The Academy of Medical Sciences

The Academy of Medical Sciences' response to the Nuffield Council on Bioethics Genome Editing Call for Evidence

February 2016

Summary

- The Academy welcomes the opportunity to respond to this timely call for evidence. Our written response has been informed by engagement with our Fellows and focuses on genome editing in the context of biomedical research and human applications.
- The Academy believes that there is a clear and valid distinction between the use of genome editing within research and its potential use for clinical purposes (whether somatic cell or germline (heritable) genome editing). Genome editing techniques have already proved to be valuable for research purposes, and their continued use will progress our basic understanding of human biology, development, and disease. The Academy believes that the research potential of genome editing techniques in this manner is therefore beneficial and should be allowed to proceed.
- Ongoing research will also provide an opportunity to better understand the potential benefits and harms associated with the use of genome editing technologies for a clinical application. In this respect, a moratorium which could directly or indirectly prevent the use of genome editing in research may be harmful.
- The science behind the clinical application of genome editing is still at an early stage. The Academy believes however that the potential of non-heritable and heritable therapeutics based on genome editing should be explored. However, their introduction must be based on a strong evidence base, be in line with societal values, and be supported by active engagement with patients and the public to effectively communicate the conditions in which genome editing can, and cannot, be helpful. Early engagement with various stakeholders is vitally important for this process and we therefore welcome the anticipatory nature of this call for evidence.
- The ethical nature of genome editing can be informed in part through comparison with other forms of scientific research and other clinical applications, which have some impact on the human genome, for example gene therapy and reproductive technologies. We are therefore encouraged that there is an opportunity to reflect on previous, and similar, discussions regarding the ethics and morality of manipulating the human genome.
- The ethical questions raised by genome editing technologies deserve ongoing consideration alongside discussions about safety and efficacy, which remain a particular concern for the potential introduction of these techniques for clinical applications.
- The Academy believes that the UK is particularly well placed to address the ethical questions, regulation, and governance of genome editing due to its extensive history of debating similar topics and robust regulatory environment.
- Although the concept of genome editing is not new, the recent advent of CRISPR/Cas9 has opened up greater avenues for biomedical research and is predicted to more easily allow the use of genome editing within a clinical capacity.

Introduction

1. The Academy of Medical Sciences promotes advances in medical science, and campaigns to ensure that these are translated into healthcare benefits for society. Our elected Fellowship includes experts drawn from a broad and diverse range of research areas.

2. We welcome this opportunity to respond to this timely call for evidence. Our response follows our initial joint statement with the Association of Medical Research Charities (AMRC), the Biotechnology and Biological Sciences Research Council (BBSRC), the Medical Research Council (MRC), and the Wellcome Trust.[1] As outlined in the joint statement, we are committed to supporting discussion around genome editing, and its use in basic and preclinical biomedical research. For this reason, we also welcome and support the statement published following the International Summit on Human Gene Editing by the Organizing Committee.[2]
3. This written response has been informed by engagement with our Fellows and focuses on genome editing in the context of biomedical research and human applications.

Perspectives on genome modification

Is there anything special about the genome that makes intervening in it different from other ways of manipulating nature?

4. A number of the Fellows that we consulted questioned the suggestion that there is anything inherently different, or special, about the genome which makes directly intervening in it different from other forms of manipulation, such as the provided example of selective breeding.
5. While it remains important to consider the ethical concerns of genome editing, we also recognise that it is important to weigh these against potential for genome editing techniques to advance biomedical research and provide clinical benefit.

To what extent can the development of genome editing techniques be regarded as distinct from or continuous with existing techniques?

6. There are some close similarities between genome editing techniques and existing gene therapy approaches, in that both have the desired outcome of correcting the effect associated with a mutation or genetic defect for a medical benefit. The ethical considerations for applying genome editing therapies to somatic cells are therefore similar to any other genetic therapy that is directed to an individual and does not cause a permanent, heritable effect.
7. Importantly however, what distinguishes genome editing techniques from earlier homologous recombination systems is their precision and efficiency. Genome editing may in fact offer a safer alternative to current gene therapies, although this must continue to be actively explored. For example, in addition to the desired genetic material, current gene therapy techniques also introduce additional material, which may carry deleterious potential. Indeed, retroviral gene therapy has been associated with the rare (although realised) risk of insertional mutagenesis, whereby the random insertion of genetic material disrupts the normal functioning of the region in which it lands. Conversely, one potential aim of genome editing techniques is to more precisely correct the defective genetic material in its natural location rather than more crudely replace it with the introduction of a full gene. Nonetheless, the frequency and implications of inaccurate, off-target events associated with genome editing needs to be fully assessed in pre-clinical work to determine the absolute chance of experiencing any negative consequences. Similarly, whether accurate and intentional modifications can nonetheless have unintentional consequences needs to be fully explored.
8. As recognised by this call for evidence, there are a number of available genome editing technologies, including those based on transcription-activator like effector nucleases (TALENs),

