



Workshop on ethical and regulatory challenges in Genome editing

22 April 2015

Nuffield Council on Bioethics, The Nuffield Foundation, 28 Bedford Square, London WC1B 3JS, 10.00- 16.00

Background to the workshop

1. Genome editing has rapidly emerged as a potentially transformative technology within the life sciences, particularly since the development of the CRISPR-Cas9 system in 2011. It has opened up a wide range of opportunities for manipulating DNA, from plant breeding to biomedicine, and revived a number of highly contested issues within bioethics. The challenge to participants in the workshop was to identify what 'important and distinctive contribution' the Council might make in this area. Three broad areas of current and future applications – to plants, animals, and humans – as well as the over-arching category of cross-cutting issues were considered.
2. The day was divided into three sessions: two morning sessions (each comprising two presentations and discussion) to provide an overview of the state of the art and the most important areas of potential application, and an afternoon 'workshop' session during which attendees were divided into four groups to develop ideas around the four key themes. The results of these discussions were then fed back and discussed by all attendees. The workshop was chaired by Council Member Dr Andy Greenfield.
3. Prior to the workshop, participants had been asked to submit approximately 300 words on what original and valuable contribution the Council could make to the emerging ethical debate in this area. Their responses were tabled at the

workshop as a departure point for discussions, along with additional submissions received from interested stakeholders elicited via a post on the Council's *Nuff' said* blog. Participants also received supplementary materials including a [commissioned background paper](#).

Presentations

The science of genome editing – current techniques, capabilities and potentialities

4. Targeted genome engineering was not applied in mammals before 1989, when different lines of research converged to produce the first targeted mutations in living mice and in cultured murine stem cells. The work was conducted by Mario R. Capecchi, Sir Martin J. Evans and Oliver Smithies and recognised in the 2007 Nobel Prize in Physiology or Medicine. This overall approach was powerful in both disease modelling and development of basic biology. It had, however, also a number of drawbacks in being rather slow, limited to one gene at a time, expensive, labour-intensive and requiring specialist skills.
5. The search for alternative models led, in 2005, to the development of 'conserved steps' genome targeting which combines a targeted cut (metaphorically: 'molecular scissors' guided by a 'biological satnav') and subsequent repair by the cell. These tools are very precise and are exemplified by two major platforms: zinc finger nucleases (ZFNs,) and transcription-activator like effector nucleases (TALENs). Each comprises a 'satnav' that is physically linked to the 'scissors' – the bacterial enzyme Fok1. Drawbacks of ZFNs are that their design and production is relatively demanding and requires expert knowledge. TALEN design is less difficult, but although the technology is very specific, it does not allow for multiplexing (simultaneous modification at multiple sites in the genome).
6. The CRISPR-Cas9 (CC9) system was derived from a defence system against viruses in bacteria and archaea. (CRISPR stands for 'clustered regularly interspaced short palindromic repeats', short repeat segments of prokaryotic DNA), and Cas9 is the protein that performs the molecular cut. It was reported in seminal papers by Jinek et al. in 2012,¹ which first described the system as

¹ Jinek M, Chylinski K, Fonfara I *et al.* (2012) A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity *Science* **337(6096)**: 816-21.

programmable, and Mali et al. in 2013,² which showed that the system worked very efficiently in human cells, instantly focussing considerable attention onto the emerging field.

