NUFFIELD COUNCIL ON BIOETHICS

Genome Editing and Human Reproduction

OPEN CALL FOR EVIDENCE

Published 17 May 2017

Closing 30 June 2017

The Nuffield Council on Bioethics is inviting written submissions of evidence to inform its examination of ethical issues arising in relation to genome editing, an emerging family of biological techniques for making precise genetic alterations to living cells, which are described briefly in part 3 of this document.

This call for evidence is divided into four parts:

1. **Questions** on which we are seeking evidence and reasoned opinion

2. **Responding** (How should you respond? How will we use the evidence you submit?)

3. **Background** (What do we mean by 'genome editing'? Why are we seeking evidence? What sort of evidence are we seeking?)

4. **Further information** about the project (terms of reference and membership of the working party on genome editing and human reproduction)

This call for evidence is open for response alongside a public survey that seeks views of members of the public on three genome editing scenarios that could plausibly arise in the future, in order to explore moral responses to these possibilities. The present call for evidence aims to gather more in-depth information from organisations and individuals with an existing interest or knowledge about genome editing and updates our earlier 2015-16 call for evidence. The questions below are similar to those in our 2015-2016 call for evidence but now focussed on human reproductive and related applications.

If you responded to the earlier call for evidence you may prefer simply to update or supplement your previous response to include more up-to-date or detailed information. Alternatively you may simply wish to let us know that your previous submission still stands – to do so please contact genedit@nuffieldbioethics.org

1. Questions

Perspectives on genome modification

We are interested in the significance attached to genome modification – as exemplified by contemporary genome editing techniques such as CRISPR/Cas9 – and the way that this is understood in comparison with other forms of scientific research and practice. In relation to genome editing specifically, we want to explore whether it is helpful to think about genome editing as a single, 'general purpose' technology, or whether it is more helpful to examine it in relation to the many (albeit overlapping) fields in which it may be used. We are interested in the extent to which genome editing is seen as simply a more powerful tool, helping to achieve aims that are already pursued by other means, or as a transformative technology, capable of fundamentally reconfiguring our ambitions and expectations.

We are interested in how different concepts, analogies, examples, and imagined future states of affairs influence our response to genome-altering technologies and how different costs and benefits are conceived. We want to explore in what way the anticipated distribution of costs and benefits among populations and across time should be matters of concern, and whether existing regulatory institutions and standards are adequate to respond to these concerns.

We are also interested in broader questions of how 'progress' is conceptualised and evaluated in relation to 'high' and 'low' technology, and how use of genome editing is conditioned by, and affects the relationship between, science and society. Finally, we are interested in how all these understandings and perspectives influence research and innovation pathways, such as the development of new medicines, plants and biotechnology products.

Indicative questions

The distinctive significance of genome interventions

- Is there anything special about the genome that makes intervening in it different from other ways of influencing the traits of offspring through reproduction (e.g. selective approaches to reproduction, such as preconception screening of partners or preimplantation testing)?

- To what extent can the development of genome editing techniques be regarded as distinct from or continuous with existing techniques? In what way are the differences significant?

Science and society

- What obligations do scientists involved in developing and using genome editing technologies owe to society and what freedoms should society allow to these scientists? Do genome scientists have any special obligations to society that are distinct from those of other scientists?

- To what extent is the development of genome editing valuable as a pure research tool (e.g. to understand human developmental biology), and to what extent is its value dependent on envisaged direct reproductive applications?

- What obligations do governments have towards society to ensure 'safe' and 'ethical' science or otherwise to shape the scientific research and development?

Science, morality and law

- What conventional moral principles, if any, does genome editing challenge?

- To what extent can the moral questions raised by genome editing be addressed using existing moral frameworks or approaches?

- To what extent are laws and legal frameworks necessary or desirable in seeking to ensure adherence to the moral principles that should inform genome editing?

- What other issues do you feel need to be discussed in the context of genome editing? What do you consider to be the issues of greatest moral concern raised by genome editing?

Biomedical research and human applications

We are interested in the ways in which genome editing might lead to benefits for human health. We are interested in research and how knowledge and methodologies are being developed through the use of genome editing that can lead to new treatments or approaches to the prevention or avoidance of disease (whether or not those treatments, themselves, involve genome editing).

We are interested in the possibility of 'germ line' modification, an area that has excited considerable commentary since the advantages of the CRISPR-Cas9 system were first described. However, we do not want to allow the level of discussion of germ line modification to obscure ethical issues that arise in relation to other applications, such as cell-based therapies for genetic and complex diseases, or the revived prospects of xenotransplantation. Moreover, we want to consider the proper context in which to evaluate the pursuit of these 'high tech' strategies and 'high ambition' clinical objectives in relation to possible alternatives and opportunity costs.

