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Human Germline Genome Editing

Changes made to the DNA in human eggs, sperm or embryos (germline cells) can be passed on to future generations.[1,2] The methods used to make such changes are referred to as human germline genome editing (hGGE).[2] This POSTnote reviews techniques available for hGGE, their safety and potential applications. It also outlines current regulation and governance of hGGE and examines issues raised by any potential future uses of hGGE.

Overview

- Human Germline Genome Editing (hGGE) involves making edits to the DNA in egg, sperm or embryo cells.
- hGGE has the potential to prevent serious heritable disorders, but there are safety and ethical concerns over its possible use.
- There has been a reported use of hGGE, resulting in the births of twin girls, in China.
- In the UK, genome editing of human germline cells in research is regulated by the Human Fertilisation and Embryology Authority. They have issued a licence for a project involving such research.
- UK law prohibits the use of hGGE as part of IVF treatment in women.
- As science advances, gaps in regulation may be exposed.

Background

Genome editing is a technique that can be used to make changes to a cell's DNA (the term 'genome' simply refers to all of the DNA in a cell).[1–3] DNA sequences contain four different components called bases (represented by the letters A, C, G and T).[4] Genome editing can be used to delete existing, add new, or replace DNA sequences.[1] Making changes to a cell's DNA has the potential to affect how that cell functions. For example, genome editing could be used to correct mutations in genes that cause one of the 10,000 disorders that result from mutations in a single gene (monogenic disorders) and to prevent such disorders from being inherited.[5,6] However, this is controversial because its safety has not been established and changes made could be passed on to future generations.[7–11]

Treatment and research in the UK involving human egg, sperm or embryos stored outside of the body is regulated by the Human Fertilisation and Embryology Authority (HFEA) under the Human Fertilisation and Embryology Act (HFE Act) 1990, as amended.[12,13] The HFE Act prohibits any embryo that has had its germline DNA altered in any way (such as through hGGE), from being placed inside a woman.[13] However, the Act allows the HFEA to grant research licences involving human embryos outside the body for specified purposes.[13] In 2016 the HFEA awarded a research licence for a project involving genome editing on human embryos.[14,15]

In contrast, regulation in some countries is less clear.[16] In November 2018, a Chinese scientist claimed to have performed genome editing in embryos which resulted in the birth of twin girls.[17,18] Doubts have been expressed as to whether the intended genome edits were successfully achieved.[19–21] Safety, efficacy and ethical concerns over this research have been voiced and the scientists who were involved in this research have been imprisoned.[19,20,22,23] This POSTnote outlines:

- techniques available for hGGE and their safety
- potential applications of, and alternatives to, hGGE
- current regulation and governance of hGGE
- concerns raised by the potential future uses of hGGE

Genome Editing

There are several different genome editing techniques.[1,3] One class of these, known as CRISPR-Cas9, is faster, cheaper, and easier to use than earlier approaches and has become the most widely used genome editing tool.[1,7,24] It consists of a three-stage process. First, a specific sequence of DNA is targeted by a guide molecule.[1,3] Second, both strands of the DNA sequence are cut by an enzyme called Cas9 so that changes can be made to it.[3] Third, once the cut is made to the DNA, the cell's own repair mechanisms repair the cut in the DNA.[3,25–27]

More recent CRISPR-Cas9 techniques known as base-editing and prime editing, allow DNA sequences to be edited without

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cutting both strands of the DNA.[27,28] These may be used to correct faults in a single DNA base pair to prevent disorders such as sickle cell disease. These techniques could enable edits to be made with less scope for error, particularly during repair, but further research is needed.[27–29]

Safety of Current Techniques

The success of all CRISPR-Cas9 based edits depend on the intended DNA sequence being located, edited and repaired with precision, without unintended side-effects.[19,22] The main safety concerns of current genome editing techniques involve:

- edits being made at an unintended DNA site
- edits made at the intended DNA site having unintended effects
- the cell's repair mechanisms repairing the cut DNA in an unanticipated way
- the edited DNA sequence not being present in all cells.