7. As in previous approaches, CC9 uses molecular 'scissors' and a 'satnav' but here these elements are separate, and the 'satnav' is not a protein, but a guide RNA (gRNA) and the 'scissors' the Cas9 protein.
8. In the CC9 system, once DNA has been cut it is repaired by one of two main mechanisms that are part of the cellular machinery: a 'cut and paste' repair mechanism (non-homologous end-joining, NHEJ), and a 'cut and bridge' repair mechanism (homology-directed repair, HDR). The NHEJ mechanism is imperfect and relatively error-prone in comparison to HDR.
9. The overall advantages of the CC9 system relative to other genome targeting systems are considerable:
 - one protein design (Cas9) fits all;
 - gRNA design and fabrication is relatively straightforward;
 - it can be used as a multiplex system to modify different parts of the genome at the same time
10. Different genome editing technologies have differing efficiencies, but there are few studies from which reliable comparisons may be made. Calculations for mouse zygotes (1-cell embryo stage) suggest that the use of CC9 increases efficiency substantially in comparison to ZFNs and TALENs.³
11. CC9 as delivered by ICSI (intracytoplasmic sperm injection into unfertilized mammalian eggs) has been shown in mice to be efficient and rapid to exploit the non-homologous end-joining repair mechanism.⁴ The combination of ICSI

² Mali P, Yang L, Esvelt KM *et al.* (2013) RNA-guided human genome engineering via Cas9 *Science* **339(6121)**: 823-6.

³ Cui X, Ji D, Fisher DA, *et al.* (2011) Targeted integration in rat and mouse embryos with zinc-finger nucleases. *Nature Biotechnology* **29(1)**: 64-67; Wang H, Yang H, Shivalila CS, *et al.* (2013) One-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-mediated genome engineering *Cell* **15(4)**: 910-918.

⁴ Suzuki T, Asami M and Perry ACF (2014) Asymmetric parental genome engineering by Cas9 during mouse meiotic exit *Scientific Reports* **4**: 7621.

and CC9 has received attention since about 65% of all assisted human reproduction cycles are ICSI (latest figures from 2007).⁵

12. Challenging aspects are that, as a young technology, the properties of CC9 are insufficiently delineated and it is inherently less specific than ZFNs and TALENs. Against this, progress has already been made to reduce off-target effects by improving the target-specificity of Cas9 (for example with 'nickases', enzymes that cause single-stranded breaks in duplex DNA), and of gRNA. Issues surrounding off-target effects might also be mitigated by advances in single-cell whole-genome sequencing technology. Work ongoing in other species might deliver further insights.⁶ However, as CC9 is already a highly evolved system, it is unclear to what extent it can be further improved.
13. Potential applications of CC9 technology include:
 - basic science, e.g. removal or alteration of DNA sequences to study their function
 - optimisation of disease modelling
 - veterinary applications: generation of disease-resistant animals, agricultural improvement; reduction of human pathogen reservoirs (e.g. swine flu)
 - human clinical applications: xenotransplantation, models to evaluate therapeutics (e.g. regenerative stem cell derivatives) prior to clinical trials, non-germ line gene therapy in adults, and germ line genome modification
14. The outcome of targeted genome modification by CC9 is not qualitatively different from that wrought by other systems, but the higher efficiency of CC9 represents a step-change that brings routine mammalian genome engineering within reach. It remains to be seen, however, whether the risk of irreducible off-target effects precludes certain applications.
15. Some significant questions and considerations concern:
 - the power of multiplex targeting and whether it can be made transient; multiplexing and aberrant effects;

⁵ Ishihara O, Adamson GD, Dyer S et al. (2015) International committee for monitoring assisted reproductive technologies: world report on assisted reproductive technologies, 2007 *Fertility and Sterility* **103(2)**: 402-413 e11.

⁶ Ran FA, Cong L, Yan WX et al. (2015) In vivo genome editing using *Staphylococcus aureus* Cas9 *Nature* **520(7546)**: 186-91.

