambit of the definition of 'reproductive cloning of a human being'. Firstly, in South African law, our courts give effect to the apparent purpose of a provision rather than its plain, literal meaning^{24,25} and there are a number of indicia that the purpose of section 57 is to specifically outlaw human reproductive cloning, including the heading of section 57 which reads 'Prohibition of reproductive cloning of human beings', and the repeated use of the word 'cloning' in section 57. Secondly, where a provision in a statute features the word 'include', the words after it define the general class of things that fall within the scope of the provision.²⁶ Thus, 'reproductive cloning of a human being' relates only to the general class of things that are defined by nuclear transfer and embryo splitting, namely cloning techniques. Accordingly, germline editing, which is not a cloning technique, would not be included in the definition of 'reproductive cloning of a human being'. Thirdly, where a provision in a statute is linked with a criminal sanction – as is the case with the definition of 'reproductive cloning of a human being' – the narrowest possible interpretation is preferred.²⁷ Applying this rule of our law, the definition of 'reproductive cloning of a human being' should only relate to cloning, and not more broadly to germline editing.

Although the application of the principles of statutory interpretation indicates that the legal position is that the clinical application of human germline editing is not prohibited, given the clumsy wording of the NHA, and the absence of case law on the subject, this position is all but certain.

Discussion

While there are some who hold that any form of genetic manipulation is morally reprehensible,²⁸ this is not a sentiment which is widely shared. Several prominent scientists and bioethicists have acknowledged that germline editing may be ethically permissible in at least some instances.²⁹ An overview of 61 ethics statements issued all over the world during the past 3 years shows that 54% of these statements take a position that germline editing should not be permitted, 30% are ambiguous or take no position, 11% are open to the possibility in the future, and 5% are open to further exploration.³⁰ However, in South Africa, the ethical and legal positions regarding human germline editing should first and foremost be informed by the values of the Constitution – most prominently dignity, equality and freedom.

The current South African ethics guidelines appear to be underdeveloped, and to be simply mimicking the position of most international ethics statements without due regard to South Africa's unique health-care needs, values, and existing legal regulatory environment. South Africa is dealing with epidemics, like TB and HIV, on a scale incomparable to the countries where some of the ethics statements referred to above originated. These diseases are undermining South Africans' quality of life, and hence their dignity; these diseases also disproportionately affect the poor, and as such exacerbate inequality. Moreover, South Africa is one of very few countries to explicitly protect the right to freedom of scientific research in its Constitution. In the present context, this right is in a mutually supporting relationship with the right to access to health care, the right to dignity and the right to equality. *Therefore, South Africa needs to be bolder (than other countries need to be) in seeking*

health-care solutions. Also consider that South Africa has a robust legal regulatory environment for health research, which would include research on human germline editing. This means that South Africa can be bold in seeking healthcare solutions *with confidence*.

When it comes to the legal regulation of the *clinical application* of human germline editing, the novelty of the technology creates uncertainty both in the context of the MRSCA and the NHA. Given the uniqueness of human germline editing (in contrast with, for instance, traditional medicines and medical devices) we suggest that *sui generis* legislation be developed to regulate the clinical application of human germline editing.

Recommended principles

In this section, we propose a set of guiding principles that we suggest should underlie and inform the regulation of human germline editing in South Africa. The first principle relates exclusively to research; the remaining four relate primarily to application, but can also be relevant to consider during the preceding research phase.

Principle 1: Human germline editing should be regulated, not banned

Given its potential to improve the lives of the people of South Africa, human germline editing should be regulated, not banned. Such research will qualify as health research, and be regulated by the relevant parts of the NHA and its regulations (discussed above). This would include a system of HREC oversight. When considering proposed research on human germline editing, an HREC should, we suggest, apply the same substantive criteria as with any other proposed health research that involves human participants who provide human biological material. One exception should be that, given the nature of germline editing (namely that the modifications made to the genome as part of germline editing are designed to be heritable and therefore may be passed on to future generations), consideration should be given to the potential long-term implications of the proposed research. This would be relevant not only with the risk–benefit analysis, but also with, *inter alia*, informed consent and, where relevant, community engagement.

Principle 2: Use the well-established standard of safety and efficacy

Following properly designed preclinical studies,¹³ new human germline editing clinical applications should be subjected to clinical trials on humans – the same as with new medicines or medical devices. Clinical trial protocols would need to be designed mindful of the fact that germline editing is designed to be heritable. This means that the first human trials may have to monitor the trial participants over multiple years, perhaps even over generations. However, as with new medicines or medical devices, human germline editing clinical applications should only be made accessible to the public if they are proven to be safe and effective.

The safety and efficacy of germline editing will of course not affect any *existing* person; given the nature of germline editing, it will affect *prospective* persons. An important question in this context is whether one can consider the interests of prospective persons in South African law? The answer is yes: In *AB v Minister of Social Development* the Constitutional Court indeed considered the interests of *prospective* persons.³¹ The Court based its eventual decision to uphold a legal prohibition on certain conduct on a factual finding that such conduct in the present would cause harm to prospective persons in the future.³¹ (Note that the concept of the ‘prospective person’ is a mental construct of a person that may exist in future, and does not refer to the pre-nate.³² Although an embryo or foetus may *become* the prospective person, an embryo or foetus cannot be *equated* to the prospective person.)³² Accordingly, we suggest that, from a legal perspective, there is solid foundation to consider the safety and efficacy of germline editing for future generations.