While the efficacy of current genome editing techniques has improved in recent years, further improvements are needed before they could be considered safe for clinical use.[19]

Potential Applications

There are two main types of application for human genome editing. The first of these is somatic genome editing, which involves editing DNA in cells that are not eggs, sperm or embryos and therefore are not heritable.[6] This type of application is being used in clinical trials in the UK, for example, for treating some types of leukaemia.[30]

hGGE is the other main potential application of human genome editing. This would be controversial because, in addition to safety concerns, it raises ethical considerations about changing the DNA inherited by future generations (see ethical justifications). While UK law prohibits hGGE, in principle it could be used to prevent the inheritance of serious monogenic disorders, such as cystic fibrosis and Huntington's disease.[10,31,32] Many of these disorders have life-long implications for the individuals affected, their families and carers, and for the NHS.[33] However, for many of the families affected by such disorders, there are existing approaches that would allow them to have children that are unaffected by their disorder. These are discussed in the next section.

Approaches to Preventing Heritable Disorders

There are several ways of preventing a heritable genetic disorder from being passed from one generation to the next that are already available in the UK.[34,35] For example, people who carry a heritable genetic disorder who desire to have a child without that disorder may choose to adopt. However, this is a complex process with criteria that may exclude this as an option for some people.[36,37] It also means that neither parent will be genetically related to the child.

If the parents want to be genetically related to the child or adoption is unavailable to them, unassisted conception can be followed by diagnostic tests. If the fetus is found to carry the mutation, the woman has the option to terminate the pregnancy.[38] An alternative route is to choose to have IVF and use Preimplantation Genetic Testing for a Monogenic Disorder (PGT-M) to select embryos that are unaffected by the condition.[34,39]

PGT-M should allow most couples affected by a monogenic disorder to become the genetic parents of an unaffected child. However, there are an extremely small number of rare cases where this may not be possible.[11,31,40] For example:

- where both parents carry two copies of a gene that causes a recessive disorder such as cystic fibrosis
- where one parent carries two copies of a gene that causes a dominant disorder such as Huntington's disease.

In these very rare cases, the parents could choose to use donated gametes so that the child would be genetically related to one of the parents.[40,41] There is currently no permissible option that would allow both parents to be genetically related to an unaffected child.[31] However, clinical use would require a change in UK legislation following considerable consultation.

Legislation and Regulation

UK biomedical research is subject to several international obligations in addition to national legislation.[11,16] These are outlined in the following sections.

International Initiatives

International obligations relevant to research involving hGGE are outlined in Box 1. They include Declarations on Bioethics and Human Rights, on the Human Genome and Human Rights and on Economic, Social and Cultural Rights. Many countries have no specific prohibitions on using hGGE clinically.[16] However, several countries (excluding the UK) have agreed to a convention that includes a prohibition on making changes to the human genome if its aim could affect future generations, (for example, using hGGE).[42,43]

Some scientists have called for a global moratorium on clinical hGGE until an agreed framework has been established.[44] Several international initiatives are aiming to develop such a framework. Some of these initiatives have built on the idea of the 'global observatory' (GO).[45] The GO advocated for an international repository dedicated to consolidating, reporting, tracking, and disseminating details of any research involving the genome editing of human cells. The aim of this approach was to advance understanding, inform further research and to encourage more transparency towards such research.[19]

The essence of the GO approach has been developed by the World Health Organization (WHO) to form its global registry for human genome editing which launched in August 2019.[46] The registry aims to track all clinical trials and research on embryos involving the human genome. This initiative is led by the WHO's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. The committee aims to advise and make recommendations on appropriate governance mechanisms for hGGE in 2020.[47]

Another initiative is the International Commission on the Clinical Use of Human Germline Genome Editing which was convened by the UK's Royal Society, the US National Academy of Science and the US National Academy of Medicine in 2019.[48] It aims to develop principles, criteria and standards for the clinical use of

genome editing of the human germline, should it ever be considered acceptable. The commission's report is anticipated during spring 2020.

Box 1: International Obligations relevant to hGGE
The international obligations outlined below bind the UK to customs relating to the safety and risks of research, and to welfare, health and disease. These will not be affected by the UK leaving the EU.

