Under embargo until 09.00 GMT Friday 27 November 2015

NUFFIELD COUNCIL ON BIOETHICS

# Genome Editing

## OPEN CALL FOR EVIDENCE

**Published 27 November 2015**
**Closing 1 February 2016**

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 1 of this document.

This call for evidence is divided into four parts:

- **Background** (What do we mean by 'genome editing'? Why are we seeking evidence? What sort of evidence are we seeking? How will the evidence contribute to our work? )
- **Questions** (divided into sections relating to plants, animals, humans, microorganisms, etc.)
- **Responding** (How should you respond? How will we use the evidence you submit?)
- **Further information** about the project (terms of reference and membership of the project working group)

# 1. 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.

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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.

Areas of research and possible application include:

- crops and livestock (*e.g.* increasing yield, introducing resistance to disease, pests and pesticides, nutritional traits, and tolerance of different environmental conditions)
- industrial biotechnology (*e.g.* developing 'third generation' biofuels)
- ecology (*e.g.* managing populations of disease vector organisms or even restoring extinct species)
- biomedicine (*e.g.* pharmaceuticals, xenotransplantation, and gene, cell and regenerative therapies)
- reproduction (*e.g.* removing hereditary disease traits from future generations)

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.

## Why are we seeking evidence?

The Nuffield Council's terms of reference charge it "to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern." 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. Accordingly, in June 2015, the Council established an interdisciplinary working group to examine questions raised in relation to genome editing. The reasoning and conclusions of this group will be thoroughly tested by the Council itself, through consultation with others, and ultimately in public debate.

As members of the working group 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.

## How will the evidence contribute to our work?

This project is being carried out in two stages. The first stage, to which this call for evidence relates, is intended to investigate the proper context for asking more practical questions about genome editing. This part of our project will be guided by questions about how we should think about genome editing, what sort of thing it is and to what sort of ethical questions it gives rise. For example, we will investigate whether genome editing itself raises any distinctively new moral questions or simply casts familiar questions in a new light.

In this first stage, we will not be addressing practical policy questions directly, questions about, for example, under what conditions (if any) a particular use of genome editing would be morally acceptable/ desirable/ required, or about who should decide when genome editing may be used for a particular purpose or in a given set of circumstances. We will move on to these in the second stage, after we have published the findings of our first stage.

We think it will be better to address the conceptual questions first, since our conclusions will inform both our understanding of which questions should have the highest priority and how we might tackle them in stage two.

## 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 across the full range of uses, from microorganisms through plants and animals, to humans. For the time being 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 divisions of our inquiry follow a familiar delineation of research subjects (microorganisms, plants, animals, humans) for pragmatic reasons. We recognise there will be much cross-over among these areas and difference within them, and we also raise a number of cross-cutting issues (such as ownership of intellectual property).

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. We do not expect anyone responding to address all of them. Please feel free to provide other information that you think may assist the working group and, especially, to indicate other questions that you think we ought to address but may have omitted.

# 2. Questions

## Perspectives on genome modification

In this section 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 manipulating nature (e.g. selective breeding of plants or animals)?
- 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, and to what extent is its value dependent on envisaged practical applications?
- What obligations do governments have towards society to ensure 'safe' science or otherwise to shape the scientific research and development?

Science, morality and law

- What conventional moral principles, if any, do 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?

## Genome editing in plant science

In this section we are interested in the significance of genome editing in plant science and the way that this family of technologies is understood in comparison to alternative ways of modifying the characteristics or development of plants.

We are interested in where current research is heading, how quickly, under whose control and for whose benefit. We would like to know about how various factors, such as law and regulation, constrain or enable developments (including any difficulties owing to regulatory complexity or inconsistency). We would also like to hear about the role of commercial competition and market forces, and the importance of scale. We would like to understand the significance of intellectual property rights, among other external and discretionary conditions, in shaping research, innovation and access to products. We would like to understand the relationship between research and innovation in the publicly funded, not-for-profit and commercial sectors, and the implications of this for common interests.

**Indicative questions**

Current research

- What is the current state of the art in the field? 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?
- Are gene drives an area of particular interest or concern and, if so, why?

Conditions of research and innovation

- What are the main 'drivers' and 'obstacles' for plant genome editing in relation to envisaged endpoints?
- What direct or indirect influence does historical public discussion surrounding genetic modification of plants have? What is (and what should be) the current level and focus of public debate?

Outcomes

- What are the main anticipated benefits and costs (including safety and other risks) of genome-edited plants? In what ways, if any, are they significantly different from alternative GM technologies?
- Are there particular issues raised by genome editing in relation to ecological stability, biological diversity, technology transfer between countries, and equitable sharing of the benefits of research?
- To what extent, and in what way, does and should the distribution of anticipated benefits and costs of using genome editing in plants influence research and innovation?
- To what extent are public and commercial interests in genome editing in plants complementary? In what circumstances might they come into conflict?
- What other important questions should or might we have asked in this section?

## Genome editing in animals

As with other areas of research we are interested, in this section, in where current research is heading and how quickly, under whose control, and for whose benefit. We are also interested in understanding what is driving and constraining this research, and would like to hear about how law, regulation, policy, finance and competition shape developments.

We would like to know about the potential impact of genome editing on the way animals are treated and used for a variety of human ends, including in laboratories (*e.g.* to provide models for human disease), for food (*e.g.* varieties of livestock, including chickens, pigs, cattle, sheep and fish), as resources (including, potentially, tissues and organs for animal-to-human transplantation) and even for

companionship. We are interested in the impact of genome editing on animal welfare and its application in veterinary medicine. We would also like to know about the potential impact of genome editing on our visions for future food supply, and the policy, economics and regulation of food production and consumption.

