NUFFIELD COUNCIL ON BIOETHICS

Identifying key developments, issues and questions relating to techniques of genome editing with engineered nucleases.

Background paper

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Summary

1. This paper discusses scientific, ethical and governance aspects of genome editing with engineered nucleases. First, the scientific state of the art for three major genome editing techniques and their current applications in humans, animals and plants are discussed. Ethical concepts and issues arising from these technologies are then identified. The next section raises considerations pertaining to governance of genome editing. Finally, questions for the Council to consider are raised.

Introduction

2. Genome sequencing and similar initiatives have increased our understanding of the structure of the genome in many organisms. However, an inability to precisely manipulate any chosen base pair in a genome (particularly in more complex cells and species) has meant that functional understandings of genes have lagged behind.[1]

[1] Gersbach CA. (2014) "Genome engineering: the next genomic revolution." *Nature Methods,* 11(10): 1009-1011; Gersbach CA, Gaj T, and Barbas CF. (2014) "Comparing Genome Editing Technologies." G*enetic Engineering & Biotechnology News,* 34(5): 1, 32-34. It may be noted that there have been other tools that could precisely modify a sequence, such as the "hit and run" method. Other tools such as ENU chemical mutagenesis were also capable of subtly altering the genome. However, these methods were slow and complex.

3. Developments in genome editing using engineered nucleases (endonucleases) are intended to facilitate researchers to precisely alter genes or genomes in many species. Genome editing has been said to be revolutionising biology.[2] If these techniques continue to show success, it will be possible to alter or replace virtually any component of any genome; from a single base pair of DNA to a whole gene or series of genes.

4. Two features of genome editing together set it apart from previous techniques: (i) it can make very specific and precise changes to the genome, with decreasing error rates; and (ii) it is often simpler and less expensive to establish in basic science laboratories, when compared with other techniques previously used to alter the genome. To this end, genome editing may be a disruptive technology, in that its implementation may have "the capability to overthrow the current dominant technology…"[3]

5. Genome editing will give rise to ethical considerations. Given both the improved precision of genome editing and its broad potential applications, issues that have already been considered surrounding genetic modification may need to be re-visited. It appears that genome editing does not raise any significant new ethical concerns arising from the application of the techniques themselves, but that their likely broad applicability as well as their precision give rise to concerns of *scope* that may change the ethical and governance landscape. This technology presents us with the possibility of a 'tipping point' in genetic modification that will require reassessment of the ethics, policy, governance and law surrounding its use.

6. Genome editing also offers opportunities to consider optimal strategies for governance in this emerging field. At present it appears that much genome editing will be subject to existing local and EU laws. However, these are imperfect and genome editing may provide further impetus for revisiting legal regulation more broadly. Genome editing also offers opportunity to consider and evaluate approaches to governance; to consider the value that explicit governance would have; and to deliberate what might contribute to an ideal governance approach.

State of the Art: the Science of Genome Editing

7. Editing a genome involves introducing a change to a chosen target site within a cell. The change can take numerous forms, from introducing a targeted small

[2] Kuzhabekovaa A, Kuzma J. (2014) "Mapping the emerging field of genome editing." *Technology Analysis & Strategic Management*, 26(3): 321-352.

[3] Trisolino A. (2014) "Nanomedicine: Building a Bridge Between Science and Law." *Nanoethics*, 8: 141-163. Note that this definition has been given in the context of nanotechnology; however it may be readily applicable to other emerging and emergent biotechnologies, including genome editing.

deletion to effecting a precise and targeted sequence change. Genome editing has resulted from combining knowledge about protein chemistry and DNA cleavage to develop new systems to create desired changes to a given gene(s) or genome.[4] Applications of genome editing are diverse and potentially limitless.[5]

Techniques of genome editing with engineered nucleases

8. Genome editing methods have two main steps: (i) an engineered nuclease (endonuclease) is either made in the laboratory or allowed to self-assemble inside a cell, to then cut a desired sequence in the genome; and (ii) a cell's inherent DNA repair machinery will then repair the cut and introduce the desired change.[6]

9. Endonucleases are proteins that fuse a customisable domain (which binds to a chosen DNA sequence) with a nuclease that can cut DNA.[7] Endonucleases can introduce a variety of changes to a cell, including single base pair changes or insertion/deletion of whole genes.[8]

10. All cells utilise two main DNA repair mechanisms.[9] The first is nonhomologous end-joining (NHEJ). Here, cleaved ends are joined back together via an efficient but error-prone process. The second is homology-directed repair (HDR), in which an external DNA fragment acts as a homologous template for the repair. This method is more accurate but less efficient than NHEJ. In genome editing, NHEJ effects a 'knockout' of gene function, while HDR can be used to edit single nucleotides or to introduce other precise changes.[10]

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[4] Segal DJ, Meckler JF. (2013) "Genome engineering at the dawn of the golden age." *Annual Reviews of Genomics and Human Genetics*, 14: 135–58; Perez-Pinera P, Ousterout DG, Gersbach CA. (2012) "Advances in targeted genome editing." *Current Opinion in Chemical Biology,* 16: 268-277; and Gaj T, Gersbach CA, Barbas CF. (2013) "ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering." *Trends in Biotechnology*, 31(7): 397-405.

[5] Gersbach CA. (2014) "Genome engineering: the next genomic revolution." *Nature Methods,* 11(10): 1009-1011, p1010.

[6] de Souza N. (2012) "Primer: Genome editing with engineered nucleases." *Nature Methods,* 9(1): 27; Ciccia A, Elledge SJ. (2010) "The DNA damage response: making it safe to play with knives." *Molecular Cell*, 40: 179–204. For a helpful summary of these techniques, see: Science Media Centre (2014) "Genome Editing". Fact Sheet. Available at: http://bit.ly/13Alz0q (Accessed 18 December 2014).

[7] Joung JK, Sander JD. (2013) "TALENs: A widely applicable technology for targeted genome editing." *Nature Reviews Molecular Cell Biology*, 14(1): 49-55.

[8] For a review, see: Zhang F, Wen Y, Guo X. (2014) "CRISPR/Cas9 for genome editing: progress, implications and challenges." *Human Molecular Genetics*, 23(Review Issue 1): R40-R46.

[9] For a more detailed explanation of these methods, see: Lieber, MR. (2010) "The Mechanism of Double-Strand DNA Break Repair by the Nonhomologous DNA End Joining Pathway." *Annual Reviews of Biochemistry*, 79: 181-211.

[10] Reviewed by: Joung JK, Sander JD. (2013) "TALENs: A widely applicable technology for targeted genome editing." *Nature Reviews Molecular Cell Biology*, 14(1): 49-55; Lombardo A, Naldini L. (2014) "Genome editing: A tool for research and therapy: Targeted genome editing hits the clinic."