- **The Universal Declaration on Bioethics and Human Rights.**[49] Article 3(2) states that the interests and welfare of the individual should have priority over science or society. Article 4 requires that the benefits to patients and research participants should be maximised and any possible harm to such individuals should be minimised. Article 16 states that the impact of life sciences on future generations, including on their genetic constitution, should be given due regard. Article 20 requires that all risks related to medicine, the life sciences and associated technologies should be assessed and managed.
- **The Universal Declaration on the Human Genome and Human Rights.**[50] Article 5(a) states that research, treatment or diagnosis affecting an individual's genome shall be undertaken only after prior assessment of the potential risks and benefits involved, and in accordance with any national law. Article 10 states that no research concerning the human genome should prevail over respect for the human rights, freedoms and dignity of individuals or groups of people. Article 12(b) states that the applications of research concerning the human genome shall seek to offer relief from suffering and improve the health of individuals and humankind.
- **The International Covenant on Economic, Social and Cultural Rights.**[51] Article 12 sets out the right to enjoy the highest attainable standard of physical and mental health by reducing rates of stillbirth and infant mortality, ensuring the healthy development of children and preventing, controlling and treating diseases.

Regulation of hGGE in the UK

The HFE Act 1990 established the HFEA as the UK's independent regulator of fertility clinics and of treatment and research involving human egg and sperm cells, and human embryos outside of the body.[52] The HFE Act, as amended, prohibits all activities involving human embryos outside the body unless they are licensed.[13] Activities for which licences may be granted are detailed in Schedule 2 to the Act and include treatment and research. Under this Schedule, a treatment licence cannot authorise altering the DNA of a cell while it forms part of an embryo. There is one exception to this statement; under the Mitochondrial Donation Regulations 2015, there are prescribed treatments to replace mitochondrial DNA to prevent serious mitochondrial disease.[53,54]

Research licences may be issued to authorise the creation, keeping or use of embryos in a project specified in the licence. Licences may only be granted for research involving one or more of the eight principal purposes specified in Schedule 2 to the Act, and only if the proposed research in relation to these is deemed to be necessary or desirable by the HFEA.[13] Overall, the legislation means that:

- Genome editing of human sperm, egg or embryo cells as part of a fertility treatment for a woman is prohibited.
- The HFEA can license research involving genome editing of human sperm, egg or embryo cells.
- As research in this area advances, there may be several potential novel treatments that are not covered by the Act.

Scope of UK Legislation

Research in the area of assisted reproduction moves rapidly, and the legislative framework needs to be updated to keep pace with developments.[32] Moves to introduce clinical use of hGGE in the UK would require Parliament to approve changes to legislation, including the HFE Act.[55] Advances in research are already leading to innovations that are not covered by the Act. For example, two such areas include treatments involving transwomen and editing germline cells inside the body.

The first of these arises because Section 3 of the HFE Act prohibits edited embryos from being placed inside a woman who has been female from birth (a ciswoman).[13] Advances in surgery mean that womb transplants are now possible.[56] To date, 13 live births have been recorded around the world following such surgery.[57] This means that currently the Act would not prohibit the placing of a genome edited embryo into a transwoman who had received a womb transplant, as long as the edited embryo is less than 14 days old.[13] Researchers wishing to place a genome edited embryo into a transwoman would need to obtain a research licence from the HFEA to edit the genome of the embryo.

The second area arises because the Act only covers edits made to germline cells outside of the human body. Any edits made to germline cells inside the human body (in vivo) would not be prohibited by the HFE Act but may be covered by other regulations, such as those on clinical trials, gene therapy and human tissues.[58–60] In vivo edits have been demonstrated in mice but have yet to be attempted in humans.[61–63] In both of these cases, bringing the research into the regulatory scope of the Act would require the primary legislation to be amended.

Considerations on the Use of hGGE

In 2017, a report published by the National Academies of Science, Engineering and Medicine (NASEM) on Human Genome Editing, suggested principles for its governance and clinical use.[64,65] The report is the product of a year-long, in-depth consensus study, and the principles it advocates have been endorsed globally.[66] The principles include ethical justification, compelling medical rationale, a robust evidence base to support its clinical use, and engagement with the public. The following sections look at these considerations in more detail.

Ethical Justifications

Ethicists have considered the potential ethical issues raised by hGGE.[11,31,67,68] Many of these issues have also been considered in debates on other reproductive technologies, such as PGT-M and mitochondrial donation. These issues largely fall into three categories:[11]

- Individuals and families directly involved with hGGE
- Wider, indirect impacts on society
- Impacts on future generations

Individuals and Families involved with hGGE

Some ethicists suggest that hGGE raises potential issues of consent and long-term monitoring for those people born as a result of using the technology.[2,69–71] These arise because such individuals could not have consented to the intervention and may not be inclined to follow through on decisions made on their behalf (long-term monitoring for the benefit of their welfare).[31,69] However, such considerations also apply to other reproductive technologies.[34,35,68,72,73]

