NUFFIELD COUNCIL ON BIOETHICS – GENOME EDITING AND HUMAN REPRODUCTION: SOCIAL AND ETHICAL ISSUES: A SNAPSHOT OF THE ISSUES RAISED

TAMSIN CORNWELL
Senior Associate, Pinsent Masons LLP

In July 2018 the Nuffield Council on Bioethics concluded an enquiry prompted by developments in gene editing technology, including CRISPR-Cas9, and published its report 'Genome editing and human reproduction: social and ethical issues' ('the Report').[1] This article seeks to highlight certain issues raised by the enquiry and discussed in the Report that are of particular interest, on the basis that these issues are, or should be, of interest to society as a whole.

Introduction

The development of genome editing technologies, including ZFNs,[2] TALENs[3] and CRISPR[4]-Cas9, and the continued progress in this area has led to the potential, in the near future, for heritable genome editing interventions – that is, alterations to the DNA sequence of an embryo, or a sperm or egg cell prior to fertilisation, with such alterations having the potential to be passed to future generations.

The speed of development of science in this area has been significant. In 2015 a research team in China published a paper recording the first study to use gene editing techniques in human embryos.[5] This paper sparked varied responses from the scientific community. Two journals, *Nature* and *Science*, published commentaries calling for the research to be strongly discouraged or halted altogether.[6] Conversely, others in the scientific community have published commentary citing a moral imperative to continue such research.[7] The use of the term 'moral' provides an indication as to why individuals within the scientific community hold such opposing views on this topic.

The development of gene editing technologies such as CRISPR-Cas9 and their refinement (both in terms of safety and efficacy) increases their potential application. One application for this technology would be heritable genome editing interventions. Such interventions, if permitted at some point in the future, will affect not only (1) individuals (for example prospective parents seeking a genetically related child without the DNA associated with a genetic disease, and the future person to be produced from the intervention) but also (2) society and (3) future generations related to the future person and humanity in general. The Report considers how the introduction of heritable genome editing interventions could impact on the groups identified above and associated social and ethical issues.

Although it is possible that the potential of these techniques will never be realised (possibly because scientists will be

1) http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL-website.pdf.

2) Zinc finger nucleases.

3) Transcription activator-like effector nucleases.

4) Clustered regularly interspaced short palindromic repeats.

5) Liang *et al.*, 'CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes', *Protein Cell* 2015, 6(5):363–372.

6) Lanphier *et al.*, 'Don't edit the human germ line', *Nature* 2015, Vol 519 and Baltimore *et al.*, 'A prudent path forward for genomic engineering and germline gene modification', *Science* 2015, 348: 36–38.

7) Savulescu *et al.*, 'The moral imperative to continue gene editing research on human embryos', *Protein Cell* 2015, 6(7):476–479.

unable to produce techniques with acceptable levels of efficacy and safety), given the potential impact of such techniques it is prudent that social and ethical considerations keep pace with the development of this technology. Likewise, it is important that the debate surrounding the social and ethical considerations is wide ranging and is not limited to the scientific community and law-makers. The recent enquiry undertaken by the Nuffield Council on Bioethics and the Report arising from this are an important contribution to this debate.

The Science and its Potential Clinical Application

There are a number of techniques for genome editing, including ZFNs, TALENs and CRISPR-Cas9. The latter is a relatively new method which is popular due to its relative efficiency, low cost, ease of use and its potential to make edits at several sites in the genome in a single procedure.

The promise of CRISPR-Cas9 is significant, but it is important to put this in perspective. This technology is still in development and there is a chance that it will never reach the levels of safety and efficacy necessary to justify its use in the clinical setting. As the Report notes, the technology offers great promise and great uncertainty.

The technology could benefit couples carrying a genetic condition who wish to have a child genetically related to them but want to ensure that the child does not inherit the condition. Other options are currently available, namely unassisted conception, followed by pre-natal diagnosis to confirm the presence or absence of a genetic disease in the foetus, and IVF incorporating pre-implantation genetic diagnosis. However, there are circumstances where those current techniques are not an option, namely: (1) dominant genetic conditions where one of the prospective parents carries two copies of the disease-causing gene; and (2) recessive genetic conditions where both prospective parents carry two copies of the disease-causing gene. In these circumstances gene editing technologies such as CRISPR-Cas9 could offer hope.