11. Three main approaches to genome editing have emerged: zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPR).[11]

12. **Zinc Finger Nucleases (ZFNs)** were among the first genome editing technologies.[12] Existing knowledge about how zinc finger proteins recognise and bind to DNA has now enabled synthetic proteins to be created that incorporate the DNA binding domain of zinc finger proteins. Each zinc 'finger' binds to a DNA sequence of 3 base pairs. Zinc Finger Nucleases (ZFNs) were subsequently created by fusing several linked 'fingers' to a sub-part of an endonuclease called the Fok-1 endonuclease. ZFNs will recognise 18-36 base-pair DNA sequences.[13]

13. The method by which Fok-1 works means that ZFNs need to work in pairs (dimers), each binding to one strand of the target DNA sequence. Designing a ZFN therefore requires significant technical expertise. This, combined with other limitations such as a need to screen many potential ZFNs to find suitable matches and the (then) cost of DNA synthesis, meant that ZFN technology has not become widely used.

14. **Transcription Activator-Like Effector Nucleases (TALENs)** are derived from pathogenic bacteria found in plants.[14] They are more accurate than ZFNs, as the binding DNA sequence is longer.[15] Researchers have created synthetic TALEs and fused them to the same sub-part of the Fok-1 endonuclease as for ZFNs to create TALENs, which bind to a target sequence of around 13 base pairs.[16]

15. Some limitations remain with TALENs. Every site in DNA to be targeted for cleaving requires a specific TALEN to be created. This requires specific expertise in recombinant DNA methodology and takes time. Further, TALE proteins are large; which led to difficulties in 'packaging' them up in delivery vehicles (vectors) to insert them into some kinds of cells.

Nature Medicine, 20: 1101-1103. HDR requires the desired DNA template to be introduced to the target cell together with the endonuclease.

[11] van der Oost J. (2013) "New tool for genome surgery." *Science,* 339: 768-9.

[12] Urnov FD, Rebar EJ, Holmes MC, *et al.* (2010) "Genome editing with engineered zinc finger nucleases." *Nature Reviews Genetics*, 11(9): 636-46.

[13] de Souza N. (2012) "Primer: Genome editing with engineered nucleases." *Nature Methods,* 9(1): 27.

[14] Joung JK, Sander JD. (2013) "TALENs: A widely applicable technology for targeted genome editing." *Nature Reviews Molecular Cell Biology*, 14(1): 49-55.

[15] Segal DJ, Meckler JF. (2013) "Genome engineering at the dawn of the golden age." *Annual Reviews of Genomics and Human Genetics*, 14: 135–58.

[16] de Souza N. (2012) "Primer: Genome editing with engineered nucleases." *Nature Methods,* 9(1): 27.

16. **Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9** genome editing comprises a Cas9 endonuclease guided to its target sequence by a specifically designed guide RNA (gRNA) of around 20 base pairs. It is a naturally occurring system in prokaryotic (simple) cells[17] but works in both simple and more complex cells.[18]

17. The CRISPR-Cas9 approach involves introducing both a messenger RNA (mRNA) encoding the Cas9 protein and a gRNA into a cell. The mRNA is then translated inside the cell to produce the Cas9 endonuclease *in vivo*, which in turn forms a complex with the gRNA. This complex then seeks out the target site of interest. Once binding has taken place, the Cas9 protein creates either a single- or double-stranded break in the DNA helix, which triggers the cell's inherent DNA repair processes.[19]

18. CRISPR-Cas9 offers advantages over ZFNs and TALENs in that the gRNA can be designed to match almost any sequence - which offers greater flexibility. No protein engineering is required. CRISPR-Cas9 also allows several gRNAs to be introduced to a cell at once, allowing multiple changes to be made simultaneously.[20]

19. No genome editing method is perfect. The Cas9 protein, for example, targets and binds to other places in the genome; a problem known as 'off-target' cleavage.[21] Additionally, while genome editing methods can encourage one method of DNA repair over the other, concerns remain that unwanted DNA repair events will still occur, particularly because HDR remains less efficient (and thus less common) than NHEJ.[22]

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[17] For further information, see: Gersbach CA. (2014) "Genome engineering: the next genomic revolution." *Nature Methods,* 11(10): 1009-1011.

[18] Mali P, Yang L, Esvelt KM, *et al*. (2013) "RNA-Guided Human Genome Engineering via Cas9." *Science* 339(6121): 823-826; Cong L, Ran FA, Cox D, *et al*. (2013) "Multiplex Genome Engineering Using CRISPR/Cas Systems." *Science*, 339: 819-823.

[19] Single stranded 'nicks' have emerged later than initial double-stranded cuts; as one mechanism to improve the accuracy of this technique.

[20] Cong L, Ran FA, Cox D, *et al*. (2013) "Multiplex Genome Engineering Using CRISPR/Cas Systems." *Science*, 339: 819-823.

[21] Reviewed by: Marx V. (2014) "Gene editing: how to stay on-target with CRISPR." *Nature Methods,* 11(10): 1021-1026; Segal DJ, Meckler JF. (2013) "Genome engineering at the dawn of the golden age." *Annual Reviews of Genomics and Human Genetics*, 14: 135–58; and Tsai SQ, Joung JK. (2014) "What's Changed with Genome Editing?" *Cell Stem Cell*, 15: 3-4.

[22] Joung JK, Sander JD. (2013) "TALENs: A widely applicable technology for targeted genome editing." *Nature Reviews Molecular Cell Biology*, 14(1): 49-55; Tsai SQ, Iafrate AJ, Joung JK. (2014) "Towards a functional understanding of variants for molecular diagnostics using genome editing". *Nature Medicine*, 20: 1103-04.

Applications of genome editing

20. Genome editing has putative applications in **gene or cellular therapies.** ZFNs have been shown to be able to be used in complex, as opposed to simple, cells.[23] TALENs has modified genes in human somatic and pluripotent stem cells.[24] Zygotic use of germline gene therapy using CRISPR-Cas9 limits the effects of Duchenne Muscular Dystrophy in mice.[25] Other heritable conditions that may be amenable to therapies utilising genome editing include sickle cell anaemia and cystic fibrosis.[26]

21. Genome editing may also have utility in treating HIV/AIDS. A ZFN that targets a gene involved in HIV infection is currently undergoing Phase 2 clinical trials.[27]

22. Genome editing will also have applications in **clinical medicine**, such as in cancer diagnosis or treatment.

23. Genome editing may also have applications in basic science, including **developmental** and **structural biology**, such as investigations of gene structure, function and regulation.[28] Targeted gene changes in cell lines could: help understand the role of specific mutations in tumorigenesis; introduce mutations to study drug resistance; or study cancer pathogenesis and treatment.[29]

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[23] Genovese P, Schiroli G, Escobar G, *et al*. (2014) "Targeted genome editing in human repopulating haematopoietic stem cells." *Nature,* 510: 235-240; Lombardo A, Naldini L. (2014) "Genome editing: A tool for research and therapy: Targeted genome editing hits the clinic." *Nature Medicine*, 20: 1101-1103.

[24] Reviewed by: Joung JK, Sander JD. (2013) "TALENs: A widely applicable technology for targeted genome editing." *Nature Reviews Molecular Cell Biology*, 14(1): 49-55.

