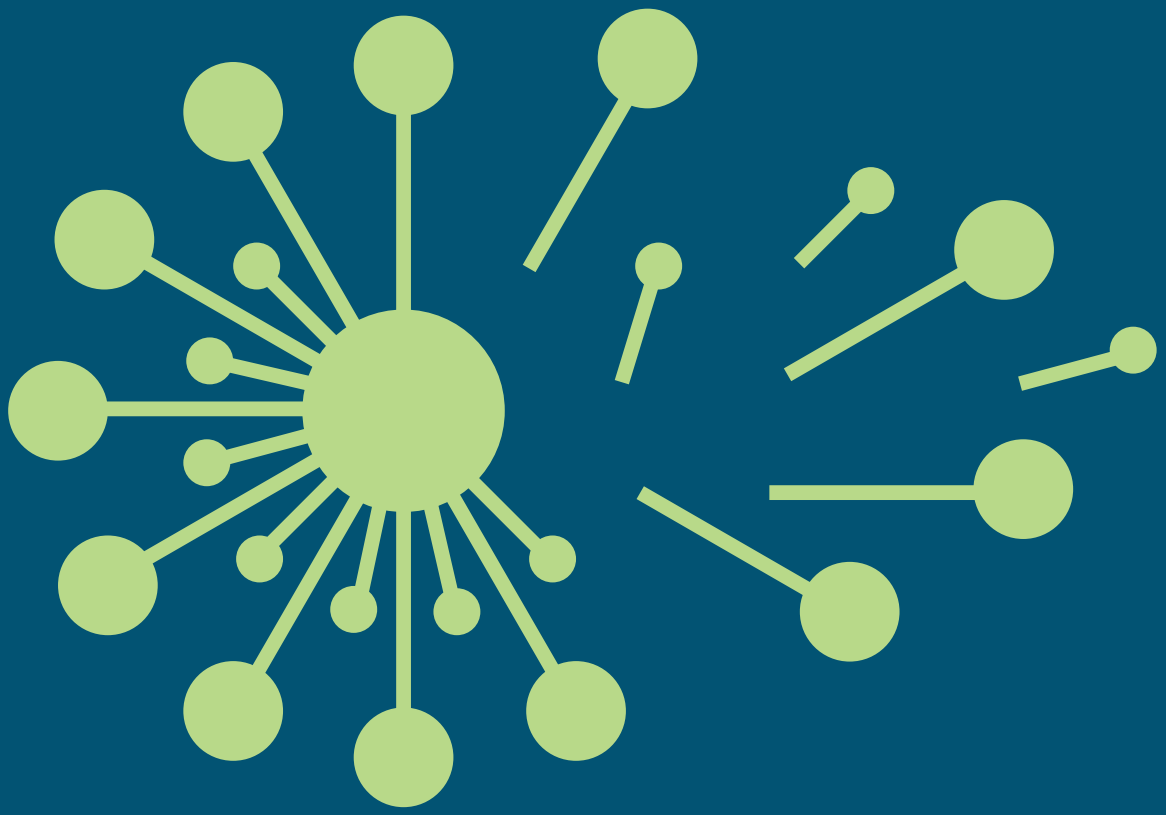
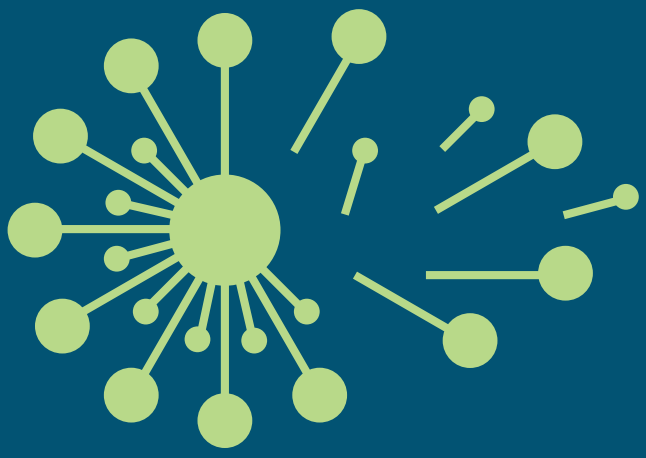
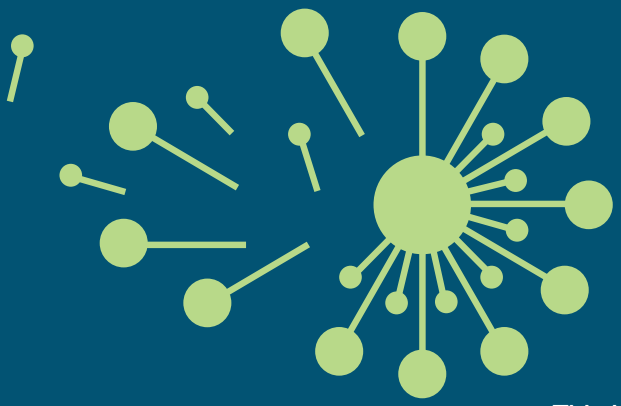