Principle 3: Non-therapeutic uses of germline gene editing may be permissible

Non-therapeutic uses of germline editing are viewed by some as ethically problematic.^{33,34} Such uses are often referred to as genetic ‘enhancement’ because they are viewed as nothing more than an endeavour to enhance people without valid moral justification. In Western bioethics in particular, ‘enhancement’ is viewed as morally reprehensible largely because it is seen as reminiscent of the state-sponsored eugenics programmes of early 20th-century Britain, America and Nazi Germany.³⁵ It is for this reason that ethics statements such as the one issued by the Association for Responsible Research and Innovation in Genome Editing (ARRIGE) in 2018, claim that genetic modification of the CCR5 gene to prevent children from contracting HIV is a genetic enhancement, and is therefore unnecessary and unethical.³⁶

Whether this line of thought should have bearing on the South African position should be questioned, given that the equivalence between enhancement and eugenics is contested. As pointed out in the literature,^{37,38} whereas state-enforced eugenic regimes used coercive means that *violated* procreative freedom in an attempt to create ‘better people’, individual uses of germline editing technologies, by contrast, *promote* procreative freedom by leaving their application up to individual choice. Furthermore, the assumption that there are no morally justifiable reasons for enhancement applications of germline editing is another issue worth questioning, given that several noteworthy bioethicists²⁹, and reputable ethics bodies such as the Nuffield Council on Bioethics, have opined that there may be circumstances where genetic enhancement would be ethically justifiable¹¹.

One such instance is the potential use of germline editing for the selection of desirable genetic traits in future offspring, in a way similar to choosing embryos using the information generated by pre-implantation genetic testing. It has been predicted that genetic selection against single-gene disorders (also known as Mendelian disorders) is one of the few likely candidates for which germline editing technology will be used, given that it provides parents who are both carriers for such diseases a means to have a child that is genetically related to them.³⁹ There is no reason, in principle, why germline editing could not be used for the selection of other single-gene traits – and perhaps even traits that are the product of the interaction of multiple genes. There is, further, no apparent reason why this would be deemed unacceptable in South Africa given that the genetic selection of gametes and embryos for non-medical reasons is permissible in our law (with the exception of sex selection, which may only take place to prevent a serious medical condition).⁴⁰ There is, in fact, a reason why this would be deemed to be a favourable alternative to genetic selection via pre-implantation genetic testing: Genetic selection using germline editing technology does not entail the destruction of multiple embryos that do not possess the desired genetic traits. This is an ethically compelling consideration for societies – such as South Africa – where the embryo is viewed by some as having a special moral status such that its destruction, in the context of medically assisted reproduction, ought to be avoided.⁴⁰

While we do not make the claim, as some have, that this or any other application of germline editing is a basis for a moral duty to enhance future generations,⁴¹ in our view a blanket prohibition on non-therapeutic applications of germline editing is inappropriate, as there may be ethically and legally defensible justifications for such applications. As such, we suggest that both therapeutic and non-therapeutic applications of germline editing may be permitted.

Principle 4: Respect parents’ reproductive autonomy

Although human germline editing is an issue of broad societal interest, the choice to use germline editing – once it is safe and effective to use, and made available to the public – should be made by individual prospective parents. This is because, as recognised by the Nuffield Council on Bioethics,¹¹ the use of germline editing technology intersects with the high premium modern liberal democracies give to the need to respect the reproductive goals of persons seeking to become parents.¹¹ While some consider human germline editing an unprecedented

intrusion into the destiny of future generations, others have argued that it is in no way meaningfully different from other ways in which parents can influence their children.⁴² Underlying these arguments is the claim that human germline editing falls within the ambit of socially accepted and legally protected interests of parents in making decisions relating to reproduction. It is for this reason that, in the American context, the National Academies of Sciences, Engineering, and Medicine 2017 report on human genome editing notes that: 'Access to heritable genome editing would be consistent with the broadest legal and cultural interpretations of parental autonomy rights in the United States.'¹⁸ In South Africa, reproductive autonomy finds protection in section 12(2)(a) of the Constitution, which provides that: 'Everyone has the right to bodily and psychological integrity, which includes the right— (a) to make decisions concerning reproduction'. While this right has historically been interpreted primarily in the negative sense, i.e. in relation to the rights of individuals to choose *not to have children*, our courts have also acknowledged in recent years that reproductive autonomy also applies in the positive sense, i.e. in relation to rights of prospective parents to choose *to have a child* – including through the use of new reproductive technologies.³¹ In so far as human germline editing technology may be viewed as a reproductive technology, reproductive autonomy extends to the use of germline editing in order to, for instance, allow parents who are both carriers of a genetic disorder to have a genetically related child who is free of that genetic disorder.