[25] Long C, McAnally JR, Shelton JM, *et al.* (2014) "Prevention of muscular dystrophy in mice by CRISPR/Cas9-mediated editing of germline DNA." *Science*, 345(6201):1184-8. Cells took up the endonuclease with varying efficiency, however even mice showing low rates of uptake showed improvement.

[26] Joung JK, Sander JD. (2013) "TALENs: A widely applicable technology for targeted genome editing." *Nature Reviews Molecular Cell Biology*, 14(1): 49-55.

[27] For review, see: Lombardo A, Naldini L. (2014) "Genome editing: A tool for research and therapy: Targeted genome editing hits the clinic." *Nature Medicine*, 20: 1101-1103; Perez, E. E. et al. (2008) "Establishment of HIV-1 resistance in CD4+ T cells by genome editing using zinc-finger nucleases." Nature Biotechnology, 26: 808-816; Tebas P, Stein D, Tang WW. (2014) "Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV." *New England Journal of Medicine*, 370: 901-910.

[28] Perez-Pinera P, Ousterout DG, Gersbach CA. (2012) "Advances in targeted genome editing." *Current Opinion in Chemical Biology,* 16: 268–277.

[29] Tsai SQ, Iafrate AJ, Joyng JK. (2014) "Towards a functional understanding of variants for molecular diagnostics using genome editing". *Nature Medicine*, 20: 1103-04.

24. Genome editing is also being applied in **non-human animals.** CRISPR-Cas9 is being used in mice; a key 'model' organism.[30] The birth of transgenic monkeys (albeit mosaic ones) engineered using this system has also recently been reported.[31] Another study in pigs was able to create transgenic animals without them being mosaic; but only through combining genome editing with somatic cell nuclear transfer (cloning).[32] TALENS has been used in frogs, rats, pigs and cows; among others.[33]

25. Genome editing also has applications in **plants**, such as producing gene changes in crops more quickly than methods involving chemical mutagenesis. For example, ZFNs have been used to introduce herbicide resistance to crops such as tobacco and corn. These and other ZFN products are already being made available commercially. TALENs has been used to introduce infection resistance in rice.[34]

Is genome editing a discontinuous/disruptive technology?

26. No consensus has yet emerged as to whether genome editing is discontinuous with traditional genetic modification. It could be viewed as either an incremental or a disruptive/discontinuous technology (defined in paragraph 4 above). Differences include: having greater control and precision over sequence changes; greater effectiveness of the technology and fewer problems with "off target" insertions (which may influence risk assessments). However there are also similarities with existing genetic modifications: some of the changes that genome editing could give rise to include restoring normal gene function, similar to current gene therapy techniques. Concerns about "off target" effects will still arise.[35] A compromise view may therefore be that while the methods of genome

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[30] Editorial. (2014) "Genome editing for all." *Nature*.32(4): 295; Harms DW, Quadros RM, Seruggia D, *et al*. (2014) "Mouse Genome Editing Using the CRISPR/Cas System." *Current Protocols in Human Genetics,* 15.7.1-15.7.27.

[31] Niu Y, Shen B, Cui Y, *et al*. "Generation of gene-modified cynomolgus monkey via Cas9/RNA-mediated gene targeting in one-cell embryos." *Cell*, 156(4): 836-843. For a review, see: Cathomen T, Ehl S. (2014) "Translating the genomic revolution - targeted genome editing in primates." *New England Journal of Medicine,* 370(24): 2342-2345. This could lead to more precise models of neuropsychiatric conditions.

[32] Zhou X, Xin J, Fan N. (2014) "Generation of CRISPR/Cas9-mediated gene-targeted pigs via somatic cell nuclear transfer." *Cellular and Molecular Life Sciences*. doi10.1007/s00018-014-1744-7, published online 2 October 2014.

[33] Reviewed by: Joung JK, Sander JD. (2013) "TALENs: A widely applicable technology for targeted genome editing." *Nature Reviews Molecular Cell Biology*, 14(1): 49-55.

[34] Kathiria P, Eudes F. (2014) "Nucleases for genome editing in crops." *Biocatalysis and Agricultural Biotechnology,* 3: 14-19; Reviewed by: Joung JK, Sander JD. (2013) "TALENs: A widely applicable technology for targeted genome editing." *Nature Reviews Molecular Cell Biology*, 14(1): 49-55

[35] Kuzma J, Kokotovich A, Kuzhabekova A. (2012) "History Repeats Itself? Governance of New Methods for Targeted Genetic Modification in the U.S." Society for the Study of Nanoscience in

editing are continuous with previous tools, its applications or uptake may be disruptive.

27. An overarching consideration to the categorisation of genome editing as 'discontinuous' or 'disruptive' is what impact this should have on its ethical evaluation and governance.

Ethical issues in genome editing

28. As a form of genetic modification with broad application, genome editing automatically gives rise to a range of ethical considerations already explored in other contexts. Rather than reiterate these, the aim of this section is to identify how these considerations manifest in virtue of genome editing and what new concerns from its application have not arisen elsewhere.

29. Although some genome editing raises a specific instance of an established ethical concern, such as the possibility of unintended changes to the human genome, at this stage of development there appears to be little to support establishing a new ethical area of genome editing within the field of bioethics. However, this is not to say that genome editing does not give rise to any ethical issues.

30. The key ethical concerns raised by genome editing arise from the implications of the **scope** of the techniques. This is best captured by Gersbach: "[c]ollectively, these technologies have created a scientific paradigm that envisions the genome as an infinitely editable piece of software."[36] The development of genome editing could mean that we are able to quickly, efficiently, and cheaply alter the genome. This, in turn, allows the potential for changing many more aspects of the genome in humans, animals, plants and other organisms, and on a significantly greater scale than has previously been considered. Accordingly, we must ask whether and how significant increases in scope are ethically relevant.

31. One means of capturing the ethical relevance of scope is directly through consequentialist reasoning. If we increase the magnitude or scale of outcomes, this directly feeds into the analysis in terms of weighing up the positive and negative consequences of any activity. However, this approach is simply a means of accounting for 'more of the same' in terms of the already recognised ethical concerns surrounding genetic modification. There remains a question as to whether an increase in scope is ever able to create an additional ethical

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Society (S.NET) Annual Conference, University of Twente, Netherlands, October 22-25, 2012. Presentation available at: http://bit.ly/1yZGLF8 (accessed 17 December 2014).

[36] Gersbach CA. (2014) "Genome engineering: the next genomic revolution." *Nature Methods,* 11(10): 1009-1011, at p1010.

concern that did not arise from activity carried out at a lower level previously.

32. Normative reasoning surrounding issues of scope can become relevant when the activity in question reaches a level where it can precipitate significant change. This is a so-called 'tipping point' issue.[37] When applied to genome editing, this arises through it becoming widely available. As use increases, a tipping point is achieved where expectations are likely to rise to the point where genome editing would become a norm in many areas of life. This also makes its application potentially **disruptive**.