Genome editing and human reproduction: social and ethical issues

short guide



NUFFIELD COUNCIL ON BIOETHICS



This brief guide outlines the main themes and key findings of the Nuffield Council on Bioethics inquiry prompted by the prospect of heritable genome editing interventions in humans, concluding in July 2018.

This inquiry was carried out by an interdisciplinary working party that included members with expertise in biology, human reproduction, genome editing, law, and ethics.

To inform its deliberations, the working party invited contributions from a wide range of people, including through an open call for evidence, an online questionnaire, research interviews, fact-finding meetings, and panel interviews.

The development of genome editing applications in human reproduction was one of the areas identified as requiring further ethical scrutiny in the Nuffield Council on Bioethics' previous report *Genome editing: an ethical review*, published in 2016.

Contents

Overview

The first part of this guide page 5
looks at the potential future use of genome editing to enable people to have children who are genetically related to both parents but who will not inherit certain characteristics from them, such as heritable diseases or predispositions to disease.

The second part of this guide page 7
sets out the ethical considerations raised by these potential uses of heritable genome editing interventions, as they relate to:
- the people immediately involved, i.e. the prospective parents and their future children;
- others in society who may be indirectly affected, and society as a whole; and
- future generations, and the human species in general.

The third part of this guide page 11
explains what conditions would need to be met if the law were to change to permit heritable genome editing interventions and how these ethical considerations might inform the development and application of governance measures.

Key findings of this inquiry

We conclude that the potential use of heritable genome editing interventions to influence the characteristics of future generations could be ethically acceptable in some circumstances, so long as:

- it is intended to secure, and is consistent with, the **welfare of a person** who may be born as a consequence of interventions using genome edited cells; and

- it is consistent with **social justice and solidarity**, i.e. it should not be expected to increase disadvantage, discrimination, or division in society.

- We recommend that research should be carried out on the safety and feasibility of heritable genome editing interventions to establish standards for clinical use.

- We recommend that social research should be carried out to develop greater understanding of the implications of genome editing for the welfare of the future person.

- We recommend that before any move is made to amend UK legislation to permit heritable genome editing interventions, there should be sufficient opportunity for broad and inclusive societal debate.

- We recommend the establishment of an independent UK body to promote public debate on the use of genomic and related technologies to respond to societal challenges; to help to identify and understand the public interests at stake; and to monitor social, cultural, legal, and health impacts.

- We recommend that governments in the UK and elsewhere should work with international human rights institutions, such as the Council of Europe and UNESCO, to promote international dialogue and to develop a framework for international governance of heritable genome editing interventions.

- We recommend that heritable genome editing interventions should only be licensed on a case-by-case basis subject to:

  - assessment of the risks of adverse clinical outcomes for the future person by a national competent authority (in the UK, the HFEA); and

  - strict regulation and oversight, including long-term monitoring of the effects on individuals and social impacts.

Introduction

What is a genome?

The term 'genome' generally refers to the entire sequence of DNA of an organism. The genome includes sequences of DNA with specific functions that are involved in the production of the proteins and other molecules needed to carry out biological roles such as development, energy production, and fighting disease.