- the influence of epigenetic marks;
- whether there is a more specific vision regarding future applications among users of these technologies and if so, if it is sufficiently explicit and open to broader debate
- the role of basic science – limits in understanding genetics and biology in the development of applications of the CC9 system, including medical applications in humans

Genome editing in plant science and agricultural biotechnology

16. Genome editing with CC9 was presented in the context of alternative strategies for plant genetic modification such as the use of TAL effectors (TALENs), zinc finger nucleases (ZFNs), oligonucleotide-directed mutagenesis and meganucleases. Many of the underlying principles are shared by CC9-mediated genome modification in other systems (e.g. mammals): genome editing appears to allow ‘ultimate fidelity’ through site-specific targeting and greatly improves ease of use. One hallmark of the technology is that the induced changes in organisms are not necessarily traceable, so that they might be indistinguishable from naturally occurring variation. It was suggested that this might be problematic for regulation and, as a consequence, might give rise to a lack of trust among users or consumers in scientists and regulators working in this area.
17. Other editing and modification approaches and some of their features are:
- use of TAL effectors: these provide better modularity (which might have an impact on the study of epigenetics), but not the same ease of use. Modularity is also being evaluated with a view to improving CRISPR-Cas9, but not yet in plants
 - ODM (oligonucleotide-directed mutagenesis): ‘replacement technology’ in which no foreign molecules are integrated, however, low frequency, and therefore restricted in application
 - Zinc finger nucleases (ZFN): are considered outdated, and are not used anymore in plants
 - Meganucleases (sequence-specific endonucleases targeting long recognition sites): complicated to customise

18. CC9 is already by far the most frequently used system in basic plant science, while in mammalian cells other options beyond site-specific cutting are available, including those that allow multiplexing.
19. Current plant editing proceeds by the design of a 'satnav' and 'scissors'. These are expressed from DNA introduced by *Agrobacterium tumefaciens*, DNA transfection or a 'gene gun'. The resulting transgenic plants can be either regenerated directly or edited cells from them can be selected, and plants subsequently regenerated.
20. Plants that have been edited so far include the standard models, *Arabidopsis* sp., tobacco, and *Brachypodium* sp. as well as economically relevant crops such as tomato, maize, millet, rice, wheat, and sweet orange.
21. Plant science applications of genome editing technologies that have been proposed are:
 - basic science
 - identification of new targets for crop improvement
 - removal of antinutritionals and allergenic or toxic substances
 - accumulation of valuable metabolites
 - engineering of disease resistance (e.g. rice resistance to *Xanthomonas oryzae*, causing leaf blight; wheat resistance to powdery mildew)
 - removal of traits negatively affecting quality, storage or processing
 - product development (e.g. fragrant rice)
22. Technological developments with a potential impact on genome editing are:
 - safe harbour integration (a region of the genome that is considered to be both transcriptionally active and the disruption of which does not lead to adverse effects)
 - localised trait stacking (producing transformed plants by combining two or more genes of interest)
 - tissue-/organ-specific editing
 - non-integrative editing (leaving no DNA residue)
 - epigenetics (e.g. changed methylation status)
23. Bottlenecks of applying genome editing in plants are:
 - the low frequency of homology-directed repair (HDR) in plants

- editing tools are integrated as transgenes into the organism
- off-target effects
- on-target, but inappropriate/unwanted genetic alterations
- mutations generated when cells are cultured
- the lack of single-gene traits with economic relevance
- lack of basic science understanding

Genome editing in animals

24. The focus of research to date is on genome editing applications in mammals such as monkeys and, for agricultural applications, in livestock species including pigs (currently the most promising research species), goats, sheep and chickens. In these areas of research and application, CC9 technology is accessible, easy to handle and cost-effective. These factors may increase the complexity of the ethical issues involved, albeit that those issues may not be substantially new.
25. Current genome editing projects and potential future applications are in:
- agriculture, e.g. commercial fish farming
 - models of human disease
 - xenotransplantation, where much progress has been made
 - pharming (genetic engineering of farm animals to produce pharmaceuticals)
 - cell/protein bioreactors (for the synthesis of pharmaceutical protein complexes)
 - disease resilience and resistance of livestock, e.g. pig virus ASFV (causing a lethal hemorrhagic disease of domestic swine with high economic impact in Africa and other parts of the world) and RELA gene (associated with African swine fever virus infection)⁷
 - enhanced growth and reproduction
 - disease vector management in ecosystems (e.g. mosquitoes that transmit Malaria and Dengue fever) and other wildlife applications, in particular when combined with 'gene drives' to accelerate proliferation of traits in populations (e.g. to control insect pests or reverse herbicide resistance in weeds)

⁷ Lilloco SG, Proudfoot C, Carlson DF et al. (2013) Live pigs produced from genome edited zygotes *Scientific Reports* **3(2847)**: 1-4.