33. This potential increase in scope would have implications for our ethical evaluation and the need for policy, regulation and governance of genome editing. Current governance may no longer be sufficient to deal with the wider implications surrounding access, resources and social impact previously identified but only within the context of a much smaller scale. It is useful to consider analogous areas where this sort of phenomenon has manifested. One example, albeit on a smaller scale, is cosmetic surgery. This was initially developed in response to specific treatment demands for those with recognised significant debilitating conditions and was regulated as therapeutic surgery. As techniques improved and costs decreased, elective demand increased and a wider range of conditions were considered as suitable. With huge increase in availability and uptake, new regulation was required to manage the range of conditions, quality of procedure, resources, etc. that are considered as suitable for surgery.

Overarching ethical issues relevant to all applications of genome editing

34. There are some broad ethical issues that are relevant to all applications of genome editing. **Safety** will always be a concern with new techniques. Germ Line Modification (GLM) has well-recognised safety concerns and the ongoing instance of off-target mutations in genome editing means that safety should continue to be considered.[38] With therapeutic uses in humans where there are already existing beneficial treatments, risks from off-target cleavage need to be well managed.

35. In other areas, most notably those involving genetic modification to plants and animals, there is often a desire to utilise a **precautionary principle** approach, whereby (i) the activity is prohibited to protect us from harm in advance of

[37] The notion of a tipping point has been popularised recently by authors such as Gladwell M (2000) *The Tipping Point,* London: Abacus.

[38] Zhang F, Wen Y, Guo X. (2014) "CRISPR/Cas9 for genome editing: progress, implications and challenges." *Human Molecular Genetics*,23(Review Issue 1): R40–R46; Pauwels K, Podevin N, Breyer D, *et al*. (2014) "Engineering nucleases for gene targeting: safety and regulatory considerations." *New Biotechnology,* 31(1).

scientific certainty about its causes and (ii) the burden of proof is shifted to the proponent of an activity to show it is safe before use.[39] Whether this risk-aversion is a reasonable or overly cautious approach to take in general is open to debate but it is clear that it should not necessarily be a default position for any new technological development.[40] What evidentiary thresholds are required both in terms of potential benefits or harms by a newly developed technology is primarily a matter for regulators.

36. **Benefits:** The range and scope of genome editing mean that a large number of specific benefits might arise in terms of generating desirable genetic outcomes, including permanent solutions to problems of disease and the welfare of future generations, plus environmental and socio-economic benefits through, for example, improved agricultural properties in plants.

37. **Resources and Social Justice** concerns depend significantly upon how the development and commercialisation of genome editing advances. Genome editing can be an inexpensive and efficient means of altering genes. However, issues such as patenting and commercialisation might make the methods more expensive to utilise, particularly in developing countries. Access to desired patented applications, such as disease-resistant seed crops, may also mean that restrictions or higher costs are placed on using genome editing methods in a way that might limit uptake (or allow only certain privileged parties to make use of it to the detriment of those unable to afford the costs).

38. **Dual Use:** Limiting potential for misapplication of research to other fields (the 'dual use' problem) through creating a cheap, effective method of gene transfer.[41] These might include the genetic manipulation of viruses, gene transfer as a weapon or 'designer' animal models, or commercial exploitation in crops and animals to produce specific traits.

[39] Although there are numerous formulations and different strengths for the principle. See O'Riordan T, Cameron J (eds.). (1994) *Interpreting the Precautionary Principle*, London: Earthscan.

[40] See e.g. Harris J, Holm S. (1999) "Precautionary Principle Stifles Discovery." *Nature*, 400: 398; Harris J, Holm S. (2002) "Extending human lifespan and the precautionary paradox." *Journal of Medicine and Philosophy*, 27: 35-368; Hughes J. (2006) "How not to criticise the precautionary principle." *Journal of Medicine and Philosophy*, 31: 447-464; Araki M, Nojima K, Ishii T. (2014) "Caution required for handling genome editing technology." *Trends in Biotechnology* 32(5): 234-237. For a criticism of the application of the precautionary principle in ethical analysis in the related field of synthetic biology, see: Smith K. (2013) "Synthetic biology: a utilitarian perspective." *Bioethics*, 27(8): 453-463.

[41] Kelle A. (2013) "Beyond Patchwork Precaution in the Dual-Use Governance of Synthetic Biology." *Science and Engineering Ethics*, 19: 1121-1139; Smith K. (2013) "Synthetic Biology: A Utilitarian Perspective." *Bioethics*, 27: 453-463.

39. Like synthetic biology,[42] genome editing also raises ethical concerns about "**directed evolution**". What should inform the scope of genome editing? Who should select what properties of a particular organism to edit?[43]

[42] The Royal Society, Synthetic Biology Project page. Available at: https://royalsociety.org/policy/projects/synthetic-biology/ (Accessed 17 December 2014).

[43] Bensaude Vincent B. (2013) "Ethical Perspectives on Synthetic Biology." *Biological Theory*, 8: 368-375; Silver, PA, Way, JC, Arnold, FH, *et al*. (2014) "Synthetic Biology: Engineering Explored." *Nature*, 509: 166-167. For a more in-depth discussion of the ethical and legal aspects of directed evolution, see: Mehlman MJ. (2012) "Will directed evolution destroy humanity, and if so, what can we do about it?" *Saint Louis University Journal of Health Law & Policy*, 3: 93-122.

Ethical issues arising from the use of genome editing in humans

40. There is an established literature discussing the ethical concerns surrounding genetic modification in humans. Much emphasis is placed on germ-line modification (GLM), often focusing on irrevocable and unforeseen risks to future generations. These are already covered in other reports for the Nuffield Council on Bioethics.[44] Here, the focus is on areas that are of particular relevance to genome editing. That being said, these established concerns surrounding GLM might be re-visited in light of scope considerations, whereby widespread changes to germ-lines might be considered problematic in a way that more restricted occurrences would not.

41. Genome editing also offers a means of overcoming or reducing some of the current problems within somatic **gene therapy**.[45] Previous techniques have resulted in unregulated integration of genetic elements into the genome during clinical trials. The preciseness of genome editing ameliorates this problem. Although the possibility of off-target mutations is not eliminated, genome editing not only reduces the risks associated with gene therapy but also allows for greater nuances in genetic modification.[46]

42. Although still some time away, genome editing techniques present the possibility of gene targeting without the need for *in vitro* selection, thereby mitigating concerns about the discarding of embryos.[47] However, it will not be able to cease all embryo 'waste', as existing limitations inherent in all IVF will remain (such as assessment of embryo quality prior to implantation).

43. Although genome editing techniques present a relatively low cost means of achieving genetic modification, the wider issue of **equity in distributing its benefits** remain. The most prominent of these concerns are:

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[44] Frankel MS, Hagen BT. (2011) *Germline therapies: Background paper.* Available at: http://bit.ly/1wOL2wS (accessed 17 December 2014).

[45] It is reasonable to classify some applications of genome editing in humans as therapy, rather than, for example, enhancement or reproductive choice, because (a) it seeks to correct or prevent diseases and disabilities through the addition and expression of genetic material or correct missing or aberrant genetic functions under the the HUGO definition of gene therapy, as presented in Chadwick R. (2009) "Gene Therapy." in *A Companion to Bioethics*, 2nd edition (eds. H Kuhse and P Singer), Wiley-Blackwell, Oxford. (b) It is not subject to Non-Identity arguments and hence directly benefits existing individuals rather than possible future individuals (see Wrigley A, Wilkinson S, Appleby J. "The Ethics of Mitochondrial Replacement." (under review in *Bioethics*).)