Genetic variation

Increasing understanding and knowledge of the human genome is complicating our understanding of states of 'health' and 'disease', and challenging the idea that a clear distinction can be drawn. There are many complexities in the relationship between genetic variation (differences in the DNA sequence that may lead to physiological differences between people), and health and disease, for example:

- all humans have a similar genome, although there are many small variations between the genomes of different people, making each person's genome unique;
- some genetic variants are strongly associated with disease – many others predispose people to disease in certain circumstances;
- a particular genetic variant can be associated with different effects in different people;
- multiple genetic variants may interact with each other, and/or with environmental or lifestyle factors, to affect susceptibility or resistance to a particular disease in each of us;
- new genetic variants can arise spontaneously and, in some cases, these can be inherited (i.e. passed on to offspring); and
- sequencing of more people's genomes is likely to reveal many new genetic variants associated with disease and other inherited characteristics.

What is genome editing?

Genome editing is the deliberate alteration of a selected DNA sequence in a living cell. Genome editing techniques can be used to alter how a gene functions, for example, by changing a variant of a gene that may give rise to disease to one that does not. As well as modifying the genome itself, the technique can be used to modify the epigenome – a set of chemical modifications associated with the genome that can control gene activity, e.g. changing gene expression without changing the DNA sequence.

CRISPR-Cas9 is an example of a relatively new method of genome editing that is now widely used in research. It is popular because of its relative efficiency, low cost, ease of use, and its potential to make edits at several sites in the genome in a single procedure.

Genome editing and human reproduction

Genome editing could potentially be applied in the context of assisted reproduction to alter a DNA sequence(s) of an embryo, or of a sperm or egg cell prior to fertilisation. The aim would be to influence the inherited characteristics of the resulting person.

We refer to these as 'heritable genome editing interventions' since the altered DNA may be passed to future generations.

One use of heritable genome editing interventions would be to have a child while excluding a particular heritable disorder that the child might have inherited from their biological parents. However, there are many complexities in the relationship between genomes and individuals' wellbeing, so even if genome editing could ensure the child did not have the a genetic variant associated with a particular disorder, the 'health' of that future person could not be guaranteed.

Current use and availability

Genome editing is not currently available to people for reproductive purposes. Such procedures would be illegal in many countries, including the UK.

The science is comparatively new and would require further refinement before it could be used clinically. To date, a small number of research groups in China, the

US and the UK have used genome editing techniques in human embryos grown briefly in laboratories, outside of the human body. These have not been used to create babies. More research is needed before we can establish whether any of the genome editing techniques developed to date would be an effective, safe, and viable approach in any particular circumstances.