We are also interested in proposed and potential uses of genome editing in wild animal populations, for example to control the vectors of human and animal diseases, or to manage crop pests or environmental impacts. In this connection we would like to know about the potential uses, feasibility, benefits and hazards associated with 'gene drives', which cause a selected trait to spread rapidly through a population with each successive generation.

**Indicative questions**

Current research

- What is the current state of the art in the field? 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?
- Are gene drives an area of particular interest or concern and, if so, why?

Conditions of research and innovation

- What are the main 'drivers' and 'obstacles' for genome editing in relation to envisaged endpoints?
- What direct or indirect influence do historical public discussions surrounding genetic modification, animal welfare and food safety have? What is (and what should be) the current level and focus of public debate?

Impacts

- Are there particular issues relating to ecological stability, biological diversity, technology transfer between countries, and equitable sharing of the benefits of research?
- What overall impact might genome editing have on animal lives? Can genome editing be expected to contribute to or inhibit the replacement, reduction or refinement (the '3Rs') of the use of animals in research?
- Does genome editing give rise to special moral considerations about generating artificially modified animals for research (including disease models in large or highly sentient animals) or for trivial/ commercial reasons (*e.g.* 'toy' pigs)?
- What other important questions should or might we have asked in this section?

## Genome editing in microorganisms

CRISPR-based genome editing was initially developed from research in microorganisms, specifically concerning mechanisms by which bacteria defend themselves against viruses. We are interested in applications of genome editing at the level of microorganisms, including in relation to human health, industrial production and environmental interventions. Here, as elsewhere, we would like to understand what, if anything, is distinctive about the use and potential of genome editing compared to other technologies.

**Indicative questions**

Current research

- What is the current state of the art in the field? 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 commercial applications of genome editing in microorganisms and what are the main economic drivers of development?
- To what extent is research that uses genome editing in this area continuous with synthetic biology? To what extent are the discussions, institutional capabilities, resources and measures surrounding synthetic biology relevant and helpful to genome editing in microorganisms?

Impacts

- Are there particular biosafety and biosecurity considerations relating to genome editing in microorganisms? If so, are they significantly different in degree or in kind from other research on microorganisms?
- Are there particular opportunities for genome editing research to contribute to bioremediation (e.g. mitigating the negative effects of pollution or climate change) or, alternatively, risks relating to habitat destruction or species extinction? If so, what are the risks associated with developing these opportunities and how serious are those risks?
- What other important questions should or might we have asked in this section?

## 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 the field? 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?

## Military and security considerations

We are interested in understanding the level and nature of interest in genome editing for military purposes, and the ‘dual use’ potential of genome editing research (*i.e.* the potential for it to be used for military as well as civilian purposes). Because of national security sensitivities it may be difficult to identify the nature and full extent of such interests, but it seems reasonable, given the level of investment and funding from defence ministries and agencies in related areas, such as synthetic biology, that there should be a significant interest in genome editing and its potential military applications.

**Indicative questions**

- Is there a military interest in genome editing research? What is its nature?
- What can we discover about defence funding for research and development in this area? What are the limits of our knowledge in this area and what implications might this have for decisions about research policy more generally?
- Are there areas of genome editing research that are or should be classified as ‘dual use research of concern’ (DURC)? If so, what are they and what applicable measures are there to address these concerns?

- Are there distinctive concerns about biosafety/biosecurity that are being investigated with respect to genome editing research or applications in particular?

# 3. 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 Bettina Schmietow: **bschmietow@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 www.nuffieldbioethics.org/genome-evidence.

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

**Dr Bettina Schmietow**
**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: bschmietow@nuffieldbioethics.org,
Website: www.nuffieldbioethics.org/genome-evidence

**The closing date for written evidence is Monday, 1 February 2016**.

## Guidance on submitting written evidence

It will assist the Working Group 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 www.nuffieldbioethics.org/genome-evidence.

**In addition:**

- The Working Group'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 Group 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.

# 4. Further information

## Terms of reference of the project Working Group

The terms of reference are:

- To identify and define ethical questions relating to developments in genome editing research.
- To review institutional, national and international policies and provisions relevant to genome editing, and to assess their current and likely future significance.
- To deliberate and to draw conclusions, as appropriate, about the nature of the ethical questions raised and how they might most suitably be addressed.
- To report on these matters and to make recommendations, as appropriate, for further initiatives by the Council or by other identified bodies, or for the development or revision of policy or legislation.

## Members of the project Working Group

**Andy Greenfield (Chair),** Council member, Programme Leader in Developmental Genetics at the Medical Research Council's research unit in Harwell, and a member of the Human Fertilisation and Embryology Authority (HFEA)

**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

**David Lawrence,** Council member, Non-Executive Director at Syngenta AG, Chair of the Syngenta Science & Technology Advisory Board, and a member of the Biotechnology & Biological Science Research Council

**Charis Thompson,** Chancellor's Professor and Chair, Department of Gender and Women's Studies, UC Berkeley, and Professor of Sociology, London School of Economics and Political Science

**John Dupré,** Professor of Philosophy of Science, Exeter University and Director of Egenis, the Centre for the Study of Life Sciences

**Richard Ashcroft,** Professor of Bioethics, Department of Law, Queen Mary University of London and Co-Director of the Centre for the Study of Incentives in Health

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