[46] Palpant NJ, Dudzinski D. (2013) "Zinc finger nucleases: looking toward translation." *Gene Therapy,* 20: 121-27.

[47] Smith K, Chan S, Harris J. (2012) "Human Germline Genetic Modification: Scientific and Bioethical Perspectives." *Archives of Medical Research*, 43: 491-513.

(a) **Social justice** in terms of equitable access to technology. This is a particular problem in terms of developing nations' abilities to access the technology, both in terms of the focus of the research and accessing its benefits. Most genome editing research so far appears to be focussing on biomedical and biopharmaceutical applications linked to 'Western' medicine and disease. As Kuzhabekova and Kuzma point out, "lessons from previous genetic modification (GM) technologies and applications... suggest that such concentration of technology in the hands of a few, without cooperation to work together on applications for global problems... could backfire. Greater diversification of the field, beyond elite US universities and companies and beyond a focus on developed-country problems, may be warranted."[48]

(b) Depending upon whether or not genome editing is extended to germ-line modification, this may also give rise to additional **expressivist** concerns where the attempt to eradicate certain conditions permanently implies a lack of respect for people who have genetic diseases by viewing not only the conditions as 'undesirable' but also the existence of such people in society.[49]

(c) **Commercialisation** of genome editing methods might increase its cost and availability (although this would be true of any new technique that required skill and resources to develop). However, if it also proves to be a disruptive technology then economic and resource control of genome editing would have an even greater impact as other gene-modification technologies are supplanted by it.

(d) **Detectability** of genetic changes: as genome editing techniques often use the cell's natural repair mechanisms to introduce change, it might be undetectable once it is introduced. This might lead to social problems if used to achieve illicit enhancement of natural function. Similar concerns about detectability are likely to arise with other applications of genome editing, such as in animals and crops.

44. Concerns about social justice should also be filtered through a consideration of **needs.** It is not clear that there are large numbers of people who would currently benefit from genome editing, although this may change as the techniques become applicable to a wider number of conditions.[50] Additionally, the economic advantages of genome editing could also be used to benefit those populations who live with rare diseases - groups who are often disadvantaged by the

[48] Kuzhabekovaa A, Kuzma J. (2014) "Mapping the emerging field of genome editing." *Technology Analysis & Strategic Management*, 26(3): 321-352, at p. 340.

[49] Edwards SD. (2004). "Disability, Identity, and the 'Expressivist Objection'", *Journal of Medical Ethics,* 30: 418-420.

[50] Zhang F, Wen Y, Guo X. (2014) "CRISPR/Cas9 for genome editing: progress, implications and challenges." *Human Molecular Genetics*,23(Review Issue 1): R40–R46

traditional paradigms of scientific research and innovation. There may also be no need to develop or access genome editing technology where effective alternatives are already available (for example, PGD, embryo selection, gamete selection, genetic counselling, or adoption), although genome editing may offer advantages such as reduced embryo discard or the possibility of somatic treatment after birth.

45. When considering **research and initial testing of genome editing techniques** on human populations, the following kinds of questions would need to be considered:[51]

    (a) When to begin human trials?

    (b) Which patient population(s)?

    (c) How do we assess risk in early stage human trials?

Ethical issues arising from the use of genome editing in non-human animals

46. Many ethical concerns associated with the potential risks and benefits from genome editing in humans are also applicable to non-human animals, such as the irrevocable harm to future generations of animals versus the potential to permanently eradicate certain diseases. There are also well-recognised ethical concerns surrounding the genetic modification of animals generally, such as threats to biodiversity and consumption of modified animals as part of the food-chain. These are often weighed against the perceived advantages, such as improved welfare of the animals or improved nutritional value of animal products. Genome editing is, in many regards, another means of achieving these genetic modifications, albeit on a potentially greater scope and scale. It remains likely that the most significant use of genome editing will be in its application to animals and plants. Additional considerations specific to the widespread development of genome editing are:

    (a) Questions of **social justice** for the **farming** industry such as small-scale farmers being negatively impacted by the market dominance of those able to afford genetically modified animals, or the dominance of those companies able to utilise genetic modification technology and breed livestock from it. There is also the potential for the loss of traditional farming practices should farming using genetically modified animals and crops become the norm.

    (b) **Global economic impact** - patent protection, etc. might prevent or hinder introduction of genetically modified livestock in developing nations. However,

[51] Kimmelman J. (2008) “The ethics of human gene transfer.” *Nature Reviews Genetics*, 9(3): 239-44.

there is the potential for vast gains in terms of quality, supply, etc. of livestock and associated produce for human use.

(c) **Public trust** over provenance of food supply and labelling. This may be particularly prominent given the concerns over detectability of the use of genome editing, as mentioned in 43(d).

(d) **Medical benefits** - Potential to use animals to develop pharmaceuticals and vaccines, thereby eliminating risks and maximising benefits to humans. Potential to have healthier animals, free from disease or better suited to certain environments.

(e) Genome editing leading to **greater production of transgenic animals**, efficiencies of such production notwithstanding.[52]

Ethical issues arising from the use of genome editing in plants

47. General concerns also arise over the future impact of modification of the germline in plants, as well as concerns surrounding farming and consumption. Many issues concerning the use of genetically modified plants has been the subject of a Nuffield Council report.[53] Of direct concern over genome editing in the case of plants are:

(a) **Biosafety** of species in the wild through cross-pollination, or via contact with modified plants, is already a concern with GM crops. Although use of genetically modified bacteria and other microorganisms is often used in industry for fermentation processes or research purposes, there is likewise potential for them to 'escape' into the environment. The ease and speed of colonisation of environment of microorganisms may pose problems for other organisms, including gene transfer and the multiplication of pathogenic organisms.[54]

(b) **Biodiversity** at risk from the dominance of genetically modified crops through widespread use of genome editing.[55] Fewer varieties might, ultimately, be unable to respond to new environmental problems without

[52] Combes RD, Balls M. (2014) "Every silver lining has a cloud: the scientific and animal welfare issues surrounding a new approach to the production of transgenic animals." *ATLA,* 42: 137-45.

[53] Nuffield Council on Bioethics. (1999). *Genetically Modified Crops: The Ethical and Social Issues,* Nuffield Council on Bioethics: London.

[54] Wilson M, Lindow SE. (1993). "Release of recombinant microorganisms." *Annual Review of Microbiology*, 47: 913-44.

[55] However, it should also be noted that genome editing may also be used to increase biodiversity through expedited mutagenesis.

human intervention, creating the potential for widespread crop failure and famine.

(c) **Consumption** of modified plants by humans and animals, as part of food chain.

(d) **Socio-economic factors** for farming. Improved yield or pest and disease resistance vs. dominance of powerful companies with patented modified seed crop.