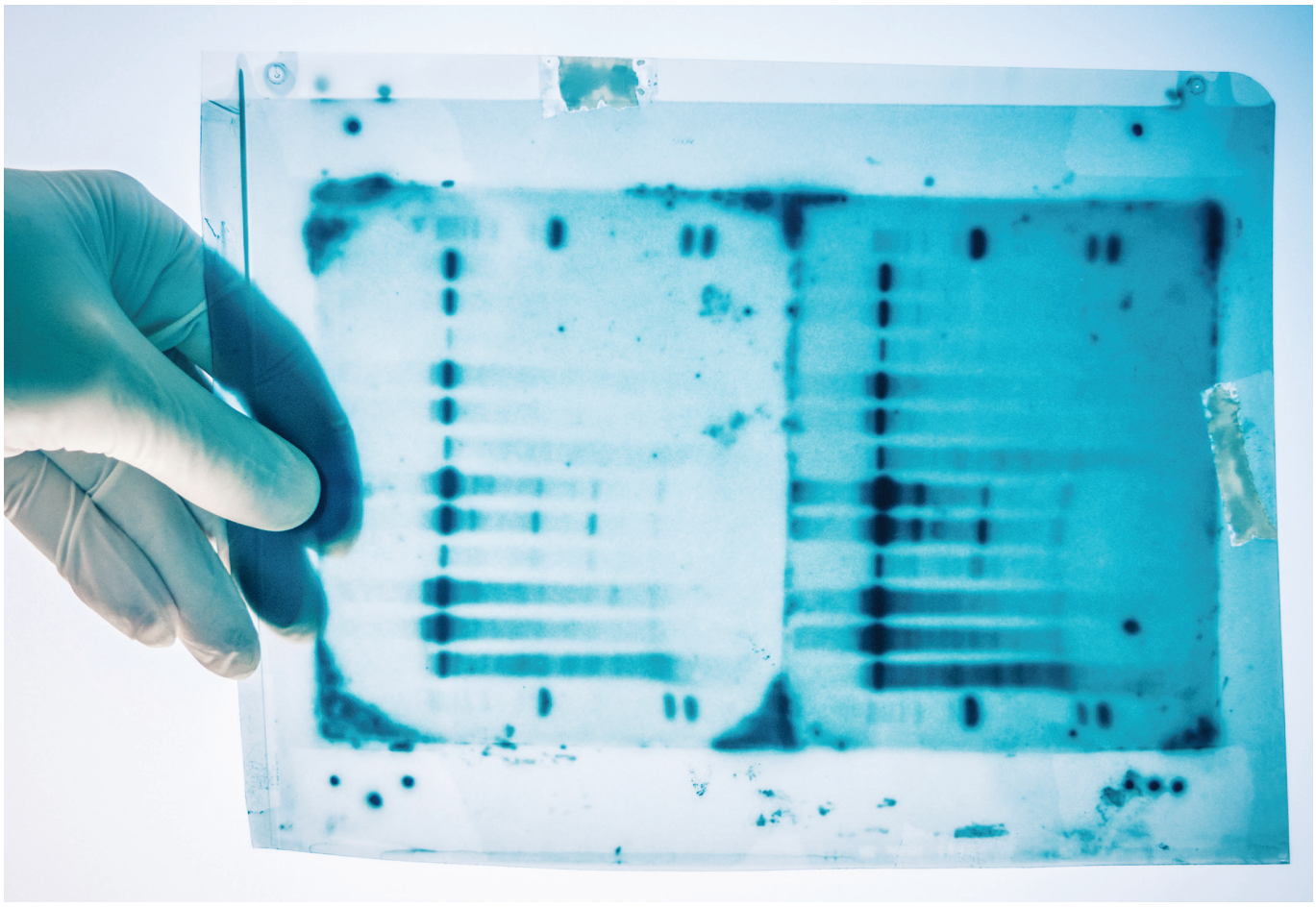
Although it is lawful in the UK to create and use genome edited human embryos, sperm, or eggs in research, under strict licensing conditions, it would be illegal to use them in assisted reproduction. It would be necessary to change the law, which may require a long parliamentary process, before this could be permitted.

What approach did we take in this inquiry?

Our ethical analysis starts with prospective parents who may find themselves facing complex reproductive decisions, having access to certain new kinds of knowledge and information, and with a range of options that they might take, including those that biomedicine, economic affluence, and the moral endorsement of the society they live in have made available to them.

Perhaps the most obvious cases concern excluding inherited genetic disorders, but genome editing has the potential to be used for a wider range of purposes.

Our inquiry asks, therefore, in what circumstances, in what ways, and to what extent, should people be permitted, enabled or assisted to pursue their reproductive goals?



The potential role of genome editing in human reproduction

Genome editing has been heralded as a possible future option for people who are affected by or carriers of an inherited genetic disorder who wish to have a genetically related child but want to ensure that their child does not have the disorder.

Currently, genetic testing may be used to confirm whether a person is affected by, or a carrier of, a suspected genetic disorder. Prospective parents often know about the presence of an inherited genetic disorder in their family, in advance of any decision about becoming pregnant. This information might be known because either (or both) of them have the condition themselves, close family members have had it, or they already have one or more children with the condition.

If whole genome sequencing of people becomes more widespread it is likely that more genetic information that could be relevant to the health and welfare of future offspring will come to light, some of which could involve the interaction of a number of different genes.

What are the current reproductive options?

Currently, if couples carrying a genetic condition wish to ensure that a child they are hoping to have does not inherit that condition (or inherit a specific variant), there are various options open to them. Not all of these options are available in all cases. There might be medical reasons to prefer one approach rather than another, although much may also depend on the preferences and expectations of the prospective parents.

If there is no overriding wish for the child to be genetically related to both parents, then these options might be considered:

- adoption; or
- sperm, egg, or embryo donation.

If there is a wish for a direct genetic link to both parents, then these options may be considered:

- Unassisted conception, followed by prenatal diagnosis to confirm the presence or absence of a genetic disease in the fetus. Termination of the pregnancy may be considered based on the diagnosis.
- IVF, incorporating preimplantation genetic diagnosis/testing (PGD/T). Early stage embryos are tested for indications of the genetic condition. One or more embryo(s) found to have the desired, or not to have the unwanted, characteristics can then be transferred to the womb.
- In rare cases in which an inherited genetic condition is transferred through the mitochondrial DNA, mitochondrial donation techniques may be an option. These techniques were the subject of a previous Nuffield Council on Bioethics report, and have recently been permitted for use as a treatment.