While the application of genome editing to single gene disorders falling into the two categories above can be envisaged, the reality is that we do not have a full understanding of how the genome functions. The majority of genetic diseases appear to be caused by the interaction of multiple genes, and/or of genes together with a variety of environmental factors. For these more complex diseases it is difficult to see how genome editing would offer a predictable way to control them, at least with the current level of knowledge of these diseases.

Ethical and Social Issues

The prospect of heritable genome editing interventions raises a myriad of ethical and social issues, a few of which will be discussed further below. The Report splits these issues into three groups: (1) the people immediately involved (prospective parents and the future person); (2) others in society who may be indirectly affected and society as a whole; and (3) future generations, and the human species in general. The authors consider various arguments for and against heritable genome editing interventions based on the impact it could have on these groups.

The People Immediately Involved – Prospective Parents and the Future Person

One view noted in the Report is that no genome editing should be permissible on the basis that procreation is a natural process that should not be 'tinkered' with by humans. This somewhat simplistic view is, however, already challenged by currently available reproductive interventions, such as IVF. Of particular note is the suggestion, attributed in the Report to the philosopher Habermas, that the knowledge that a person's characteristics have been pre-natally determined by another could impact on the individual's understanding of themselves as an autonomous and equal member of a community of free and equal persons. However, as noted in the Report, if we take this too far we fall into the trap of genetic determinism and diminish the impact of parental constraints that may be applied.

The Report acknowledges the argument that some heritable genome editing is permissible, not least because technological advances are realities to be controlled. While the use of heritable genome interventions to enhance characteristics is

difficult for some to justify, the use of such technology to exclude inherited diseases that negatively impact, to a significant extent, quality and length of life, is arguably justified. Such interventions would promote human flourishing, which such diseases inhibit. However, the Report notes that the idea of human flourishing is based on the concept of normativity which can itself be difficult to justify. This concept is arguably based on misplaced assumptions regarding the quality of life of individuals with such inherited diseases. The authors of the Report highlight the scope for dispute regarding the value of the lived experience of some forms of disability and note that disablement may occur as a result of societal attitudes to an individual's impairment. In addition, given the variability and complexity of the human genome, it is arguably absurd to specify boundaries of 'normal' and 'desirable'.

Noted in the Report is the argument that some genome editing is required, on the basis that we should in fact do all we can to maximise the welfare of future people. It is, however, unclear where this obligation starts and ends. Should it be limited to ensuring the absence of some clinically treated diseases? Or should it be extended to ensuring the presence of valued characteristics? The authors of the Report rightly note that selecting for such characteristics can place on the offspring an additional burden of expectation, raising additional questions of morality.

The authors of the Report identify a principle which they believe is necessary (though not sufficient) for heritable genome editing interventions to be morally permissible. The principle is that 'gametes or embryos that have been subject to genome editing procedures should only be used where the procedure is carried out in a manner and for a purpose that is intended to secure the welfare of and is consistent with the welfare of a person who may be born as a consequence of treatment using those cells'.[8]

Society

Attempts to influence the inherited characteristics of future generations may impact on society in a number of ways. One impact suggested in the Report is that of shifting norms, with the example provided being pre-natal screening for chromosomal abnormalities, such as Down's syndrome. It is argued that, as a result of the availability of this screening technology, prospective parents may feel social pressure to undergo testing and to terminate a pregnancy, despite Down's syndrome now being compatible with a high quality of life. Such shifts in behaviour can lead to changes in moral conclusions. As the authors note: what people typically do becomes, implicitly, what they should do.

The Report acknowledges that simply making heritable genome editing techniques available is objectionable to some, arguably expressing hostile and discriminatory attitudes towards individuals with genetic diseases or disabilities, sending a harmful message to these individuals and to wider society. Arguably the use of such interventions to ensure the absence of genetic diseases or disabilities is a reflection of society ascribing a lesser status or value to disabled people. The authors note that this could cause psychological damage to the individual but also negatively influence social attitudes towards disabled people, reinforcing inaccurate prejudices about the experience of disabled people and propagating the view that disabled peoples' lives are worth less.

