

# NUFFIELD COUNCIL ON BIOETHICS

## Response to the Science and Technology Committee (Commons) inquiry on genomics and genome-editing

January 2017

### Background

- 1 The Nuffield Council on Bioethics is an independent UK body that examines and reports on ethical issues arising from developments in biological and medical research that concern the public interest. We welcome the opportunity to comment on the House of Commons Science and Technology Select Committee inquiry into genomics and genome-editing.
- 2 This response draws mainly on [Genome editing: an ethical review](#), published by the Council in September 2016. This report considered the impact of recent advances in genome editing on biological research and the range of ethical questions to which this gives rise. It identified areas of genome editing application that need addressing urgently – human reproduction and livestock – and which the Council will explore in two further inquiries. The first of these, on human reproduction, is already underway and expected to report in late 2017. A Working Party on genome editing in livestock will start its work later this year. Given that our work on these issues is in progress and that the scope of the committee’s inquiry is wide, we have provided only general comments here. We would welcome the opportunity to elaborate on any of the points in our response at a session of the committee.
- 3 Other recent Council reports of relevance to our submission are [Emerging biotechnologies: technology, choice and the public good](#) (published in 2012), [The collection, linking and use of data in biomedical research and health care: ethical issues](#) (published in 2015), and [Medical profiling and online medicine: the ethics of ‘personalised healthcare’ in a consumer age](#) (published in 2010).

### Genome editing

- 4 From one perspective, genome editing may be regarded as a technical development in the established practice of genetic modification, albeit using a more precise tool. From another, it has the potential to transform not only biology but also the horizon of expectations and ambitions about how humans may control the biological world, with radically different implications according to the area in which it is applied. In *Genome editing: an ethical review*, we explained that how we imagine genome editing and its possibilities can strongly affect how the techniques will be developed, applied and controlled.

## ***Public Interest***

- 5 The public has an interest in genome editing, both in terms of its expectation of future social benefits, but also in possible costs and harms. The public invests in genome editing both financially (e.g. through state-funded research) and through the trust it places in scientists and innovators to help deliver the hoped-for benefits. More profoundly, there is a public interest in the ways in which different potential uses of genome editing might challenge and affect our moral and cultural values and understandings
- 6 An anxiety running through many responses to our call for evidence, held to inform our review, was the need for clear limits to distinguish morally acceptable from unacceptable uses of genome editing. While there is often no orthodox and generally accepted source of ready-made moral judgements on the complex implications of scientific research, much of the evidence we received pointed to the importance of having an open, effective and inclusive public debate in which questions about genome editing could be raised and discussed, in which different positions and arguments could encounter each other and all interests fairly represented.

## ***The impact of genome-editing on research***

- 7 The CRISPR-Cas9 genome editing system, in particular, has spread rapidly through the biological sciences. Although surprisingly hard to quantify in practice and very context dependent, the technique appears to offer a number of advantages: it is versatile, inexpensive, and relatively easy to access (kits can be bought online) and to use (it requires biological expertise, but not highly specialised knowledge or research skills), and it offers the prospect of making precise edits at multiple sites in the genome in a single procedure.
- 8 Its efficiency and specificity are comparatively high compared to other methods of genetic alteration, but are not without limitation. One challenge for researchers is the delivery of CRISPR-Cas9 into the target organism. It is often carried in inactive viruses, but there are limits to the size of an additional DNA sequence that a virus can effectively deliver. Another concern is the risk of 'off-target' editing at DNA sequences that were not supposed to be changed, though the techniques are continually being improved in this respect, and recent studies have demonstrated high specificity with no detected 'off-target' effects.
- 9 In relation to health research, ethically significant possibilities raised by genome editing include:
  - Bringing basic research and its translation into treatment closer together since the same methodology could potentially serve both to discover a gene function and to make a therapeutic alteration to treat a disease related to that gene.
  - A potential increase in the use of larger animals, such as primates, in disease research, as they may offer better 'models' for studying certain diseases than, for example, mice.