(f) **Health benefits**: increased nutritional value of plants ; decrease of unhealthy elements in foods; longer shelf-life; or increased disease resistance might lead to reduced use of pesticides (with wider health and environmental benefits than those simply gained from consuming the plants)

(g) **Public trust**: over provenance of crops, whereby detectability of the use of genome editing is extremely difficult (as raised in 43(d)).

48. Although GMOs have met with strong public opposition, in order to meet growing demand for food production there is "a need to develop...plant genome modification techniques that are acceptable to consumers and government regulators."[56] Precision genome editing is seen as the latest tool for the accelerated development of new crop varieties. As a tool for crop breeding, any general ethical concerns about genome editing will be applicable to this area, which has not previously come under the same scrutiny or regulation as those surrounding genetic engineering and GMO crop development.

Governance, Regulation and Policy in Genome Editing

49. There is currently little specific governance of genome editing technology in any jurisdiction. Some have raised concerns about this lack of specific regulatory oversight.[57] Others suggest that determining governance approaches now may remain premature, although examining parallel and overlapping technologies to glean 'lessons' in this context may be appropriate.[58] Scientists interviewed about governance of genome editing have similar concerns about governance that they do with existing methods of genome modification and have expressed a desire

[56] Katheria P, Eudes F. (2014) "Nucleases for genome editing in crops." *Biocatalysis and Agricultural Biotechnology,* 3: 14-19, at p. 14.

[57] Araki M, Nojima K, Ishii T. (2014) "Caution required for handling genome editing technology." *Trends in Biotechnology* 32(5): 234-237.

[58] Kuzhabekova A, Kuzma J. (2014) "Mapping the emerging field of genome editing." *Technology Analysis & Strategic Management*, 26(3): 321-352.

for change.[59] At a minimum, it does seem appropriate to query how genome editing will be governed and to use the opportunity it presents to query what ideal governance of emerging and emergent biotechnologies might comprise.

50. A broader consideration is to query what role governance could or should play in the development of any new technology. What aspects of genome editing should be regulated, and how? While it is perhaps too early to answer this question, considerations of the approach to governance and the need for regulation of genome editing should not be forgotten as the field continues to develop.

Legal permissibility of genome editing in the United Kingdom

51. Genome editing will need to be assessed to determine which laws and other regulatory instruments will apply and whether these will be satisfactory. At a brief glance, it would seem that at least the following laws and regulations will be relevant.

52. Applications of genome editing relating to **somatic gene therapy** in humans would need to adhere to the standard requirements for this research and therapy; namely adhering to the *Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended)*. All applications for approval of research would need to be assessed by a research ethics committee that meets EU clinical trials directive requirements.[60]

53. Changes to be introduced that would alter the **human germ line** would currently be prohibited under the *Human Fertilisation and Embryology Act 1990 (as amended).* The Act does not allow a licence that will authorise "altering the genetic structure of any cell while it forms part of an embryo."[61] Regulations currently being proposed to facilitate mitochondrial transfer would also not appear to allow genome editing to be used.[62] Using genome editing in **human embryonic cells** may be possible under licence if the purpose of such use is for research only.[63]

[59] Kuzma J, Kokotovich A, Kuzhabekova A. (2012) "History Repeats Itself? Governance of New Methods for Targeted Genetic Modification in the U.S." Society for the Study of Nanoscience in Society (S.NET) Annual Conference, University of Twente, Netherlands, October 22-25, 2012. Presentation available at: http://bit.ly/1yZGLF8 (accessed 17 December 2014).

[60] See: http://www.hra.nhs.uk/about-the-hra/our-committees/gtac/ (accessed 27 November 2014)

[61] Human Fertilisation and Embryology Act 1990, Schedule 2, para 1(4).

[62] See the consultation on the draft regulations: http://bit.ly/1cbkE9Y (accessed 27 November 2014).

[63] Human Fertilisation and Embryology Act 1990, Schedule 2, para 3(4).

54. Modifying **non-human animals** using genome editing will be subject to existing regulations that govern all such research, including transgenics.[64]

55. Regulation of genome editing in **plants** will require consideration of existing European Union and UK legislation.[65] International instruments such as the *Cartagena Protocol on Biosafety* will also be relevant. Current regulatory regimes may be problematic for plant genome editing.[66] EU regulation, for example, depends on the methods used to introduce a genetic modification; but not all genome editing methods will be readily detectible in end products.[67] The UK Biotechnology and Biological Sciences Research Council (BBSRC) has highlighted this limitation and has suggested that a plant's traits should be assessed for risk and impact rather than using a methods-based approach.[68] In this way, regulating novel plants will become more like regulating medicines.

56. The current definition of "genetic modification" in the *Environmental Protection Act* 1990 defines "genetically modified" as pertaining to an organism's genes or other genetic material that are "artificially modified."[69] The Act further defines "artificially modified" to mean "altered otherwise than by a process which occurs naturally in mating or natural recombination."[70] Genome editing uses introduced nucleases to alter DNA using a cell's inherent repair machinery. It is not yet known whether introduced nucleases are transient or permanently held within cells.[71] Whether and if so which forms of genome editing would be considered "artificial" under the EPA needs further investigation.[72] The BBSRC

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[64] Relevant instruments include the *Animals (Scientific Procedures) Act 1986* and the requirement to notify the Scientific Advisory Committee on Genetic Modification (Contained Use).

[65] EU instruments include EU Directive 2001/18/EC, which regulates GMO release in both a research and a commercial context; Food and Feed Regulation 1829/2003, which governs authorising GM food and feed, including labelling; and the Traceability and labelling regulation 1830/2003. English instruments include the *Environmental Protection Act 1990* (which implements directive 2001/18/EC), the *Genetically Modified (Deliberate Release) Regulations 2002* as well as additional regulations that implement EC directives 1829 & 1830. There are similar regulations in the devolved administrations.

[66] Kuzma J, Kokotovich A. (2011) "Renegotiating GM crop regulation." *EMBO Reports*, 12(9): 883-888.

[67] Podevin N, Devos Y, Davies HV, *et al*. (2012) "Transgenic or not? No simple answer! New biotechnology-based plant breeding techniques and the regulatory landscape." *EMBO reports*, 13: 1057-1061.

[68] Biotechnology and Biological Sciences Research Council (2014) "New techniques for genetic crop improvement: position statement" London: BBSRC. Available at: http://bit.ly/1DVMa4N (Accessed 10 December 2014).

[69] s106(4)(a)

[70] s106(4A)

[71] Pauwels K, Podevin N, Breyer D, *et al*. (2014): "Engineering nucleases for gene targeting: safety and regulatory considerations." *New Biotechnology,* 31(1).

