Summary

The latest genome editing technologies provide faster, simpler and cheaper methods of selectively manipulating the genome. Although genome manipulation has been possible for decades, the accessibility of these new technologies, such as CRISPR/Cas9, means that they can be used far more widely than existing technologies. Genome editing is already being used in multiple applications and has enormous potential to speed research and facilitate useful and effective applications which could be beneficial to human health. However, the full implications of these technologies are often unknown. For this reason, these technologies will challenge existing ethical and regulatory infrastructures in a number of ways: the speed of technological change threatens existing infrastructures and processes for assessing benefit and harm; the consequences of using genome editing may be uncertain; and they may have global impact. Novel forms of ethical and regulatory collaboration are required which foster and enable self-regulation rather than adopting moratoria against gene/genome editing: this is on the basis that these will stultify research which has the potential to be profoundly beneficial, and also that these will tend to be disregarded in those countries where existing regulatory infrastructure and ethical review are poor, where, paradoxically, the need for effective regulation is most acute.

About the PHG Foundation

Introduction

1. The PHG Foundation is an independent, not-for-profit health policy think-tank that has a mission to make science work for health – providing knowledge, evidence, tools and opportunities to help policy and decision-makers put advances in the life sciences and digital health technologies within the reach of every citizen in the form of effective, affordable and more personalised healthcare. We seek to do this by grasping the potential of new technologies to improve healthcare; by envisioning a future where more effective and affordable healthcare is possible based on personalised medicine, personalised prevention and better strategies for controlling disease; and by shaping the health policy debate through a dynamic process of multidisciplinary engagement to explore issues, resolve barriers and develop consensus. The PHG Foundation has no relevant financial or other interests to declare.
Our approach to this consultation

2. In this response we have focused on the areas that relate most closely to our objectives, namely: conceptual perspectives on genome modification; and biomedical research and human applications. However, we acknowledge that the boundaries between plant, animal, viral and human genome editing are not clearly defined: this is because many genes are shared between organisms, and establishing scientific and clinical validity and utility in biomedical research almost always requires basic science often involving animal and other models.

Perspectives on genome modification

3. The significance of genome interventions

The latest genome editing technologies, in particular CRISPR/Cas9, are a significant addition to the scientific tool kit. Uptake of CRISPR has been particularly fast and widespread, and research in this field is moving forward incredibly quickly due to:

- Ease of use compared to currently available methods
- Speed of use
- Lower cost of methods

The extensive benefits to the practice of scientific research of using these technologies are outlined in point 7. However, the accessibility of the technology has removed barriers to its widespread use, which also presents challenges. In the UK, we should ensure that existing regulatory infrastructure is able to manage this increase in use and application. Another is that genomes can be edited on a much larger scale than was possible using previous methods, meaning that a subsequent increase in effort is needed to ensure that the changes being made, and their consequences, are understood.

4. The obligations of scientists

The regulation of gene editing and the discussion surrounding the ethics and the legal constraints should be framed according to the use to which gene editing is put. At one end of the spectrum, the new gene editing technologies are tools that make the practice of science quicker, cheaper and more efficient. At the other end of the spectrum, the possibility of easier human germline editing has important ethical and societal implications. The scientific community has already begun to self-regulate in this regard by holding discussions both in the literature and at meetings to develop consensus statements on the use of genome editing, particularly human germline editing. A collaborative community is being formed to discuss these issues and it is vital that this community and others like it are supported and encouraged.

5. The intersecting nature of genome editing applications

The genome editing of cells, microorganisms, animals and plants has applications across different sectors, and the implications of the editing will vary depending upon the application. While editing the genome of a malaria-carrying mosquito to drive a gene that makes them resistant to the malaria parasite could have a significant impact on the spread of the disease, there could be unknown ecological consequences. Genome editing of microorganisms could have wide-ranging implications for industry, drug discovery and medical research. Many genome edited animal models are being used in laboratories world-wide with implications for medical research.
6. **Science, morality and the law**

Governments have obligations to their citizens to protect against foreseeable harms. These obligations, which are part legal and part ethical, form part of the social contract between states and their citizens. In the context of human health, the ethical imperatives of beneficence and non-maleficence guide decision-making. As described in point 7 existing applications offer foreseeable benefits e.g. more effective and targeted treatments. However, the harms associated with genome editing are not clear: this is partly because the technologies are in early development, and are sometimes unknown, inaccurate (e.g. there is the potential for off-target effects), or the wider societal effects of adopting incremental changes is unclear (and thus the ultimate endpoints in terms of goals and solutions are uncertain). This reinforces the need for a regulatory approach that is dynamic, flexible and context dependent.