- Using genetically altered animals to study the effects of gene mutations that are specific to a family or individual, introducing an unprecedented kind of (more direct) connection between an animal model and an individual patient.
- 10 Potentially increased rates of experimentation, facilitated by genome editing, may prompt a number of additional concerns for some people, including:
- The possible consequences of an increased demand for the use of human embryos for research involving genome editing.
  - The risk of scientific publishing and communication moving too slowly to keep pace with experimentation, meaning a lack of coordination among research groups and duplication of work, which may in turn have consequences such as unnecessary increases in the number of animals used in research.
- 11 In our 2016 review we described the impact of genome editing in a number of fields, however we have focused our response here to the developments we found to raise particular ethical issues and which require further scrutiny that are also within the remit of the committee's inquiry – namely wildlife and ecosystems, food production and human health.

### ***The impact of genome editing on wildlife and ecosystems***

- 12 Wild species tend to adapt to their conditions through natural selection, where a spontaneously arising genetic trait aids survival and reproduction and spreads throughout a population over generations. Researchers have discovered a way to accelerate the inheritance of a selected genetic variant using a technique called a 'gene drive'. The aim is that the genetic variant spreads through a population regardless of whether or not it improves the chances of survival of members with that variant.
- 13 Applications of gene drive technology include the eradication of insect pests and disease vectors, reduction of invasive species and management of ecosystems. The convergence of gene drive systems with the CRISPR-Cas9 genome editing system to effect specifically targeted genomic modifications has been described as a 'game changer' in the field, including as a means to prevent the transmission of communicable diseases. Gene drive systems using CRISPR-Cas9 have been applied in research on organisms including mosquitoes and yeast.

### ***Ethical and other considerations relating to gene drives***

- 14 There are potentially significant public health benefits arising from the use of genome editing to modify the natural environment. For example, its ease of use and relative efficiency offer the potential to eradicate insect pests and vectors of disease directly, including many insect-borne tropical diseases such as dengue, malaria and Zika. There are, similarly, economic benefits to cost-effective pest control in agricultural regions.
- 15 However, the convergence of gene drive and genome-editing technologies raises a range of concerns about biosafety and environmental release that go beyond those raised about potentially hazardous biological research and genetically

modified organisms (GMOs). A major potential for benefit, as well as a major source of concern, are initiatives designed to spread a deliberate modification rapidly throughout a population in the interests of public health. These raise a number of ethically contentious issues:

- The effects of gene drives are difficult to predict and may include system effects and unintended consequences.
- Once released into the wild, gene drives may be difficult to control.
- Their effects may be irreversible.
- There is a possibility of gene drives being put to malicious uses, for example to intentionally cause an ecological catastrophe.
- The deployment of technologically advanced gene drives and genome editing systems in resource-poor countries also raises questions about ethically contentious conditions for technology transfer which need careful consideration.

16 The values and priorities of recipient communities are important considerations and cannot simply be assumed – they will depend on many factors, and efforts must be made to engage with the range of expectations of the communities who will be most affected, while recognising that the issues or consequences may not be confined within national borders.

17 Our report argues that precautionary approaches, while offering clear indications of principle, are extremely difficult to give effect to through regulatory practice. For example, the approach embodied in the *Cartagena Protocol on Biosafety*<sup>1</sup>, which is being elaborated in local measures around the world, is not well suited to genome editing enabled by gene drive systems. The introduction of gene drives requires flexible and adaptive models of innovation governance ('responsible innovation') that involve built-in opportunities for reflection and break points, and especially that avoid creating technological momentum. Particular attention needs to be given to issues of global justice in technology transfer from high-income countries to low- and middle-income countries.

18 Given the risks and benefits, the political legitimacy of any decision to release genome-edited organisms into the environment becomes especially important. Taken together, the experience with genetically modified mosquitoes to date, the procedures required to bring GMOs to market, and the evolving international policy framework, suggest it is likely to be a number of years before genome-edited organisms are ready for large-scale release into the wild. Well before then, substantial ethical and societal questions will need to be addressed.