Also noted is the argument that there is value in human fragility that would be lost if disabilities were made to disappear; for example, the experience of fragility can give rise to valuable human traits of care, compassion and generosity. The question the Report notes is whether we value the good of fragility enough to be willing for our children to take their chance as its bearers.

The Report identifies a second principle such that heritable genome interventions should only be permitted 'in circumstances in which it cannot reasonably be expected to produce or exacerbate social division or the unmitigated marginalisation or disadvantage of groups within society'.[9]

Future Generations and Humanity in General

Heritable genetic interventions raise issues of responsibility not only to the next generation but also to future generations. As stated previously, the human genome is complex and the Report acknowledges the potential for adverse effects to incubate, only becoming evident after several generations, by which point they might have diffused to multiple descendants.

8) The Report, at 75.

9) The Report, at 87.

In light of the ways in which health services in different countries operate, if heritable genetic interventions were to become clinically available, it cannot be assumed that access will be distributed equally. The Report notes that this inequality could lead to advantageous genetic characteristics being concentrated in certain groups or geographical areas with other (disadvantageous) characteristics being concentrated in other groups, leading to the creation of the 'gene rich' and the 'gene poor'.

Governance

In the United Kingdom, the Human Fertilisation and Embryology Act 1990 prohibits the use of genome editing techniques in human embryos or gametes for use in reproduction. The use of embryos and gametes in research and in clinics is licensed and regulated in the United Kingdom by the Human Fertilisation and Embryology Authority (HFEA).

The Report notes that the legislation elsewhere in Europe is a mixture of formal legal prohibitions and administrative guidelines. Some countries prohibit any use of human embryos in research. Some only permit research that is supposedly 'for the benefit of the embryo' (for example, Italy). Others, such as Sweden, permit embryo research but prohibit heritable genetic modification of human embryos. The majority of states prohibit the creation of embryos specifically for research (the United Kingdom being a notable exception).

While there is no international treaty that explicitly governs genome editing in humans, the authors of the Report note that there are relevant treaties in international law. The UNESCO[10] Declaration suggests that germ line interventions could be contrary to human dignity. The Oviedo Convention[11] states that the aim of any genome modifications must not be to introduce changes that can be passed on to future generations.[12] The EU Charter of Fundamental Rights (CFREU) 2000 has provisions closely based on the Oviedo Convention. On the right to integrity of the person, the CFREU prohibits 'eugenic practices, in particular those aiming at selection of persons'.

Conclusion

The enquiry by the Nuffield Council on Bioethics and the Report arising from this are an important contribution to the debate surrounding gene editing technologies.

The overall conclusion in the Report is that there is no categorical reason to prohibit heritable genome editing interventions. In certain circumstances it is ethically acceptable, namely where: (1) it is intended to secure, and is consistent with, the welfare of the person who may be born as a consequence of interventions using genome edited cells; and (2) it is consistent with social justice and solidarity. The Report provides a number of recommendations including (but not limited to) the need for research into the safety and feasibility of heritable genome editing interventions as well as the social implications of such interventions, and the need for broad and inclusive societal debate.

The authors of the Report also highlight the need for broad and inclusive debate and dialogue both within the United Kingdom and internationally, prior to any amendment to UK or international law. It is suggested that the likely impact on those most vulnerable to potentially adverse social effects (for example, stigmatisation and discrimination) should be assessed and mitigating policies developed through consultation with such vulnerable people. The authors note that monitoring and review mechanisms should also be put in place.

Although outside the direct remit of the enquiry, others have noted the potential for patents covering gene editing technologies such as CRISPR to be used to (1) ethically restrict access to controversial technologies, for example to prevent the use of such technology without rigorous scientific and ethical controls, or (2) ethically promote access to such technologies, for example to require licensees to establish access plans and/or price controls.[13] Future debate would do well to include further consideration of the ways in which the patent system in the United Kingdom, Europe and elsewhere could provide answers to at least some of the ethical and social concerns raised by genome editing technology.

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

11) The Council of Europe's Convention on Human Rights and Biomedicine.

12) The United Kingdom has not signed and ratified the Oviedo Convention.

13) J.S. Sherkow, 'Patent protection for CRISPR: an ELSI review', *Journal of Law and the Biosciences* 4(3), 1 December 2017, 565–576.