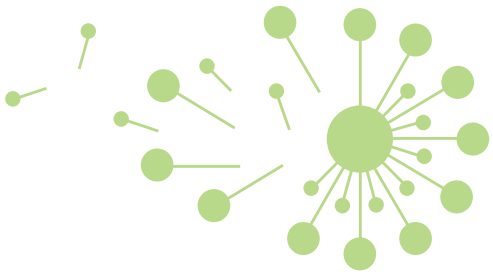
Where might genome editing come in?

Heritable genome editing interventions are not currently available as a reproductive option, but they could be in the future. The aim would be to edit a sequence of DNA in an embryo, sperm, or egg, in order to replace a variant of a gene that has one kind of effect with another known variant that has a different effect (for example, to replace a disease-causing variant with a non-disease variant). The edited DNA would then become part of the genome of the growing embryo so that any future person resulting from that embryo, sperm, or egg would have that variant in all their cells.

At present, we only know of a few, rare circumstances where genome editing would be the *only* option available for having a genetically related child while excluding a specific condition (i.e. where a given couple could not conceive a child who did not inherit that condition). These rare examples include:

- dominant genetic conditions, such as Huntington's disease, where one of the prospective parents carries two copies of the disease-causing gene; and
- recessive genetic conditions such as cystic fibrosis or sickle cell anaemia where both of the prospective parents carry two copies of the disease-causing gene.

There are other cases, however, in which it is possible, but very difficult, to achieve the birth of a genetically



related child with desired characteristics using alternative approaches, such as:

- where the aim is to exclude predispositions to complex disease;
- where there is a need to increase the number of available embryos with desired characteristics (where selection following preimplantation testing would reduce the number significantly, making a live birth less likely); and
- where the aim is to select for multiple characteristics that are inherited independently (where it is less likely that an embryo with these would be found).

Beyond these circumstances, there is potential for genome editing to be used to influence a wider range of characteristics. If heritable genome editing proves to be a viable reproductive technology, it is possible that its repertoire of uses could expand. People may come to consider it as a reasonable alternative to existing selective techniques, and as a means to include variants in a way that selective techniques could not achieve.

It is possible that genome editing could be used in future for:

- building in resistance or immunity to a disease;
- increasing tolerance to environmental conditions; or
- enhancing senses or abilities.

Factors affecting the potential of heritable genome editing interventions to become widely used

There are big 'ifs' with genome editing in the context of human reproduction. Will it work? Will it be safe? How would it compare to other options? Who could afford it?

At this stage, we cannot confidently predict the extent to which the use of heritable genome editing interventions might spread if it were to be approved, the range of possible uses, or the potential for it to displace other selective technologies. The main influences on its potential as a technology are likely to include:

- the knowledge, skills, and resources needed to use it efficiently;
- public attitudes and opinions;
- investment in research; and
- the parallel development of other technologies and treatments (for example, therapeutic or preventative genome editing interventions for existing people – so-called 'somatic gene therapies').

Knowledge about the genome

The extent to which heritable genome editing interventions might become a part of assisted reproductive technologies will depend on developing our understanding of the genome (which contains the target sequence) and of the editing techniques themselves.

One of main reasons that it is hard to predict how useful genome editing will be is that we do not have a full understanding of how the genome functions. Although some single gene disorders are well-understood, most disease seems to be caused by the interaction of multiple genes, or of genes together with a variety of environmental factors. Many characteristics that differ between people, such as behaviour or intelligence, are more complex still. It is improbable that genome editing would offer a way to control these predictably.

The increasing availability and use of whole genome sequencing will enable the production of more knowledge about the genome but drawing insights from vast amounts of data will be a challenge. It remains to be discovered how closely many human characteristics can be associated with a particular genetic variant or combination of variants. Consequently, the range of potential uses of genome editing is hard to predict.

Public attitudes and opinions

Whether heritable genome editing interventions are used at all, and how their use might be expanded will also depend on public attitudes and opinions and prevailing social norms (the ways in which we expect people to behave in society). These may change over time, possibly as a result of the way the technology is introduced, taken up, or offered alongside existing assisted reproductive technologies. So that practice takes account of these norms, policies for the use of genome editing for any particular purpose should be informed by public interests that are identified and understood through broad and inclusive societal debate.