- new applications in agriculture (livestock), e.g. commercially important birds, in particular, the chicken – however, some of these advances are contingent on an improved understanding of how to manipulate chicken zygotes and cleavage-stage embryos
26. These advances have led to an increase in media interest and attention by regulatory and funding bodies as well as the commercial (research) sector. A distinctive factor characterising these developments is a perceived need to advance applications in livestock given the projected steep increase in world population and a need for sustainable agricultural output. Such applications are likely to engage public opinion, which may have a significant effect on the manner in which they are adopted.

Current and future applications to humans, human tissue and human cells

27. Novel considerations around the application of genome editing for human genetic engineering derive from the specificity and simplicity of CC9 in comparison to previous methods and the possibility of efficient somatic as well as germ line modification.
28. There are, however, a number of technical and biological issues that might limit potential uses, in particular:
- off-target effects
 - on target but unwanted effects
 - mosaicism (desired changes not effective in all/enough cells)
 - altered cells would need a genetic advantage over other cells to be safely and effectively grafted back into humans, and it is not clear yet how such an advantage might be established without also increasing risks, for example, of cancer
29. Current and potential future applications are in the areas of:
- basic understanding of the role of specific genes and processes in certain cell types, such as
 - organ-specific stem cells in the gut, neural stem cells, spermatogonial stem cells;

- o pluripotent stem cells, including applications with relevance to germ line modification, such as 'gastruloids' (mouse embryonic stem cells exhibiting behaviour similar to cells in the early mouse embryo *in vitro*) and primordial germ cells;
 - o preimplantation embryos, where work in mouse models might not be as relevant to early human development as previously thought)
 - for the creation and study of models of human genetic disease (*in vitro* and in animals)
 - to treat diseased somatic cells, such as in
 - o genetic disease affecting a specific cell type
 - o cancers
 - o agents of infectious disease (viruses, bacteria, parasites, etc.)
 - to avoid/prevent genetic disease (germ line therapy) through correcting genetic mutations in early embryos or in germ line stem cells (in subsequent generations).
30. Potential germ line applications could be in areas where existing techniques such as preimplantation genetic diagnosis (PGD) cannot be used or are inefficient. However, these are relatively few, for example, where the correction of Y chromosome defects is at stake; to eliminate or perhaps correct mutant mitochondrial DNA, in combination with PGD and prenatal diagnosis (PND) in dominant genetic disease (e.g. late onset, such as Huntington's; dominant genetic forms of Alzheimer's disease, or breast cancer) and for chromosomal rearrangements. Offset against this are the risks that are inherent to PGD (which may diminish with technological improvement), the lack of availability of unaffected embryos and the inherent wastefulness of PGD with regard to the number of embryos produced in relation to those that may be selected for transfer.
31. An important question would be whether, if the gene editing methods are very efficient and safe, they should supplant PGD as this would have the potential to remove the mutated gene and therefore the risk of genetic disease from families or the population (except for *de novo* mutations). This would potentially apply not only to highly penetrant mutations but also to those predisposing to disease.
32. There may also be prospects for genetic enhancement, e.g. in:
- disease resistance: infectious disease (e.g. HIV); cancer;
 - enhancing dietary tolerance (tolerance to lactose; gluten, etc.)