[1] *Genome editing in human cells - initial joint statement.* http://www.acmedsci.ac.uk/viewFile/55e6b4e90f49c.pdf
[2] International Summit on Human Gene Editing. (2015). *On Human Gene Editing: International Summit Statement*. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a

zinc-finger nucleases (ZFNs), and CRISPR/Cas9 (and its derivatives and similar alternatives). Both TALENs and ZFNs directly bind to the DNA to be edited, whereas the DNA cutting component of the CRISPR system (the Cas9 enzyme) requires an RNA guide to be directed to the target DNA. Although there are technical differences in the precise way these techniques work, all genome editing techniques ultimately share the same basic use as a molecular tool to edit the genome. Consequently, all genome editing technologies can be conceptually considered in parallel and as a continuum of techniques.

9. The tools can also be used to modify the level of gene expression, which is dictated by 'epigenome' marks associated with DNA and associated proteins, rather than the DNA sequence itself. By linking proteins that control gene expression (such as chromatin modifiers, transcriptional activators, or transcriptional repressors) to nuclease-dead forms of the genome editing proteins (that is, forms of the protein which cannot cut DNA), it is possible to guide them to specific areas of the genome where they can alter the epigenome marks and therefore alter gene expression. As nuclease-dead proteins do not cut DNA, these do not lead to alterations in the DNA sequence that can be inherited, but can lead to long-lasting epigenetic effects, which accumulating evidence suggests can be passed on to succeeding generations.
10. This call for evidence does not refer to a particular technique, nor to an existing area of research, but rather to the conceptual idea of using molecular approaches to alter genes or gene expression. The field of genome editing and its desired outcomes are therefore conceptually unaltered by the emergence of CRISPR/Cas9 - the most recent genome editing tool. In turn, the fundamental ethical questions posed by genome editing also remain broad and wide-reaching.
11. However, it is important to recognise that CRISPR/Cas9 has some notable differences compared to other techniques. Despite being largely in its infancy, CRISPR/Cas9 is distinguished for its relative efficacy, accuracy, speed, affordability, and ease of use. These distinctions are important because the rapid emergence of CRISPR/Cas9 has opened up greater avenues for biomedical research and is predicted to more easily allow the use of genome editing within a clinical capacity. It is therefore timely and important to actively engage in ongoing ethical and regulatory discussions.

What obligations do scientists involved in developing and using genome editing technologies owe to society, and what freedoms should society allow to these scientists? Do genome scientists have any special obligations to society that are distinct from those of other scientists?

12. Scientists involved in the development or use of any innovative technologies have a responsibility to consider the relevant ethical issues that are of importance to society. The transparent communication of any basic developments, and the identification of problems, is in turn vital to ensure public trust, limit inaccurate or confusing reporting (especially for technologies that may have clinical applications), and help various stakeholders make informed decisions regarding the use and eventual application of the technology. In this regard, genome scientists have a responsibility to work to the same standards as all other scientists.
13. As previously stated in our initial joint statement, the Academy recognises the importance of delineating the different contexts in which genome editing technologies have been, or in principle might be, used.[3] There is a need to distinguish the use of this technology within a research context compared to a clinical context, and between somatic and germ cells. This is

[3] *Genome editing in human cells - initial joint statement.* http://www.acmedsci.ac.uk/viewFile/55e6b4e90f49c.pdf

also a welcome distinction made in the statement from the International Summit on Human Gene Editing.[4]

14. With this in mind, we suggest that societal concerns surrounding the clinical application of genome editing techniques are considered separately from their use within research. Ongoing dialogue between scientists and society about the distinct merits (and limitations) of genome editing within these two contexts will therefore be important, and should be encouraged.

To what extent is the development of genome editing valuable as a pure research tool, and to what extent is its value dependent on envisaged practical applications?