Ethical considerations and conclusions

Our ethical analysis starts from consideration of how the reproductive goals and decisions of prospective parents are embedded within a context of knowledge (*about the role of the genome and about their own genetic status*) and possibilities for action (*provided by the social and technological context*) that links different types of interests and responsibilities (*of individuals to each other and to society, and of society to individuals*).

We have divided the ethical considerations into three sets, relating to the interests of:

- the people immediately involved, i.e. the prospective parents and their future children;
- others in society who may be indirectly affected and society as a whole; and
- future generations, and the human species in general.

People immediately involved

The key interests to consider are the reproductive interests of parents, and the welfare of the future person.

Reproductive interests of parents

These are principally:

- the interest in having a child;
- the interest in their child being genetically related to them; and
- the interest in their child being free of inherited disorders.

There are many reasons why people want to have genetically related children, and people's interest in doing so is protected by a widely recognised human right. These interests may, for some people, be enabled by the availability of assisted reproductive technologies, which may (or may not) be publicly funded. For some people who carry or are affected by inherited genetic disorders, the use of assisted reproductive technologies, such as preimplantation genetic testing, already offer a way of managing the possibility of a future child inheriting the disorder.

Welfare of the future person

There are some important distinguishing features of heritable genome editing interventions that bear upon considerations of the welfare of the future person. The situation in which genome editing is one of a number of reproductive options is significantly different from the situation where a person already exists and any intervention might be more clearly seen as 'treating' that person. Whatever decision is made among these options is a condition of the future person's existence rather than simply affecting the condition in which they exist. This makes the question of their welfare relative not only to their own interests (*as in the case of simple treatment*), but to the interests of their prospective parents (*in having a child in the first place*). There are several difficulties encountered when thinking about the welfare of future people, however.

Welfare is more than 'good health'. Welfare incorporates not just physical health, but social and psychological wellbeing.

Context and perspective. How particular states of embodiment (which might include disability or impairment) are experienced depends, to some extent, on a person's particular circumstances, including their physical and social environment, and the availability of healthcare and assistance.

Uncertainty of expression. Although the effects of many clinically recognised genetic conditions can be predicted with some confidence, many conditions are much more complex and their expression is much harder to predict, varying greatly from person to person. Many variations must be understood in the context of the genome as a whole, as well as external, environmental factors.

The safety of the techniques used. Uncertainty about the risks of unintended consequences of the genome editing technique itself is a concern for many people. Furthermore, once the change is made in that first future person, it may be present in the genomes of their descendants, unless any steps are taken to reverse it.

Possible alternatives. Because no technique is without risk, in assessing welfare it is important to consider the relative safety of genome editing alongside alternative approaches. In the case of heritable genome editing interventions these include a range of reproductive options that might be available.

We conclude….

Reproductive cells that have been subject to heritable genome editing interventions should only be used for purposes that are consistent with the welfare of the future person.

- We recommend that research should be carried out on the safety and feasibility of heritable genome editing interventions to establish standards for clinical use.

- We recommend that social research should be carried out to develop our understanding of the welfare implications for the future person.

Others in society

The reproductive choices that individuals make have impacts most obviously for themselves and their future children. However, the ways that individual interests are pursued can have effects for others in society.

The prospect of genome editing becoming a widespread technology in human reproduction remains speculative at this stage, but if it should happen, there are potentially significant impacts for society. These include:

- **Population diversity.** Heritable genome editing could contribute to the reduction or even elimination of some serious inherited diseases from a population; on the other hand, variants associated with disease might also be associated with other, beneficial characteristics, which would also be lost.

- **Perceptions of 'normal' reproductive choices.** If genome editing were to become more normal this could bring into question the choices of people who 'refuse' to use it. A shift in behaviours and expectations may affect evaluation of the responsibilities of prospective parents towards their future children. It could put pressure on prospective parents to have children using reproductive technologies to secure conventional outcomes.