- alteration of traits in individuals (height; perfect pitch; genes for longevity) and introduction of 'non-human' traits (e.g. tolerance to cold; enhanced sensory systems)

Plenary discussion

33. Attendees were invited to identify the main areas of development and of potential ethical and regulatory impact. A number of areas and issues were raised:

- The influence of positive and negative visions among stakeholder groups for future applications of genome editing technologies and the potential for a confusion of priorities. Applications that are expected to provide commercial benefit are likely to be developed first, and these are more probable in agriculture. As a consequence, focussing predominantly on human germ line applications as the popular media have done can obscure some of these more likely early applications. These might be incremental rather than revolutionary, but have greater long term impact on agriculture as a whole. The availability of such technologies, e.g. improved disease-resistant crops, will, however, not necessarily alleviate hunger and the burden of disease in poor parts of the world, and may even distract from alternative approaches.
- Areas that need to be included in the ethical assessment are the impact of genome edited and/or synthetic organisms on the environment and how effectively these are covered by current international regulation and law (e.g. the Convention on Biological Diversity/ the Nagoya Protocol). These regulations already appear very complex and not necessarily effective, e.g. the mechanisms for compensating biodiversity-rich developing states when organisms leave their country of origin.
- Although ethical questions appear similar to issues raised in earlier debate about genetic engineering and genetically modified organisms, there appears to be an unprecedented urgency in the public debate with respect to some applications, which previously seemed 'science fiction'. This move 'from theory to actualisation' does not change the ethical questions and ethical approaches in themselves. However, what could

be seen as new are the potential for unimagined scope or scale, and the imminence of policy decisions on applications of the technology.

- It was considered that portraying genome editing as a solution to regulatory obstacles and reticent public opinion on genetic technology broadly conceived may be unhelpful. It is important to understand people's concerns rather than proceeding on the basis of insufficiently clarified assumptions about public opinion. For example, while products that evade EU GM legislation might be seen as a 'workaround', such an approach will not address or ease any fundamental concerns about the ethical, social, economic and political issues.
- From the perspective of the research sector (including the commercial research sector), there is large potential as CC9 is generally faster and cheaper than alternative approaches. The areas of immune oncology/immune cell therapy (engineering of T cells) and gene therapy for monogenic diseases are dynamic (with around 70 gene therapy trials currently ongoing). As an 'enabling' technology, there is also a perception of increasing opportunities to address more complex problems in the future, e.g. changing genes related to Alzheimer's (APOE gene); however, regulatory development may be necessary to keep pace with technological advance.
- In the field of human applications, UK law does not currently permit genome editing for human embryo modification and human germ line modification, which would require new legislation.
- A general aspect to consider in this debate is the potential for the 'fetishisation' of genes. This can also be fed by the excitement surrounding scientific and technological advances as expressed by scientists themselves, which in turn might feed 'gene-centrism': as a consequence, people may come to believe that genes have more influence than they actually do, and it remains a challenge to defuse these essentialist ideas.
- There is a need to re-open the debate on genetic engineering in the context of CC9 with a focus on germ line editing, notwithstanding the absence of conceptual novelty. This might provide an opportunity to reframe some of the issues constructively, for example, away from genetic determinism. If we assume it is acceptable to modify genes in

general, what kind of decisions in research and applying genome editing would we then take?

- A related issue is the use of language around genome editing technology and the way in which it embeds conceptions of normality and naturalness.
- Future work in ethics in this area should look at specific cases and also ask further questions relevant to the healthcare system and the broader socio-economic context, e.g. who would pay for these interventions? It would be important to have both debates – the more general and the more specific one, and focus on who is making the relevant decisions.
- With regard to concepts and ideas that are prominent in bioethics, regulation and law, there is a need for clear and agreed terminology to address questions likely to arise in connection with genome editing, e.g. the debate around human dignity; the concept of a person and when it becomes applicable; and the notion of the ‘genome’.

Workshop feedback session

34. During the afternoon session, four tables were asked to discuss different aspects of genome editing to refine views on which issues and questions the Nuffield Council could most usefully examine in order to make a distinctive and relevant contribution in this area.