### ***The impact of genome-editing on plants and animals, including in relation to food production***

19 Genome editing offers a potential contribution to the challenge of maintaining a sufficient supply of safe, nutritious food by improving the efficiency of the development and production of crops and animals for consumption. Research in

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<sup>1</sup> *Cartagena Protocol on Biosafety to the Convention on Biological Diversity*, available at: <http://bch.cbd.int/protocol/>

this area is comparatively well advanced, but has received little attention compared to other uses of genome technologies.

20 In plants, possible commercial uses include improvements in yield and pest resistance, as well as increased drought-tolerance and nutritional benefit. It is thought that genome editing could reduce the time needed to generate a desired genetic characteristic in a plant population from 7–25 years to as few as 2–3 years as the technology allows the favoured genetic combination to bypass several plant generations.

21 In animals, CRISPR-Cas9 system has been proposed for use in animals for consumption. For example to:

- improve yield – e.g. growing cattle with increased muscle mass;
- increase disease resistance, e.g. pigs resistant to African swine fever; and
- make livestock better adapted to farming or environmental conditions, e.g. hornless cattle that can be kept in confined spaces with lower risks of injury.

22 Global food production needs to increase – some say by as much as 70 per cent – to support the world’s growing population. In this context, it is important to consider whether and how genome-editing technologies can contribute alongside other approaches, such as improving the efficiency of distribution and reducing waste. The safety of food for human consumption is a key concern and, in the case of animals, there are also concerns about the welfare of intensively farmed animals. One area of dispute is whether foods produced using genome editing techniques should be classed as GMOs. This is significant because of the differences in the way that GM and non-GM foods are regulated, labelled and perceived by consumers. GM regulation imposes additional burdens on producers, which affect the economics of production. Effective regulation and labelling depend on traceability but genome editing makes analytical verification of this difficult, as an edited product may appear to all intents and purposes identical to a non-edited product.

23 There are, therefore, important questions to consider regarding the appropriateness of existing regulations and whether there is a need for new classifications or new approaches to policy and regulation. The answers to these questions could have important consequences for food security, businesses, international trade and the economics of food production. A Nuffield Council Working Party on genome editing in livestock will start its work later this year. More information on regulation of GMOs and genome editing is below.

***The impact of genome-editing on human health, with regard to treating disease, avoiding genetic disease and human enhancement.***

*Treating disease*

24 Genome editing in gene, cell and tissue transplantation-based therapies offers promising approaches to overcoming some of the difficulties that have impeded the development of medical treatments, particularly in the areas of gene therapy and xenotransplantation.

- 25 As with any new treatment, there will be questions over the safety of the technique, whether it is likely to work, and whether it should be offered as an alternative or replacement for current treatment options. The main safety consideration with genome editing in patients is the possibility of unintended or unwanted effects – for example so called ‘off-target effects’. Given concerns over the uncertainty of outcomes, a relevant consideration will be whether alterations to the genome in patients’ tissues can be neutralised or reversed.
- 26 While genome editing is a promising development in the field of gene therapy, it faces many of the delivery challenges faced by gene transfer. In particular, ways must be found to target and deliver the genome editing machinery to sufficient numbers of specified cells within the patient to ameliorate or reverse the disease symptoms. Research is moving quickly towards clinical application in some areas.<sup>23</sup>
- 27 Genome editing has, in addition, revived the prospects of another therapeutic strategy: xenotransplantation (the transplantation of tissues or organs from one species to another, for example, pig hearts into human patients) by offering a promising strategy to overcome previously intractable animal-to-human transmission of disease.