[72] If it transpires that some forms of genome editing are not covered by the EPA but such regulation is deemed desirable, section 106(4B)(a) allows for techniques to be prescribed as creating artificial modifications.

acknowledges this concern, noting that: “The boundaries between established genetic modification (GM) and non-GM techniques will become increasingly blurred as techniques develop.”[73] It is of note that the US Department of Agriculture (among other jurisdictions) has already indicated that plants modified using at least some forms of ZFNs would not be considered as genetically modified organisms (GMOs).[74]

Governance approaches to genome editing

57. If it transpires that more explicit oversight of genome editing is warranted, the question of how this technology should be governed will arise. A prevalent trend in governance of biotechnologies under uncertainty has been to utilise the **precautionary principle**. While this principle is varied in definition and application, in brief it prioritises risk-aversion, whereby a perceived risk of harm should be enough to justify regulatory intervention that will limit use of a technology until more is known as to its impact. This approach has already been briefly considered in genome editing,[75] but as we discuss above, has been subject to criticism in other contexts, including by the Council in its report on Biofuels.[76]

58. More recently, alternative approaches to governance have emerged. None of these have yet been discussed in depth for genome editing. Scope therefore exists to evaluate these approaches to determine whether and if so how each may be applicable to or desirable for governing this technology.

59. Recent scholarship in nanotechnology[77] and synthetic biology[78] has included evaluations of **anticipatory governance.**[79] This “can act on a variety of inputs [throughout society] to manage emerging knowledge-based technologies while

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[73] Biotechnology and Biological Sciences Research Council (2014) “New techniques for genetic crop improvement: position statement” London: BBSRC. Available at: http://bit.ly/1DVMa4N (Accessed 10 December 2014).

[74] See, for example: http://1.usa.gov/1Afs30N (accessed 27 November 2014); see also Araki M, Nojima K, Ishii T. (2014) “Caution required for handling genome editing technology.” *Trends in Biotechnology* 32(5): 234-237.

[75] Araki M, Nojima K, Ishii T. (2014) “Caution required for handling genome editing technology.” *Trends in Biotechnology* 32(5): 234-237.

[76] Nuffield Council on Bioethics (2011) *Biofuels: Ethical Issues.* London: Nuffield Council on Bioethics. Available at: http://nuffieldbioethics.org/project/biofuels-0/ (Accessed 18 December 2014)

[77] Barben D, Fisher E. Selin C, *et al*. (2008) “Anticipatory governance of nanotechnology: Foresight, engagement, and integration.”' in: Hackett EJ *et al* (Eds) *The Handbook of Science and Technology Studies*, 3rd edition. Cambridge, MA: MIT Press, pp. 979-1000.

[78] Wiek A, Guston D, Frow E, *et al*. (2012) “Sustainability and anticipatory governance in synthetic biology.” *International Journal of Social Ecology and Sustainable Development*, 3(2):25-38.

[79] Guston DH. (2014) “Understanding 'anticipatory governance'.” *Social Studies of Science,* 44: 218-242.

such management is still possible."[80] In other words, anticipatory governance aims to emerge with the science rather than react to it.[81] It requires foresight, engagement and integration. Foresight involves reflexively anticipating potential applications and uses of the technology in advance. Engagement involves promoting a role for a variety of stakeholders to consider their role in the development of the relevant technology.[82] Integration involves taking up foresight and engagement in "sociotechnical processes to shape their eventual outcomes."[83] The challenges in undertaking anticipatory governance in genome editing will be to anticipate relevant scenarios; to engage stakeholders such as various publics who may still be "latent" and to encourage researchers who may not have had to deal with governance to appreciate its relevance to their work.

60. A slightly different framing of governance is **adaptive governance**. Adaptive governance combines four properties: (i) recognising participants and publics truly collectively; (ii) managing relationships and research stewardship to promote trustworthiness; (iii) being adaptive to changes and developments in genome editing; and (iv) flexibility - avoiding a 'one size fits all' approach.[84] An adaptive approach to governance therefore builds flexible regulation while making a commitment to incorporate new information as it becomes available. This may suit genome editing as a diverse field, although latent publics may still pose a problem.

61. **Responsible research and innovation** (RRI) has recently gained traction in the European Union[85] and with UK Research Councils.[86] While there is not yet a single definition or approach to RRI, Owen *et al* suggest three common features: (i) democratic governance over the appropriate rationale and end-points for

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[80] Guston DH. (2008) "Preface." In: Fisher E, Selin C, Wetmore JM, Eds. *The Yearbook of Nanotechnology in Society: Presenting Futures, vol 1*. New York: Springer; cited by: Guston DH. (2014) "Understanding 'anticipatory governance'." *Social Studies of Science,* 44: 218-242 at 219.

[81] Barben D, Fisher E. Selin C, *et al*. (2008) "Anticipatory governance of nanotechnology: Foresight, engagement, and integration."' in: Hackett EJ *et al* (Eds) *The Handbook of Science and Technology Studies*, 3rd edition. Cambridge, MA: MIT Press, pp979-1000.

[82] Guston DH. (2014) "Understanding 'anticipatory governance'." *Social Studies of Science,* 44: 218-242 at 219.

[83] Barben D, Fisher E. Selin C, *et al*. (2008) "Anticipatory governance of nanotechnology: Foresight, engagement, and integration."' in: Hackett EJ *et al* (Eds) *The Handbook of Science and Technology Studies*, 3rd edition. Cambridge, MA : MIT Press, pp979-1000, at p988.

[84] Adapted from: O'Doherty KC, Burgess MM, Edwards K, *et al*. (2011) "From consent to institutions: Designing adaptive governance for genomic biobanks." *Social Science and Medicine*, 73(3): 367-374.

[85] European Commission. (2011) *DG Research workshop on Responsible Research & Innovation in Europe*, Available at: http://bit.ly/1Ag4Ds2 (Accessed 18 December 2014); Sutcliffe H. (2011) *A report on responsible research and innovation*. London: MATTER. Available at: http://bit.ly/10veDQN (Accessed 18 December 2014).

[86] See, for example: http://www.epsrc.ac.uk/research/framework/area/ (Accessed 18 December 2014)

research and innovation (including determining both the targets and impact research should have); (ii) broadly framed responsiveness to current and future innovations and their impacts to both science and society; and (iii) framing 'responsibility' within a climate of all stakeholders working under uncertainty.[87] RRI is also hallmarked by contemporaneous interaction between researchers and regulators. However Owen *et al* also point out that while in theory RRI is laudable, the practical scope for this approach to facilitate regulation in a complex and uncertain research environment may not be so straightforward.

62. A final approach to governance of genome editing might be **self-regulation**. This can be favoured where external oversight is perceived to be ineffective or intrusive. It will be interesting to observe whether central tenets currently being employed in synthetic biology, such as commitments to sharing resources and non-commercialisation, are also desirable or feasible in genome editing. Sharing resources suits the 'component-building' and standardisation goals of synthetic biology.[88] Will there be equivalents in genome editing?

A need for specific policy? An ethical governance response to genome editing

63. The above discussion indicates that genome editing does fall within the scope of at least some current laws and regulations, although these are imperfect. There are also several Governance approaches that may work - all of which involve quality engagement, flexibility and foresight. However, what is not yet known is whether genome editing requires a specific governance response, or whether it should be divided up according to applications, such as broad governance of crop development using genome modification of whatever kind.

64. We do know that concern over current governance in genome editing has been expressed.[89] Whatever form it takes, governance in genome editing may benefit from the following considerations:
    - Taking a mid- to long-term view, rather than specifically regulating early iterations, thus avoiding 'piecemeal' regulation that may lead to inflexibility;[90]

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87 Owen R, Macnaghten P, Stilgoe J. (2012) "Responsible research and innovation: From science in society to science for society, with society." *Science and Public Policy*, 39: 751-760.