Plant applications

35. The group considered this area to be definitely appropriate for a Nuffield Council project, although it should not be focussed on one particular technology but rather on ‘next-generation plant breeding’ and its impact on, e.g. food supply and/ or a vision for future agriculture more generally.
36. A key issue in this area is the risk assessment and regulation of new products, which may become less effective due to the speed of implementation and efficiency of available and developing technologies. With the imminent arrival of technologies outlined at the meeting, this area is

clearly time-sensitive and issues could 'scale up' quickly leaving insufficient time for conceptual analysis and risk assessment. Currently, regulatory decisions on modified organisms are based on the procedure for introducing changes in DNA and not the outcome/ product and potential risks. If it becomes impossible to detect whether a product is genetically modified, or where it is produced in another jurisdiction, regulation may lose its purchase.

37. A consideration of criteria for ethical regulation would be useful as it is currently missing in the EU; this should include how to manage the introduction of new products and assess its implications, although there is an expectation that with the anticipated change of scale and broader range of territories involved it will become harder to control products in international markets. The traceability of gene-edited products and enforcement of such regulation is likely to be inefficient, leaving regulatory loopholes.
38. Another issue of concern is access to the new technologies to larger and more diverse groups of users. The CC9 genome editing technology is more affordable and accessible than its predecessors. This may reduce commercial barriers to market entry, offering advantages for small companies or empowering communities. Alternatively, small users might be out-competed or pressured to use proprietary technologies provided by more powerful actors. The assessment of such consequences cannot easily be carried out in advance and possibly only in broad terms; in addition, social context evolves over time; and there might also be changes in power balance between consumers and industries. In theory, accessibility of the technology and diversification of use for different agricultural needs in different parts of the world, for example, should become easier as the potential for 'customisation' is a central feature of the technology.
39. The potential for customisation might also be harnessed for dual-use/ bio-terrorism. Effectiveness of regulation in this area might be impeded by the 'invisibility' of the technology.
40. To be able to inform the public and other stakeholders, there is a need for more transparency and easily available information on how products are being introduced. The public might not be primarily concerned about being offered gene-edited products but more about being informed and involved. This could seem rather 'top-down', however, and there is a need to accommodate diversity of opinion and culture in any approach to public engagement. Scientists, for example, might tend to consider the short-term implications of their research to the exclusion of its broader implications. The

range of knock-on effects may not be obvious – such as the cultural and religious significance of particular organisms or environments – and they are often only considered after research with commercial involvement has already started.

41. The benefits of plant genome editing are not visible for the greater public. Any perception of societal benefit can be overturned with a single untoward incident. This risk is partly due to ineffective communication, but it is not sufficiently on the agenda of scientists who sometimes appear unaware of the dynamics of public debate.
42. Addressing these issues can be difficult given the speed of advance. For example, assessing implications is limited by using ‘genome editing’ as a very broad umbrella term. The term ‘editing’ was also perceived to have negative implications.

Animal applications

43. Issues concerning genome editing applications seemed to the group to be a very timely subject for a potential report as developments in this field and regulatory impact have recently accelerated (e.g. several cases of engineered animals are under consideration by the FDA in the US).
44. The inclusion of such applications would present an opportunity to revisit issues that, although well discussed were nevertheless not fully resolved, such as future foods and the shape of future agriculture more generally, risks attached to different technologies and the control of unintended effects (see, in particular, recent attention to ‘gene drives’).
45. As in the GM debate, the public is not only concerned about emerging scientific developments, but there is a new urgency to the debate on its applications; for example, new food products resulting from editing might be imminent. The proximity of this real world impact changes the nature of the debate. The Council could also revisit unresolved conceptual issues that arise such as the value of ‘authenticity’ and questions about species distinctions.
46. Advances in genome editing might lead to an increase in the use of animals, both for food/agricultural products and in research but also confront us with questions regarding our relationships to, and treatment of animals more generally, as well as regarding agriculture and agricultural practices as a

whole. Some suggest, for example, that technological 'solutions' are in fact a doomed attempt to fix something that is 'inherently broken' (e.g. in relation to 'factory farming').