#### *Avoiding genetic disease*

- 28 Scientists estimate that there are more than 10,000 known, inherited, single-gene conditions, which, collectively, are thought to affect millions of people worldwide. The use of genome editing in combination with assisted reproductive treatments could prevent the transmission of some of these conditions (e.g. thalassaemia or cystic fibrosis) to future generations, by making changes to the DNA of a very early stage embryo that will be replicated in all cells in the body as it grows.
- 29 Genome editing may offer an alternative approach to familial disease prevention, especially in certain (albeit rare) cases where established methods such as pre-implantation genetic diagnosis (PGD) would not be effective. Of all the potential applications of genome editing that have been discussed, the genetic alteration of human embryos in vitro has consistently generated the most controversy. Research undoubtedly has some way to go before any application of this sort could be contemplated and, in the UK at least, the transfer of an edited embryo to a woman is currently prohibited by law. Many people have concerns about the possible use of genome editing in human reproduction, for example, about the implications of making genetic changes that will be passed on to future generations. Whether it should, in future, be offered as an ‘alternative’ reproductive treatment depends not only on the outcomes, risks, costs, etc., but also on other factors including how reproductive choice is valued, and the extent of society’s

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<sup>2</sup> See for example Tebas P, Stein D, Tang WW, et al. (2014) Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV *New England Journal of Medicine* 370(10): 901-10.

<sup>3</sup> See also Cyranoski D (2016) CRISPR gene-editing tested in a person for the first time, *Nature* 539:479, available at: <http://www.nature.com/news/crispr-gene-editing-tested-in-a-person-for-the-first-time-1.20988>

interest in people's choices and welfare, which may, in turn, have consequences for governance and regulation.

- 30 A much discussed issue is how to distinguish between acceptable and unacceptable uses of genome editing. There are concerns that the use of genome editing may facilitate the spread of 'consumer' or 'liberal' eugenics, driven primarily by the choices of parents, which could, in turn, exacerbate divisions or inequalities in society. Some people may also be ethically opposed to the practice of pre-determining a person's genetic characteristics, arguing that this constrains their future choices in unacceptable ways. These questions are particularly acute when the reason for genome editing is not unambiguously a medical one.

### *Human enhancement*

- 31 Genetic variations may not always directly cause disease, but may be associated with an increased risk of developing a certain disease or, conversely, have a protective effect against a certain disease. For example, a recent laboratory trial of genome editing of preimplantation human embryos reported the introduction of a gene variant offering protection against HIV. Genome editing also raises the possibility of 'engineering' humans with desirable genetic traits, for example to suit specific environmental conditions or to enhance athletic ability.
- 32 Enhancement could take place either through gene therapy or through interventions around reproduction. Many of the moral and societal questions that arise in respect of the use of genome editing beyond treatment and (arguably also) prevention of disease are not new and have been raised in relation to gene therapy and embryo selection following PGD. Others have been discussed in the context of gene doping (e.g. improvements in skeletal muscle) where its effects may be time-limited.
- 33 Because such applications, even for limited purposes, are controversial, it is necessary to consider carefully how to respond to such possibilities before they become a practical option. As mentioned above, following on from *Genome editing: an ethical review*, published in September 2016, the Council is currently embarking on a separate inquiry on genome editing in human reproduction, and we are expecting to publish the report later in 2017. We would welcome the opportunity to discuss progress on this project at a session of the Committee

### ***Impact of genome-editing in other areas***

- 34 Other issues relating to genome editing which may be of interest to the Committee's inquiry, include the changing patterns of technology use, including military and national security initiatives, artistic and cultural activities, and private experiments by community groups or individuals. These are also covered in our report.

### ***The regulatory environment***

- 35 It is not possible to summarise regulation of genome editing in a coherent way, because the technique is being utilised in a number of different fields of application: there are no 'genome editing' regulations. Questions therefore arise regarding,

firstly, the extent to which existing law and regulations cover the novel technique of genome editing and, secondly, whether, if they do so, they do so appropriately given the distinctive features of the technique and its products.