We are interested in the translation from research into treatment and whether genome editing raises any special considerations, either about the assessment or management of risk, or about who should assess the safety and acceptability of therapeutic use. We would like to examine, for example, whether genome editing requires different decisions to be made or other decision makers to be involved, compared to the introduction of other medical treatments.

We are interested in the fitness and preparedness of regulatory systems and the variation in regulatory provisions among different countries. We would like to examine the importance attached to global consensus and the prospects of reaching and sustaining it. We are particularly interested in who is framing the global debate and who should be involved in such discussions, and we are interested in the consequences of demurral or fragmentation of governance.

Indicative questions

Current research

- What is the current state of the art in relation to human therapeutic and reproductive applications of genome editing? What are the current technical limitations and constraints/ bottlenecks?

- What are the main directions of travel? What are the envisaged endpoints/ applications?

- What is the rate of travel? What are the expected timescales for realising the envisaged endpoints?

Conditions of research and innovation

- What are the main 'drivers' and 'obstacles' in relation to envisaged endpoints?

- What bearing do international ethical debates and agreements (e.g. high level statements or calls for moratoria) have on the pace or organisation of research?

- Who should lead and who should be involved in setting policy for research and human applications of genome editing? Is this significantly different from other kinds of experimental or reproductive medicine?

Impacts

- Have advances in genome editing affected what research is funded, what research strategies are used (*e.g.* derivation of stem cells) or the comparative development of therapeutic strategies?

- What are the significant decisions that need to be taken before therapeutic use of genome editing may be contemplated (for non-heritable and heritable genetic changes) and who should have the responsibility for those decisions?

- Are the benefits and costs of treatments that involve genome editing likely to be distributed equitably (or any more or less equitably than existing or alternative treatments)? In what way might genome editing differentially affect the interests of people in vulnerable or marginalised groups?

- What other important questions should or might we have asked in this section?

2. Responding

How should you respond?

We would prefer it if you would send your response to us electronically. Responses can be sent via email to genedit@nuffieldbioethics.org, with *Genome Editing: call for evidence* in the subject line. Please ensure that you also include a completed response form with your submission. A blank form may be downloaded from http://nuffieldbioethics.org/project/genome-editing/public-survey-call-evidence.

If you would prefer to respond by post, please send your submission to:

Dr Anna Wilkinson
Nuffield Council on Bioethics
28 Bedford Square
London
WC1B 3JS

For information about obtaining a large print version of this call for evidence, please contact us in the following ways:

Telephone: +44 (0)20 7681 9619
Email: awilkinson@nuffieldbioethics.org,
Website: www.nuffieldbioethics.org/genome-editing

The closing date for written evidence is Friday, 30 June 2017.

Guidance on submitting written evidence

It will assist the Working Party if you would:

- limit your response to one single Word-formatted document, preferably of no more than 2,000 words in length, and preferably submitted by email;

- include a short summary in bullet point form at the beginning of the document;

- have numbered paragraphs throughout; and

- ensure that your submission is accompanied by a completed response form, which can be downloaded from http://nuffieldbioethics.org/project/genome-editing/public-survey-call-evidence.

In addition:

- The working party's final report may make public the evidence received during the project in full, or in selected quotation. Please state in the response form whether you wish your submission to be made public.

- If you wish to include private or confidential information in your submission, please discuss this with us before submitting it.

- Material that has previously been published should not form the basis of your submission.

- If you reference your own previously published work in your submission and feel that the working party would benefit from reading it in the published form, please send us electronic or hard copies of the referenced items together with your submission.

- Please contact us if wish to submit evidence but are unable to do so by the closing date.

3. Background

What do we mean by 'genome editing'?

Genome editing is the alteration of a selected DNA sequence in a living cell by cutting the DNA molecule at a chosen point and either removing existing elements of the genome or deliberately introducing a new sequence.

Genome editing techniques make use of a large family of proteins, first discovered in the 1960s, that are able to cut the genome at specific sites. Since around 2005, new and programmable families of genome-cutting proteins have been described – including Zinc Finger Nucleases, TALENs and RNA- (CRISPR-) guided endonucleases – that allow cuts in the DNA to be targeted to any point in the genome.[1] After the cut is made, repair mechanisms that exist naturally within every cell rejoin the severed DNA ends, either by pasting them together with small insertions or deletions of genetic information ('indels'), or by using a different strand of genetic material as a template for repair.[2]

Among the recent genome editing technologies, CRISPR-based methods are particularly promising owing to their relative efficiency, low cost and ease of use, and the possibility of making edits at multiple places in the genome in a single procedure. This has led to their rapid diffusion and broad uptake across biology. Although most uses of genome editing so far have been in research, the potential applications seem to be unlimited, given that variations of the technique are applicable to all genomes.

We think it is impossible to consider normative questions about research (questions about its value and what research should be pursued, for example) in isolation from questions about the broader context, including the societal conditions under which it is carried out and the possibilities to which it might lead. This is why we think it is important to consider current research together with its potential non-research applications and, at the same time, why these uses should be a matter for public reflection beyond any narrow community of users.