47. Effects on 'natural ecology' and our relationship with it could be considered, for instance in regard to re-engineering extinct species and the creation of new ones.
48. Other aspects of animal applications raising ethical issues include biosecurity, questions related to species boundaries and the instrumental use of non-human primates, humanising animals and producing tissues for xenotransplantation.
49. Consideration of regulation was felt to be necessary, in particular the aspects of traceability and transparency. Questions suggested included:
 - Does it make a difference if changes in organisms cannot be detected?
 - What are the merits of trait-based v. process-based regulation?
 - Is international regulation, including regulation in related areas such as the Convention on Biological Diversity, coherent, proportionate and effective?
 - What are the implications for intellectual property, and for public trust in relation to new products and emerging markets?
50. The scope of such a project starting from animal applications is potentially extremely wide and should be carefully circumscribed as the framework will influence how the issues are understood, for example, whether ethical questions should be presented as comparing animal and plant applications, or rather as affecting agriculture generally.
51. Another important way in which the work of the Council could influence policy would be in discussing and delineating research priorities and the allocation of research funding in this area.
52. Other issues noted concerned applications in the areas of human disease vectors and companion animals.

Human applications

53. This area seemed to the group to be ostensibly the most contentious, at least in relation to how options are presented to the wider public. There is

insufficient easily-accessible information available to the wider public and this paucity should be addressed, including issues such as scope of technological advance, scientific and social goals, and future visions for the technology.

54. There appears to be an ethically relevant distinction between somatic cell editing (and its various applications) and germ-line applications, with the first not being as contentious while the germ-line applications raise more complex questions.
55. It is unclear at present, however, whether and to what extent there are useful clinical applications for the latter. In any case, the relevant level of safety would need to be established and then demonstrated.
56. The possibility of curing diseases v. enhancement was raised, with examples mentioned including Alzheimer's disease and influenza. Questions raised included how to define the likely benefits and how to establish these in diverse cases. A related issue mentioned was the use of finite resources for applications that might not be clinically important. A related consideration was commercial interest in the area and its short and longer-term implications.
57. The group considered that gene therapy could relatively quickly become more common with genome editing, although it seemed more likely that next-generation sequencing technology and PGD will be a preferred strategy if available. This might also mean that potential targets for gene therapy increase, feeding expectations of further applications.
58. Any work undertaken by the Council should try to 'future-proof' these considerations by making them technology-neutral.

Cross-cutting issues

59. The group framed the issues in this broad area by asking the following question: are there common conditions in the areas of plant, animal, and human application or should they be treated separately?
60. They concluded that the pace of transformation resulting from the availability of genome editing technologies has a wide-reaching impact on the ethical landscape.
61. Another common theme was the need to define the components of what would constitute a 'fair' governance system.

62. A third prominent issue was the promotion or constraints on the wide diffusion of benefits generated by the technology and the impact of patenting in this respect. The Council could consider how the issue of access might transform the ethical landscape.
63. A final and overarching issue was how to create and sustain the conditions for an informed public debate and, in return, how particular responses and positions are conditioned or influenced by public opinion.

General concluding discussion

64. In summing up, the following suggestions with regard to the focus and scope of a new Council project were made:
 - A decision has to be made on whether initially to cover the broad scope of applications of genome editing, or rather to focus more narrowly on a specified subset. One proposal was to cover applications in plants, animals, and humans or to cover agriculture and medicine (broadly conceived), either in succession or in parallel, but not in one single full report. The broad conception would make it unfeasible to keep focus on contentious areas of applications and make it harder to keep all relevant technological developments in view. This led to the proposal of a modular approach, which might not be explicitly about 'genome editing' at all.
 - Alternatively, and given a perception of wide public concern, the intended piece of work could primarily address challenges in human applications, and add considerations in other fields, perhaps with agriculture as a 'linking' topic. However, this might arguably point to a 'human exceptionalism' approach; a more overarching topic might be the 'ethics of stewardship of nature'.
 - It was noted that the debate at the workshop did not include the important areas of bacterial or viral applications, which might also have implications for distinguishing fields of applications by reference to 'species' and might be considered as separate areas of work.
 - The Council could usefully create and provide a 'go-to resource' or relevant documents that contain impartial information and scientific

data. A related task might be to clarify the issues and concerns more helpfully than was the case in earlier debates about GM.