- **Attitudes towards disabled people.** The existence of reproductive technologies and prenatal diagnosis techniques that provide information about genetic disorders to inform the selection of embryos or termination of pregnancies is thought by some people to reinforce negative messages about disability, and to propagate the view that a disabled person's life is not worth living. This could lead to stigmatisation and discrimination. A practical consequence of there being fewer people with certain disabilities could be that there is less professional and public familiarity and social acceptance of these conditions, and less investment in research, treatment and support services.

- **Equity and justice.** If access to genome editing is unequally distributed, for example, because of the financial cost, the potential benefits will not be shared equally amongst those in society. This may exacerbate and reinforce existing social division and inequality.

We conclude….

The use of heritable genome editing interventions would only be ethically acceptable if carried out in accordance with principles of social justice and solidarity.

- We recommend that heritable genome editing interventions should be permitted only after their impact on others who might be adversely affected has been assessed, including through consultation with such people; and measures to mitigate these effects have been put in place.

- We recommend that arrangements should be put in place to monitor the effects of heritable genome editing interventions on those who might be adversely affected; and there should be measure to require periodic review of authorisation of the procedures and to trigger a moratorium if necessary.

Future generations and humanity in general

Consideration of the potential consequences of heritable genome editing interventions for future generations of the human species leads to the question of whether genome editing involves a threat to our common humanity.

It could be argued that if the aim is to replace a genetic variant with another variant that is found elsewhere in the human population, this may not be as troubling from an ethical perspective as introducing a novel variant that is not currently found in the human population, as the latter might be perceived as a 'non-human' genome. However, linking human identity to the possession of a particular kind of genome is both difficult and unnecessary.

- It is unlikely that we will ever know all the genetic variants that exist everywhere in human population.
- It would bring into question the status of genetic variation that occurs (and has occurred) as a result of undirected evolutionary processes.

We take the view that there is much more to being human than the possession of a particular kind of genome and that the entitlement to human rights does not depend on the possession of a human genome (even if such a thing could be described) or on the presence of a particular set of variants.

We conclude….

If heritable genome editing were to become feasible, those whose genomes have been edited should be entitled to the same enjoyment of human rights as everyone else.

We therefore recommend that governments in the UK and elsewhere should develop an international Declaration affirming that people born as a result of genome editing interventions, and their descendants, shall be entitled to the same enjoyment of human rights as everyone else.

Ethical principles

Taking all of these findings together, we conclude that the potential use of genome editing to influence the characteristics of future generations could be ethically acceptable in some circumstances, but only if certain conditions are met.

We propose two ethical principles to guide the development and application heritable genome editing interventions.

The use of heritable genome editing interventions should be intended to secure, and be consistent with, the welfare of a person who may be born as a consequence of interventions using genome edited cells.

The use of heritable genome editing interventions should be consistent with social justice and solidarity so that it should not be expected to increase disadvantage, discrimination, or division in society.

Recommendations for governance and further actions

This section sets out our proposals for legal, regulatory, policy, and other measures that could help to ensure that genome editing in human reproduction is researched, tested, and used in accordance with the principles of welfare and social justice set out above.

Public debate

Genome editing has received considerable interest from the scientific media and, to a lesser extent, from the mainstream and news media. There have also been a number of initiatives in recent years to promote public engagement and dialogue on genome editing, either with members of the general public, or with more specific stakeholder groups such as patient organisations. These initiatives have helped to inform debate, and to develop an understanding of public attitudes and reasoning.

It is desirable that work is carried out now to promote and support broad and inclusive societal debate, so that the public interest in heritable genome editing interventions can take shape to inform the development of governance.

Recommendations on supporting public debate

We recommend that broad and inclusive societal debate on heritable genome editing should be encouraged and supported without delay.

In the UK

- An independent body or commission should be established to promote and coordinate societal debate on genome editing and related areas of scientific and technological development. It should monitor the impact of technological innovation on society and contribute to developing national and international norms for governance.

Internationally

- Support should be provided for continued international monitoring and dialogue on genome editing, through:
  - a global observatory or international association; and
  - the work of international human rights institutions, such as UNESCO and the Council of Europe.

UK law and regulation

In the UK, the law does not currently allow the use of genome editing techniques in human embryos or gametes (sperm or egg cells) for use in reproduction. This is prohibited under the Human Fertilisation and Embryology Act 1990, which defines the legal requirements for the use of gametes and embryos outside of the body, for research and in clinics. The use of embryos and gametes in research and in clinics is licensed and regulated in the UK by the Human Fertilisation and Embryology Authority (HFEA).