**Biomedical research and human applications**

**Genome editing (non-germline)**

7. **Direction of travel**

CRISPR/Cas9 is already being used as a tool by the scientific community. Current uses in the medical sphere are:

i) Development of models to carry out disease research and study basic biology.

The development of new cell lines is allowing researchers to study the basic biology of cells, and also to use gene editing machinery as a tool to study the effects of regulating gene activity. These models are also being used in drug discovery, to support the finding of druggable targets, studying resistance to therapy, and screening. CRISPR/Cas9 is having a significant impact on the development of animal models, for example mouse models of disease. Developing new models can now take 3-4 months, compared to 1-2 years using currently available methods, and depending on the genetic background required.

ii) Ex vivo clinical use, in particular to treat blood or immunological disorders.

This involves a bone marrow transplant of patient's own edited cells or donor cells. This has already been used in the clinic to treat a case of acute lymphoblastic leukaemia in a one-year old child (see point 11). Other research efforts are focussed on developing treatments for blood disorders such as sickle cell anaemia and eye disorders such as retinitis pigmentosa.

iii) Other ex vivo clinical use – delivery of CRISPR/Cas9 editing machinery to specific tissues or organs.

One area of research that has shown promise recently was highlighted by three papers in the 22 January 2016 issue of *Science* where researchers used viral vectors to deliver CRISPR/Cas9 editing machinery to successfully edit faulty copies of the dystrophin gene in mouse models of Duchenne muscular dystrophy, leading to improvements in symptoms.

**Germline genome editing**

8. **Direction of travel**

The scientific community is self-regulating research in this area to a certain extent. The contribution of the community to the debate will be discussed further in point 9. Germline editing has already been carried out in non-viable human embryos by
researchers working in China, and there is an application under consideration by the HFEA to use gene editing in embryos for scientific research in the UK, to understand the role of certain genes in the earliest stages of embryo development.

9. **Role of international ethical debates**

A number of organisations have already called for moratoria on emerging techniques for engineering gametes and editing the human genome. For example, the International Bioethics Committee (a UNESCO committee) has argued that “the human genome is the heritage of humanity” (para 115 and Article 1 of the Universal Declaration on the Human Genome and Human Rights 1997), and that this creates a global responsibility which falls on the international community as a whole and cannot be met by States and governments. On this basis, UNESCO has called for an international legally binding instrument to ban human cloning for reproductive purposes and a moratorium on genome engineering of the human germline. We oppose this call on the basis that a moratorium would be disproportionate: it would take insufficient account of the potential risks and benefits of the technology and the context, (including existing safeguards and potential narrowly circumscribed applications). It is also unclear how an international approach could be achieved given the plethora of national approaches to regulating the human genome, where countries have adopted starkly opposing views, informed by culture and religion. If a global policy on germ-line gene editing were to be adopted, a key question is how a consensus view could be achieved without compromising these strongly held convictions.

10. **Significant decisions that need to be taken/responsibility for decision making**

In the UK, through the HFEA and other organisations, we have good frameworks in place to manage and regulate the use of germline editing, and other regulation to manage the production and use of genetically modified organisms and gene therapy. The recent discussions and consultations on mitochondrial donation provide an excellent framework to guide the discussion on genome editing, particularly germline editing. It is important that research proceeds on a proportionate basis, with oversight from statutory agencies, to ensure that research is licensed and is necessary and proportionate. If research proceeds in this way, we support calls to legalise germ line gene editing research in the UK on the basis that it could vastly increase our understanding of basic science.

11. **Equity and equitable access**

Genome editing has already been used in the UK to treat acute lymphoblastic leukaemia in a one-year old girl, who received a treatment containing edited T cells from a donor. In this case the team treating the girl were involved in research into this new method and were able to obtain a compassionate use dispensation to try the treatment. However since genome editing also has the potential to have an impact on diseases where treatment options are limited or non-existent: for example Duchenne muscular dystrophy, retinitis pigmentosa, and blood disorders such as sickle cell anaemia, there is likely to be increased demand for these technologies in the future. Whilst these technologies will initially be developed in the research arena

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1 The Human Fertilisation and Embryology Act 1990

2 The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015
by specialist centres, it is important that once they become ready for clinical implementation (i.e. they have been established as safe and effective) that they are commissioned as specialist NHS treatments, to ensure that there is equity of access across the NHS.

12. From a global perspective, there is potential for genome editing to be adopted preferentially by highly developed countries. However the technology of gene editing is likely to generate new knowledge that could ultimately be universally beneficial.

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