- Important considerations relate to the effects of globalised research (including different cultural aspects). Separate reports could tackle cultural diversity more efficiently and in more depth. It was suggested, although not unproblematically, that, for example, there is a more negative attitude to genetically-modified foods in Europe than in the USA, where, conversely, medical applications are highly contentious.

Programme

9.30	Coffee available	
10.00	Welcome and introduction	Andy Greenfield, Chair
10.15	Presentation 1: the science of genome editing – current techniques, capabilities and potentialities	Anthony Perry
10.45	Presentation 2: current and future genome editing applications in plant science and agricultural biotechnology	Sebastian Schornack
11.15	Coffee	
11.30	Presentation 3: current and future genome editing applications in animal biotechnology	Bruce Whitelaw
12.00	Presentation 4: current and future genome editing applications in humans	Robin Lovell-Badge
12.30	Chaired discussion	
13.00	Lunch	
13.45	Welcome back and instructions for afternoon session	Andy Greenfield
13.55	Group discussions of key themes	
14.40	Feedback from tables and chaired discussion	
15.45	Wrap-up and close	Andy Greenfield

Attendees

Guests

Dr Sarion Bowers

Research Policy Advisor, Wellcome Trust Sanger Institute, Hinxton, Cambridgeshire

Dr Paul Burrows

Executive Director, Corporate Policy and Strategy, Biotechnology and Biological Sciences Research Council (BBSRC)

Dr Sarah Chan

Deputy Director of Institute for Science, Ethics and Innovation (ISEI) & Research Fellow in Bioethics and Law, University of Manchester

Professor Jim Dunwell

Crops research group, School of Agriculture, Policy and Development, University of Reading

Professor John Dupré

Director, Centre for the Study of Life Sciences (Egenis); Professor of Philosophy of Science, University of Exeter

Mike Edbury

Head of Risk and Regulation, Government Office for Science

Professor Andrew George

Deputy Vice-Chancellor (Education and International), Brunel University London; Chair of the National Research Ethics Advisors' Panel

Alison Hall

Programme Lead (Humanities), PHG Foundation

Julian Hitchcock

Counsel, Lawford Davies Denoon life science law firm

Dr Michael Hopkins

Science Policy Research Unit (SPRU), University of Sussex

Dr Ian Hudson

Chief Executive, Medicines and Healthcare Products Regulatory Agency (MHRA)

Dr Victoria King

Senior Portfolio Developer, Genetics and Molecular Sciences, Wellcome Trust

Dr Robin Lovell-Badge

Group Leader and Head of the Division of Stem Cell Biology and Developmental Genetics, Francis Crick Institute, London

Dr Claire Marris

Department of Social Science, Health and Medicine, King's College London

Dr Menelas Pangalos

Executive Vice President, Innovative Medicines and Early Development Biotech Unit, AstraZeneca

Dr Patrick Middleton

Head of Engagement, Biotechnology and Biological Sciences Research Council (BBSRC)

Dr Anthony Perry

Laboratory of Mammalian Molecular Embryology, University of Bath

Dr Sue Price

Consultant in Clinical Genetics; Human Fertilisation and Embryology Authority (HFEA)

Dr Sarah Rappaport

Policy Officer, Wellcome Trust

Dr Sebastian Schornack

Research Group Leader, The Sainsbury Laboratory, University of Cambridge

Dr Sarah Testori

Human Fertilisation and Embryology Authority (HFEA)

Keith Thompson

CEO, Cell Therapy Catapult

Michael Walsh

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