NUFFIELD COUNCIL ON BIOETHICS

Response to the Public Call for Evidence for the International Commission on the Clinical Use of Human Germline Genome Editing

October 2019

Introduction

The Nuffield Council on Bioethics' response to this Call for Evidence draws on the conclusions and recommendations of our report '*Genome editing and human reproduction: ethical and social issues'*, published in July 2018. This report followed an in-depth inquiry with extensive consultation and engagement with a range of stakeholders. We have responded below to a selection of the questions from the call for evidence, to which our work is most relevant.

Qu 1. Which diseases and conditions, if any, do you see as appropriate for human germline genome editing?

This is not a straightforward question as any answer needs to take account of factors other than the nature of the condition, which are important in any assessment of 'appropriateness'. The answer will be different depending on:

- whether we are talking about first use of genome editing (innovation) or the use of an intervention of demonstrated safety and efficacy, and;
- the circumstances in which it is used (not limited to the clinical ontology of the case in question).

In our own inquiry we did not base our findings on distinguishing medical from non-medical (or 'enhancement') uses but on *what constitutes a good reason* for permitting the use of genome editing in an embryo, taking into account the sociotechnical circumstances. Our approach was based on an examination of the interests and responsibilities of those involved/affected by the use of genome editing.

Our inquiry found that the value placed on genetic relatedness and on reproductive interests and preferences was often assumed but seldom examined. In our inquiry we approached the potential uses of genome editing by asking ***'in what circumstances, in what ways, and to what extent, should people be permitted, enabled, or assisted to pursue their reproductive goals?'*** in order to bring these considerations into the frame.

There are few, rare circumstances in which 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 would 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 some complex diseases;
- 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).

Perhaps the most obvious cases for genome editing in future would concern couples with known inherited genetic disorders who wish to exclude the disorder in their genetically related child. Genome editing has the potential to be used for a wider range of purposes, however.

However, in assessing the proportionality of the intervention, the relevant standard is different from the standard for introducing a new medical treatment. Genome editing does not treat a condition in an existing person but rather brings about the existence of a new person, in order to satisfy the reproductive preferences of prospective parents. For example, their preference may be to have a child who is genetically related to them both, but who will not inherit a characteristic that any child they might have without the procedure might inherit (or, alternatively, who will inherit a characteristic that any child they might have without the procedure might not inherit).

Qu 2. If there were to be an appropriate use case for human germline genome editing, what evidence would be needed to proceed to first in human use?

In our report we point to further research that would be necessary before any move is made to implement genome editing in human reproduction, but it is important to emphasise that securing such evidence is far from sufficient grounds on which to proceed in this direction.

The research we recommend should be undertaken is:

- research to establish the clinical safety and feasibility of genome editing should be supported in the public interest in order to inform the development of evidence-based standards for clinical use; and
- social research that would help to understand the welfare implications for people born following heritable genome editing interventions (for example,

involving people born following preimplantation genetic testing) should also be supported in the public interest.

This evidence should be assessed by a competent authority (such as, in the UK, the Human Fertilisation and Embryology Authority) drawing on such additional expertise as is required.

There is a further question about the order in which the social processes for determining the content of the public interest and technical research should proceed. We believe that it is important that broad and inclusive societal debate should precede the definition of a 'roadmap' for any particular innovation trajectory. This broad and inclusive societal debate is necessary to inform the development of public policy to guide potential innovation in the public interest. We have not said that unchallenged public support should be a necessary condition to proceed (although it would be challenging to proceed in the face of public hostility, given the public interest). Furthermore, we recognise that no procedure for engaging the public is uncontroversial. Nevertheless, a procedure that can reflect on and inform public values should be an indispensable condition (as it was in the years following the invention of *in vitro* fertilisation in the UK, where legislative reform would be necessary to permit genome editing in human reproduction in any case).

Should the outcome of such a process favour proceeding in principle, we recommend that the governance measures identified in our report should be put in place. These include ensuring that account is taken of the potential for unintended societal impacts, including consultation with those potentially in positions of vulnerability. We believe that measures of this nature are required in order to respect the guiding principles identified in our report. These were that:

> *Gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be used only 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.*
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> **and**
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> *The use of gametes or embryos that have been subject to genome editing procedures (or that are derived from cells that have been subject to such procedures) should be permitted only 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.*

In any consideration of the potential future application of genome editing in the context of human reproduction, we are firmly of the view that these wider considerations, and the encouragement of wider debate are a vital part of any definition of a pathway towards implementation.