As far as the families of children born as result of hGGE are concerned, the technology could enable individuals and families with genetic disorders to become the genetic parents of children that are unaffected by their disorders.[10,33] Its use, like PGT-M, could also potentially end the cycle of challenges faced by families living with a disorder.[33,74]

Wider Impacts on Society

Two main wider implications for society have been identified by ethicists: the potential impacts on people with genetic disorders, and equity of access to hGGE.[8,11,33,75] Concerns about the first focus on whether increasing the rarity of a disorder might reduce the support available for individuals and families affected by them.[8,68,76] There are also concerns that it might increase the stigmatisation and marginalisation of people living with genetic disorders, and of families who choose not to use such technologies.[6,8,68,76,77] Other related concerns are that developing and offering techniques such as hGGE could be considered to devalue people living with genetic disorders while increasing the pressure (from family and/or medical professionals) to access and use it.[8,68,77,78]

In the absence of equitable access to the technology, the main concern is that the potential use of hGGE might be confined to those who have the financial and cultural capital to access it.[8,33,75] However, achieving equitable access is likely to be very difficult in practice.[8,31,79,80]

Impacts on Future Generations

If clinical use of hGGE were permitted but were confined to medical applications, it might change the composition of the human gene pool by reducing the prevalence of genes associated with serious inherited diseases.[2,8,31] If variants of such genes were associated with beneficial characteristics (such as, malaria immunity amongst sickle cell carriers) then these could also be lost. If the use of hGGE were permitted for non-medical uses, the possibility of introducing novel genes into the human gene pool then arises.[2,8,81,82]

Ethical Objectives

Overall, ethicists have suggested the development and application of hGGE should be guided by two ethical objectives. The first of these is that hGGE should be for the greater benefit of the individuals born as a result of its use (by outweighing potential risks) provided that their rights and well-being are protected.[6,8,11,33] The second is that its development and use should not increase disadvantage, discrimination or division of people living with genetic disorders.[6,33,68,75,80]

Medical Rationale

There is widespread agreement that compelling medical reasons are needed before considering permitting the clinical use of hGGE.[2,65,80] Considerations may include the severity of the condition being prevented, the risk of its occurrence, and the potential availability of other options for treatment. These options might include somatic genome editing and PGT-M.

If hGGE were to be authorised for clinical application in the UK, in the first instance its use would likely be extremely limited.[83] For example, it might be considered where it is the only option available to enable couples to have a genetically related child unaffected by their disorder, and/or where the potential benefits outweigh the potential risks. There are an extremely small number of cases that fall into these categories.[31]

However, ethicists have expressed concerns that new technologies tend to find a wider range of applications once they have been introduced.[84,85] For example, advances in genome sequencing and initiatives such as the 100,000 Genomes Project are increasing knowledge of the role of genetics in a wider range of complex disorders, such as cancers.[86,87] This could mean that applications may eventually expand to conditions caused by multiple genes. Additionally, over time, the uses for hGGE could also grow to include non-medical enhancements and/or aesthetics.[2,8,10,22]

Evidence Base on Clinical Use

Before introducing a new health technology, a full review of its potential clinical effectiveness (including safety), cost-effectiveness, and risks and benefits would be required. Such reviews might include health technology assessments.

The most recent safety assessment of a novel reproductive technology in the UK was the introduction of mitochondrial donation in 2015.[88] Although the technologies are different, both change the DNA inherited by future generations.[54] In the case of mitochondrial donation, safety was assessed by expert panels convened by the HFEA.[88]

Public Engagement

NASEM's report noted that there are three main approaches to public engagement:[89]

- Conducting primary research such as public surveys
- Via secondary analyses of published literature on the perceptions, acceptability, quality of life, attitudes, or values of stakeholders
- Commissioning an expert review

Several public dialogue exercises have already been reported in the UK and more are ongoing.[33,75,90,91] On the whole, findings suggest that the public are supportive of the use of genome editing for medical applications, such as preventing heritable disorders, if it is safe and is suitably regulated. In contrast, support for non-medical applications is far lower.[33,75,92,93] Research on the views of people affected by heritable genetic disorders towards hGGE is ongoing and more findings will be published as research progresses. However, there appears to be little variation on views towards hGGE between those who identify with religious beliefs and those who do not.[75,93]

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