For these reasons, we suggest that in the event that clinical applications of germline editing become available to the public, prospective parents should be permitted to choose whether they wish to use such applications for their prospective children. The choices of prospective parents in this regard should not otherwise be restrained, unless it is a limitation which is reasonable and justifiable in an open and democratic society as per section 36 of the Constitution.

Principle 5: Promote the achievement of equality of access

A concern that is often raised in debates about human germline editing is that this new technology may possibly only be accessible to the rich, with the consequence of exacerbating existing inequalities in society – particularly in societies like South Africa given the wide gap between the rich and poor, and the lack of access to health care for the underprivileged.⁴³ One possible response is that although new technologies are often expensive initially, in time they typically become far less expensive; the early adopters of new technology pay a premium for it, and essentially fund the ongoing research and development of the technology to make it more accessible. From a legal perspective, the appropriate response to the concern about exacerbating inequality is the Constitutional Court dictum that measures to promote the achievement of equality call for 'equality of the vineyard not the graveyard'.⁴⁴ In other words, the solution to the concern about human germline editing exacerbating inequality cannot be to suppress the technology, as that would mean levelling down to the 'equality of the graveyard'; rather, if the state seeks to promote the achievement of equality in the context of human germline editing it must do so by levelling up to the 'equality of the vineyard'. As bioethicist John Harris has pointed out, the appropriate approach for a state that is genuinely concerned about novel technologies exacerbating inequality, would be to take measures to make these technologies as widely available as possible, and thereby remedying the inequality and promoting human flourishing.³⁷ To illustrate: universal health coverage of medically assisted reproduction is one strategy to promote access to new reproductive technologies⁴⁵, which has yielded positive results in some jurisdictions⁴⁶. Such an approach may be viable in South Africa, which is currently in the process of implementing National Health Insurance.⁴⁷

Conclusion

Human germline editing holds the promise of improving the lives of future generations. However, how can South African scientists work towards this aim in a milieu of regulatory uncertainty? Reform is needed. Instead of panicked reactions to He's germline editing actions, such as advocating moratoria, our proposed set of five guiding principles

aims to provide a clear and realistic regulatory pathway for the South African science community to pursue human germline editing research, and eventually the clinical application thereof, in a responsible fashion aligned with the values of the South African Constitution.

For policymakers, we recommend that the relevant regulatory instruments (ethics guidelines and legislation) mentioned in this article be amended as indicated in Table 1. This represents the minimum action required to establish regulatory certainty and bring the South African regulatory environment in line with our proposed five guiding principles. A best-practice scenario would require, in addition, that the various South African ethics guidelines all incorporate the five principles.

Table 1: Recommended amendments to the current regulatory instruments for human germline editing

Regulatory instrument	Minimum required action
Health Professions Council of South Africa's ethics guidelines ¹⁵	The bans on germline therapy research and on gene modification should be removed.
South African Medical Research Council's ethics guidelines ¹⁶	(i) The ban on contemplating germline therapy should be removed. (ii) The requirement that genetically modified embryos may only be used for reproductive purposes if there is 'no potential risks for the fetus' should be replaced with the requirement that there is a favourable benefit–risk analysis for the prospective person, and for future generations.
South African Department of Health's ethics guidelines ¹⁴	–
National Health Act (NHA) ¹⁹	The definition of 'reproductive cloning of a human being' in Chapter 8, section 57(6)(a) should be amended by inserting the words 'genetically identical' before 'reproduction of a human being'. This will make it clear that reproductive cloning is banned, and not reproduction following any form of genetic manipulation.
Regulations Relating to Research with Human Participants ²⁰	–
Regulations Relating to the Use of Human Biological Material ²¹	In the alternative to amending the ambivalent definition of 'reproductive cloning of a human being' in the NHA, the same objective would be accomplished by inserting a provision in the Regulations Relating to the Use of Human Biological Material to the effect that clinical applications of human germline editing should be permitted subject to health research ethics committee oversight of clinical trials, and regulation by the South African Health Products Regulatory Authority.
Medicines and Related Substances Control Act ²²	–
New legislation	New primary legislation should be developed – based on the five principles – to regulate the clinical application of human germline editing in South Africa.

For scientists who are intending to do human germline editing research, we recommend stalling plans until, at a minimum, the HPCSA and MRC ethics guidelines are amended as per Table 1. Amending these ethics guidelines will allow HRECs to consider and approve human germline editing research, and will open the door to ministerial approval of the use of embryos in terms of section 57(4) of the NHA. Note, however,



that such research would need to remain in vitro until the NHA or the Regulations Relating to the Use of Human Biological Material have been amended as per Table 1. Once such amendment(s) have been effected, HRECs can consider and approve clinical trials (i.e. using an embryo with a modified genome for reproductive purposes), and the Minister can permit such clinical trials involving children in terms of section 71 of the NHA.

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Competing interests

We declare that there are no competing interests.

Authors' contributions

All authors contributed to the conceptualisation and writing of the article; D.T. was responsible for project leadership and funding acquisition.

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