- 36 For the reasons described in the section on food production above, genome editing is currently testing the approach to the legal regulation of GMOs in the European Union (currently transposed into domestic law); not only with regard to whether they fall under the GMO legislation, but also by precipitating a more fundamental reflection on the legislative approach and its moral and political foundations.
- 37 The regulatory response to genome edited foods in general remains uncertain. A number of crops produced using relevantly similar techniques have been approved for market in some countries. Rulings have been handed down by the Animal and Plant Health Inspection Service (APHIS), an office of the US Department of Agriculture, that place genome-edited products in development beyond the special regulatory provisions that usually apply to GMOs. The position of genome-edited products in the EU remains unclear, and the European Commission has asked Member States not to take national decisions on the status of genome-edited products pending the release of an interpretative document. This has led to concerns that persistent uncertainty is likely to lead to disinvestment, attrition of the research base (in 2012, Europe accounted for 46% of research on New Breeding Techniques [NBTs] in plants), and failing international competitiveness.
- 38 Precautionary approaches that are mandated in relation to biotechnologies are extremely difficult to give effect to through regulatory practice. As mentioned in the section on wildlife and ecosystems, the approach embodied in the *Cartagena Protocol on Biosafety* is not well suited to genome editing enabled by gene drive systems.
- 39 When considering appropriate public policy responses we would like to reiterate here a point we made in our response to the House of Lords Science and Technology Committee's enquiry on GM insects – that questions about GM research and innovation should be considered in the context of alternative ways of responding to human priorities, and in accordance with broader social values. Rather than considering GM technologies in isolation, the Council recommended a broader approach where risks and benefits of biotechnologies, such as GM, are assessed on a comparative basis. This should include assessing the risks involved in doing nothing (which in itself is not an ethically neutral act) and investigating alternative options (which may be technological, social or organisational), in order to address the same societal priorities or concerns. These recommendations are highly pertinent to the development of genome editing.

***The collection, linking and use of data in biomedical research and health care: ethical issues***

- 40 The wider introduction of genome technologies within specialised and routine healthcare raises a number of unresolved ethical issues that were discussed in the Council's 2015 report, *The collection, linking and use of data in biomedical research and health care: ethical issues*. A key question faced by data initiatives and the health systems as a whole is what uses of data should be 'expected' as part of delivering national health care with quality, safety, and cost-effectiveness



with ongoing improvement in the standards of care. It is becoming increasingly evident that there are commercial drivers behind many high-profile initiatives that have been proposed in recent years and, as empirical studies show, this is of significant concern for the public.

- 41 The issues go beyond individual privacy, especially as datasets start to be linked together, and there is a need to have governance structures in which all interests are enabled to participate and that involve continuing review and reflection on the societal implications of such initiatives. Two concerns that bear consideration are whether the case for use of large-scale secondary use of data has been adequately made, and that the benefits of data-driven health care and precision medicine will be equitably distributed. Unless there are trustworthy governance systems in place that can engage with and reflect reasonable expectations in continuously evolving circumstances, initiatives that could have wide public benefits may continue to be challenged and fail to secure public confidence. In this context we support the Science and Technology Committee's (Commons) previous [proposal](#) for a 'council on data ethics'.
- 42 With regard to the [100,000 Genomes](#) Project specifically, in order to secure ongoing public support, it is important to recognise the need for it to give a clear account of how its governance arrangements meet public interests and expectations.
- 43 Large scale initiatives such as [UK Biobank](#) and the 100,000 Genomes Project, as well as the increasing introduction of whole genome sequencing linked to NHS Digital, are key enablers for personalised (or precision) medicine. We believe that the deliberative governance approach described in our 2015 report offers a way of addressing the ethical issues associated with precision medicine.
- 44 We welcome the Committee's examination of the 100,000 Genomes initiative, and hope that this might offer an overture to a broader, inclusive public consideration of whether it provides the most appropriate model for the ethical use of genomic information generated in health services for public benefit before it becomes the *de facto* infrastructure for future projects<sup>4</sup>.

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<sup>4</sup> See paragraphs 6.62-6.66 in Nuffield Council on Bioethics (2015) *The collection, linking and use of data in biomedical research and health care: ethical issues*, available at: [http://nuffieldbioethics.org/wp-content/uploads/Biological\\_and\\_health\\_data\\_web.pdf](http://nuffieldbioethics.org/wp-content/uploads/Biological_and_health_data_web.pdf)