88 Bensaude Vincent, B. (2013) "Ethical Perspectives on Synthetic Biology." *Biological Theory*, 8: 368-375.

89 Araki M, Nojima K, Ishii T. (2014) "Caution required for handling genome editing technology." *Trends in Biotechnology* 32(5): 234-2; Kuzma J, Kokotovich A, Kuzhabekova A. (2012) "History Repeats Itself? Governance of New Methods for Targeted Genetic Modification in the U.S." Society for the Study of Nanoscience in Society (S.NET) Annual Conference, University of Twente, Netherlands, October 22-25, 2012. Presentation available at: http://bit.ly/1yZGLF8 (accessed 17 December 2014).

90 Adapted from: Lowrie H, Tait J. (2010) Guidelines for the Appropriate Risk Governance of Synthetic Biology. Policy Brief. International Risk Governance Council. Geneva: IRGC. Available at: http://www.irgc.org/IMG/pdf/irgc_SB_final_07jan_web.pdf (Accessed 27 November 2014), page 24.

- Being adaptable to changing scientific advances;
- Undertaking transparent mapping of the scientific terrain, using methods such as “tech mining”;[91]
- Ensuring quality evidence is used in assessing risk and potential applications of this technology, including considering open peer review;
- Engaging widely with stakeholders; while avoiding a purely ‘deficit model’ approach.[92]
- Ensuring openness and accountability. The approach to regulating genome editing in the United States has already been subject to criticism. It took a Freedom of Information request to indicate whether a particular form or maize created using ZFNs would be subject to GMO regulations.[93]

Questions the Council May Wish to Address

65. Should genome editing be considered as one entity for the purposes of ethical analysis? Or, should considerations of ethics and governance focus on something different, such as field of application or risks?

66. Should genome editing be seen as a potential ‘tipping point’ in genetics where the potentially huge scope of its application should itself be seen as shaping our approach to access, resources and social impact that have previously only been considered on a much smaller scale?

67. What might be the appropriate parameters and restrictions upon trials involving human subjects for the development of gene therapies using genome editing techniques, should their development prove promising?

68. Should ethical and governance considerations about germ-line modifications be re-visited in light of both the increased accuracy of genome editing and the potentially vastly increased scope of genetic modification that it might accomplish?

[91] As an example of this approach, see: Kuzhabekova A, Kuzma J. (2014) “Mapping the emerging field of genome editing.” *Technology Analysis & Strategic Management*, 26(3): 321-352.

[92] Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*. London: Nuffield Council on Bioethics. Available at: http://bit.ly/1r2mlxF (Accessed 18 December 2014); Kuzma J, Kokotovich A, Kuzhabekova A. (2012) “History Repeats Itself? Governance of New Methods for Targeted Genetic Modification in the U.S.” Society for the Study of Nanoscience in Society (S.NET) Annual Conference, University of Twente, Netherlands, October 22-25, 2012. Presentation available at: http://bit.ly/1yZGLF8 (accessed 17 December 2014). As with GMOs or synthetic biology, advocacy groups are likely to have an interest in genome editing.

[93] Kuzhabekova A, Kuzma J. (2014) “Mapping the emerging field of genome editing.” *Technology Analysis & Strategic Management*, 26(3): 321-352.

69. What sort of legal regulation would be best suited to genome editing and its applications? Is current UK and EU regulation suitable for genome editing?

70. What overarching governance approaches should be used with genome editing? Should governance be primarily informed by methods or their possible applications?

71. Is a commitment to resource-sharing feasible or desirable for genome editing? If so, which methods or applications should be considered?

72. Should the answer to whether genome editing is a disruptive technology influence how we think about the ethical or governance issues arising from its use and application?

Conclusion

73. This paper has considered the science, ethics and governance of genome editing. This field is exciting, with potentially disruptive applications across almost all living species. Ethical issues will inevitably arise, and these should be considered openly by a variety of stakeholders. Genome editing also offers new opportunities to assess how we regulate and govern emerging technologies; including limitations to current legal approaches and opportunities to assess emerging governance frameworks.

74. Many of the ethical issues in genome editing also arise elsewhere. It does, however, create something of a new context arising from the implications of the **scope** of the techniques. Potentially infinitely editable genome using an accurate and relatively inexpensive technique presents the potential for changing many more aspects of the genome in humans, animals, plants and other organisms, and on a significantly greater scale, than has previously been considered. This, in turn, brings with it the need to consider ethics and regulation in terms of magnitude and access, rather than discrete activities the technology may be used for.

75. In terms of topic selection for further consideration, genome editing may not be considered a particularly novel development in terms of opening up a new field in molecular biology. The breadth of genome editing and its status as a 'technique' (as opposed to a discrete field of research) also mean that it would be ill-advised to ring-fence an 'ethics of genome editing.' It might, however, warrant further consideration in terms of a timely intercession to develop governance and regulation on how we should approach the possibility of widespread genetic modification occurring across a range of areas.

Glossary

DNA	Deoxyribonucleic acid; the chemical that carries a person's genetic information. Most cells of a person's body contain a complete copy of that information. A DNA molecule consists of a long chain of units called nucleotides or 'bases'. There are four sorts of nucleotides: guanine, adenine, thymine, and cytosine.*
Endonuclease	An enzyme that breaks down a nucleotide chain into two or more shorter chains. It does this via cutting the internal bonds that link the nucleotides together. A similar enzyme that cuts at the end of a chain of nucleotides is called an Exonuclease.
Enzyme	Protein that causes a specific biological reaction.
Eukaryotic cell	A cell, belonging to an organism that has more than one cell, that contains a nucleus and organelles.
Mosaic	In the context of genome editing, this means that the introduced gene change was not present in every cell.
Nuclease	A biologically active chemical (enzyme) that can cut the bonds between nucleic acids; such as in DNA or RNA.
Pluripotent	"Many potentials." In a stem cell context, this means a cell that can differentiate into many different kinds of cell.
Prokaryote	A simple, single-celled organism. The cell does not contain a nucleus or any other 'machinery' found in more complex eukaryote cells.
RNA	Ribonucleic acid, a molecule similar in structure to DNA. It is the main agent for transferring information from DNA to the protein-synthesizing machinery of cells, but can also hold genetic information (as it does in the case of viruses).* Messenger RNA (mRNA) is a type of RNA that is produced via the process of transcribing DNA. Messenger RNA serves as a template to carry the message contained in DNA for the formation of relevant proteins outside of a cell's nucleus.
Nucleotide	The basic structural unit of nucleic acids (DNA, RNA). Comprised of several parts, including a base, a sugar and a phosphate.
Zinc finger protein	A particular structural motif for a small protein, which has its folds stabilised through zinc ions.

Please note: for the sake of consistency, those definitions marked with an asterisk (*) have been taken from the Nuffield Council on Bioethics 2012 report: “Emerging biotechnologies: technology, choice and the public good.”