Amending the law

There could be a long and complex legislative pathway to follow before any changes could be introduced that would permit heritable genome editing interventions. In the meantime, the law may need to be further amended to address specific potential applications that might not fall within the scope of the current regulatory regime.

Recommendations for UK law and regulation

Guided by our ethical principles of individual welfare and social justice, we make the following recommendations regarding UK law and regulation.

For future consideration of amending the law to permit heritable genome editing interventions:

We recommend that before any move is made to amend UK legislation to permit heritable genome editing:

- there should be sufficient opportunity for broad and inclusive societal debate;
- the likely impacts on people who may be vulnerable to potentially adverse social effects – such as stigmatisation and discrimination – should have been assessed, and any necessary mitigating policies have been developed in consultation with such people; and
- monitoring and review mechanisms should have been put in place.

In the future, if genome editing were ever to be permitted by law:

We recommend that genome editing should only ever take place under strict regulation and oversight by the HFEA, and that:

- the risks of adverse clinical outcomes for the individuals involved have been thoroughly assessed;
- it should be introduced only in the context of clinical studies, including long-term monitoring of the effects on individuals; and
- it should be licensed on a case-by-case basis.

International law and regulation

There is no specific international treaty that explicitly governs genome editing in humans. However, there are relevant treaties in international law, particularly human rights law:

Universal Declaration on the Human Genome and Human Rights (1997)

This UNESCO Declaration suggests that 'germ line' interventions *could* be contrary to human dignity. In 2015, UNESCO called on states and governments (among other things):

- To agree a moratorium on germ line editing at least as long as the safety and efficacy of the procedures are not adequately proven as treatments; and
- To renounce the possibility of acting alone in relation to engineering the human genome and to cooperate on establishing a shared, global standard for this purpose.

Oviedo Convention (1997)

The 'Oviedo Convention' is the Council of Europe's Convention on Human Rights and Biomedicine. It is signed and ratified by 29 of the 47 Member States of the Council of Europe (although not the UK). Under Article 13 of the Convention:

- Any genome modification (in research or in treatment) may only be undertaken for preventive, diagnostic or therapeutic purposes.
- The aim of any genome modification must not be to introduce changes that can be passed on to future generations.

The EU Charter of Fundamental Rights (CFREU) (2000)

The UK did not sign the Oviedo Convention, but as a member of the European Union (at least at present), it is bound by the CFREU, which has provisions closely based on the Oviedo Convention. The Charter does not contain an outright prohibition of genome editing, but on the right to integrity of the person, it prohibits "eugenic practices, in particular those aiming at the selection of persons".

Other rights and freedoms in international law

As well as the treaties described, a number of other rights and provisions of international law are relevant to the prospect of heritable genome editing interventions. These include:

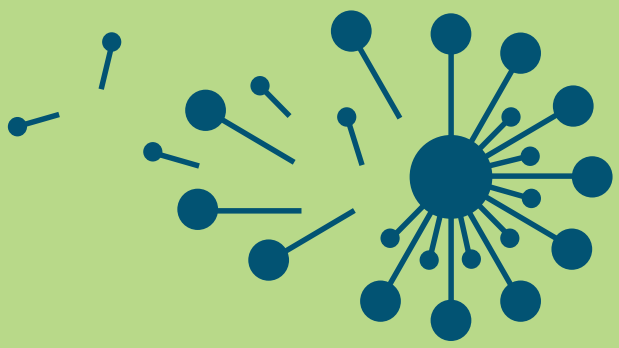
- the right to life;
- the right to physical integrity;
- the right to health;
- the right to non-discrimination;
- the right to the benefits of the scientific progress; and
- respect for human dignity.

An important recent development in international law is the emergence of a principle of 'intergenerational equity', which calls on states to take into account the rights of future generations when undertaking activities that may affect them.

Recommendations for international law and regulation

We recommend that governments in the UK and elsewhere should:

- work with international institutions such as the Council of Europe, and UNESCO to promote international dialogue and governance with regard to genome editing research and innovation;
- give consideration to the use of intellectual property rights to promote the public interest in having safe, effective and ethical heritable genome editing interventions; and
- give consideration to how to how the risks of discrimination on grounds of genetic variation may be best addressed.



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