By 'genome editing', therefore, we do not mean to refer to a particular technique or an existing area of research but, rather, to the idea of using molecular approaches to alter genes or gene expression in purposive ways, however imperfectly this may be realised through the techniques currently in use.

The idea of making controlled alterations to the genome is not new, of course, and some may see the techniques now available as new tools, much better in many respects than those available hitherto, but serving a similar range of ambitions. Others, however, may see them as transformative, opening up new horizons of possibility, leading science and technology in directions that were previously unidentified, neglected or forsworn. Either of these points of view, or any that lie between them, may be persuasive but the perspective taken may have significant implications for how genome editing will be developed, applied and controlled.

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[1] TALENs stands for 'transcription activator-like effector nucleases'; CRISPR stands for 'clustered regularly interspaced short palindromic repeats' (Cas9 stands for 'CRISPR associated protein 9'). These systems, and zinc finger nucleases (ZFNs), use endonucleases that operate as 'molecular scissors' to cut the DNA molecule at a desired point and exploit cell repair mechanisms to repair the cut using one of two pathways that are naturally present in all cells.

[2] Where the repair is mediated by the non-homologous end-joining (NHEJ) pathway, the repair will involve the uncontrolled loss or gain of DNA at the cut site. When the pathway is homology-directed repair (HDR), an extra piece of DNA is used to introduce a predictable change at the cut site, which can enable intentional insertions, including, for example, the introduction of new functional genes to the genome or the replacement of a segment of DNA that permits subtle changes to be made to an existing gene.

Why are we seeking evidence?

The Nuffield Council's terms of reference charge it "To identify and define ethical questions raised by recent developments in biological and medical research that concern, or are likely to concern, the public interest." The Council believes that genome editing raises such questions.

The Council's mode of working is primarily deliberative: it involves a process of collective reasoning by an informed group of individuals who bring a range of different skills and perspectives to the process.

As members of the working party we do not have, either individually or collectively, all the available information, nor are we likely to reflect the full range of perspectives, that are relevant to moral deliberation about genome editing. To supplement our own professional knowledge, we are gathering information from those who can offer additional information and insight. This call for evidence is one of the principal ways in which we hope to gather those inputs. Our aim is to open our inquiry as wide as possible in order to draw from sources that other forms of research might miss.

What sort of evidence are we seeking?

This is an open Call for Evidence, seeking information, insight and opinion relevant to the ethical reflection on genome editing in both research and application relating to applications in humans. We are interested in gathering:

- **Information**: references, especially recent or unpublished information that may not show up in literature research; information about current or planned research or applications; other sources of information that we should consult

- **Insight**: what are the relevant perspectives and the issues they foreground? Are any perspectives unfairly marginalised? How are different actions and outcomes valued, and on what basis? Using what frames of reference and systems of values might we understand and respond to genome editing?

- **Evaluation**: What are the potential benefits and to whom do those benefits accrue? What are the potential risks and adverse effects, and how are those risks and effects likely to be distributed? How are we to identify and evaluate the scale and significance of those benefits and risks in relation to each other?

- **Opinion**: What are the rates and direction of travel, likely applications and timescales? What is realistic and what is hyperbole? What is on the scientific horizon and what is (currently) science fiction?

The questions are indicative of our current interests. We encourage you to answer as few or as many questions as you wish, and feel free to ignore those that do not relate to your own knowledge or interests. Please feel free to provide other information that you think may assist the working party and, especially, to indicate other questions that you think we ought to address but may have omitted.

4. Further information

Terms of reference of the project Working Party on Genome editing and human reproduction

The terms of reference are:

- To examine ethical questions relating to the attempted influence of inherited characteristics in humans, in the light of the likely impact of genome editing technologies.

- To review relevant institutional, national and international policies and provisions, and to assess their suitability in the light of the ethical questions examined.

- To report on these matters and to make recommendations relating to policy and practice

Members of the Working Party

Karen Yeung (Chair), Professor of Law and Director of the Centre for Technology, Ethics & Law in Society (TELOS), King's College London

Richard Ashcroft, Professor of Bioethics, Department of Law, Queen Mary University of London

Neva Haites, Professor of Medical Genetics, University of Aberdeen

Joyce Harper, Professor in Human Genetics and Embryology, Institute for Women's Health, University College London

Julian Hitchcock, Partner, Marriott Harrison LLP

Jackie Leach Scully, Professor of Social Ethics & Bioethics, PEALS (Policy, Ethics & Life Sciences) Research Centre, Newcastle University

Tony Perry, Reader, Laboratory of Mammalian Molecular Embryology, Department of Biology and Biochemistry, University of Bath

Christine Watson, Council member, Professor of Cell and Cancer Biology in the Department of Pathology, University of Cambridge and Vice-Principal of Newnham College