Qu 3. What is the status of editing mechanisms for early stage human embryos (e.g., using different editing techniques, improving homology directed repair, etc.)? What are the factors that predict whether single nucleotide changes or other intended modifications in human embryos will be correct? To what extent will genome editing affect the viability of embryos?

We believe these technical questions should be assessed by a nationally competent body, e.g. in the UK, this would be the Human Fertilisation and Embryology Authority (HFEA). However, as there is a strong public interest in these questions and related developments, as we have stated above and elsewhere, a broad and inclusive societal debate should be a priority.

Qu 8. What is the success rate of full-term pregnancies following pre-implantation genetic diagnosis? What affects this (e.g., age, number of oocytes harvested, technique used, etc.)?

In the UK, the HFEA has collected comprehensive data on licensed assisted conception treatments since 1991, which is available via the Authority's website. 'Highlights' from this dataset are published periodically as 'Fertility trends and figures', e.g. the 2017 data set. Other bodies who would have relevant knowledge for these questions include the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE).

Qu 9. What are the appropriate mechanisms for obtaining informed consent, long-term monitoring of the future children, assessing potential effects in subsequent generations, and addressing untoward effects? Are there best practices from: a) assisted reproductive technologies; b) pre-implantation genetic diagnosis; c) gene transfer research for children; d) mitochondrial replacement therapy; and e) somatic genome editing?

Asked in this way, the question seems premature as it pre-empts the matters that we have raised above in relation to question 2. Nevertheless, we considered these matters in outline in our report and recommended that heritable genome editing interventions be introduced only within the context of well-designed and supervised studies, reporting regularly to a national coordinating authority, and that the effect on individuals and society, including over generations, should be closely monitored as far as possible, compatibly with the privacy of the individuals concerned. The closest existing model is that developed by the UK's HFEA for mitochondrial donation treatments.

However, we recognise that follow up cannot be mandated and that there is evidence of attrition in other areas where long-term follow up has been desired. The requirements of long term follow up need to be consistent with people's privacy. The HFEA would be best placed to comment/advise on these questions.

Qu 10. How should we think about the inter-generational medical (e.g., genetic changes to the genome) and ethical implications of human germline genome editing (e.g., potential harms and benefits)? How should the rights of future generations and the wider human population be taken into account?

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. We discuss this in depth in the third section of Chapter 3 of our report. It could be argued that, if the aim were to replace a genetic variant with another variant that is found elsewhere in the human population, this would not be as troubling from an ethical perspective as introducing a novel variant that is not currently found in the human population. However, 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.

In Chapter 4 of our report we conclude that 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.

We would like to emphasise that these questions cannot be answered by the science community alone and must be addressed through social processes. It is important for society to have the opportunity to shape the way in which the science develops. We strongly recommend that societal debate happens before innovative techniques have been developed, when processes can still be shaped, rather than waiting until technology is ready and it becomes a reductive yes/no permission question.

Qu 11. What international oversight structures would need to be in place to facilitate, in a responsible way, a path forward for germline genome editing?

In Chapter 4 of our report (starting at paragraph 4.13) we provide an analysis of legal and governance structures, including international instruments.

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

> ***Universal Declaration on the Human Genome and Human Rights (1997)***
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> *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".

As well as these treaties, several 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.

In our report 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 about 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.

These matters are addressed in a recent article written by our Assistant Director Dr Pete Mills "Three venues for discussing human genome editing" which emphasises that human rights institutions, international science and civil society all have a role to play and it is important that they all get to play their role.

Qu 12. Are there any topics or issues that are not covered by the above questions that you think the Commission should attend to during its deliberations?

We would merely take this opportunity to stress that society must have the opportunity to shape the way in which the science develops. Roadmaps can create technological momentum - in another Nuffield Council report, '*Emerging biotechnologies: technology, choice and the public good'* we caution against roadmapping exercises, e.g. at paragraph 6.29: "*In the context of emerging biotechnologies, roadmapping exercises can be potentially problematic, because there is a danger that they could prematurely push research in one direction, towards a single destination, rather than fostering a symmetrical appreciation of a diversity of possible pathways that might be explored, through the creation of what we described above as an anticipatory paradigm*."

In this context the role of publics and international institutions in shaping technological innovation is vital. Whilst the Commission's role in contributing a scientific voice and perspectives to this wider debate is valuable, it is important that others also have an opportunity to shape and contribute to this debate and that the public have their say at an early stage, given that genome editing is a matter of broad public interest.