15. Genome editing techniques in general (although particularly CRISPR/Cas9) have widened the possibilities of basic and biomedical research, and now allow the genetic manipulation of cells and organisms that have historically been difficult to modify.[5] As a result they are powerful technologies and have already shown great value as a pure research tool, independent of any envisioned practical (i.e. clinical) application.
16. The on-going use of genome editing techniques as a pure research tool is also fully expected to continue to have a multitude of benefits. For example, whether specifically identified changes within both coding and non-coding areas of the genome cause disease, and how they do so, can now be more quickly and cheaply explored by either recreating mutations in an initially normal cell type, or by correcting them using genome editing and assessing the effect. In a similar way, CRISPR can be used to interrogate gene function.
17. One well documented concern with using certain human cells (e.g. induced pluripotent stem cells) or animals to model disease, is that the healthy controls (to which the disease model is compared) may have multiple genetic differences compared to the disease model.[6] Genome editing tools can however be used to rapidly develop control cells or animal models which are genetically matched (isogenic) to a disease model, in that they only differ in the particular mutation or difference of interest. The benefit of such an application is that it makes it easier to more precisely determine that any differences between the control and disease models are directly caused by the one known difference. Genome edited cell lines could also be used to aid drug screens and determine drug toxicity *in vitro*. The use of genome editing techniques on embryos, within the confines of regulation laid down by the Human Fertilisation and Embryology Authority (HFEA), can also be expected to help develop the basic understanding of human biology, development, and disease in ways that have traditionally not been possible.
18. While genome editing techniques used in research are therefore valuable in and of themselves, greater experience with such technologies will also improve our understanding of them. This improved understanding will continue to inform the refinement of these tools to make them more adaptable, useful, and applicable for clinical use. Improved understanding of genome editing techniques, which can only come through continued research use, may also help mitigate any safety concerns should the technique be translated for clinical use. Similarly, such advancements can also be envisioned to benefit other practical applications such as the manipulation of other organisms for agricultural and industrial benefit.

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[4] International Summit on Human Gene Editing. (2015). *On Human Gene Editing: International Summit Statement*. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a

[5] Sander JD & Joung JK. (2014). *CRISPR-Cas systems for editing, regulating and targeting genomes.* Nature Biotechnology **32**, 347-355. http://www.nature.com/nbt/journal/v32/n4/full/nbt.2842.html

[6] Musunuru K. (2013). *Genome editing of human pluirpotent stem cells to generate human cellular disease models.* Disease Models and Mechanisms **6**, 896-904. http://dmm.biologists.org/content/6/4/896#sec-9

What obligations do governments have towards society to ensure 'safe' science or otherwise to shape the scientific research and development?

19. Governments have a responsibility to protect society from harmful science, although we recognise that the accurate identification of potential harms can be problematic and therefore welcome the anticipatory nature of this call for evidence. The authoritative oversight and input of governments is also needed to ensure that ethical considerations are discussed in a safe and productive manner, and involve the correct professional input to avoid scaremongering. Ongoing and open dialogue with the public will also be important to understand their concerns, and where possible provide a mechanism by which to offer reassurance regarding the existence of strong regulation which can prevent scenarios that cause particular ethical concern.
20. Governments also have an obligation to consider if any regulations are likely to cause or impact on medical tourism, as has been seen with stem cell therapies where patients travel to countries with more relaxed regulations, to receive often ineffective or unsafe treatments. This should therefore be considered both within the UK and internationally.
21. The Academy recognises that national (and international) resources to capture and disseminate CRISPR generated data will be useful to encourage and facilitate collaboration and data sharing. Such resources are currently lacking but one such example is CrisprGE, a repository that details (currently) 4680 discrete entries of 223 unique genes from 32 different organisms which have been edited by the CRISPR/Cas approach.[7] Similar resources to catalogue evidence of trials and other human interventions should also be developed.
22. Lastly, the Academy believes that the UK is particularly well placed to address the issue of genome editing due to its extensive history of debating similar topics and robust regulatory environment. This is discussed in more detail below in response to the question about who should be involved in setting policy (paragraph 38).

What conventional moral principles do genome editing challenge? To what extent can the moral questions raised by genome editing be addressed using existing moral frameworks or approaches?

23. The ethical questions raised by genome editing (including, but not limited to, concerns over autonomy, consent, and the 'slippery slope' of introducing heritable changes) deserve ongoing consideration alongside the discussions about safety and efficacy.
24. However, the concept of genome editing is not new, and indeed as mentioned in this call for evidence has its origins as early as the 1960s. As also discussed above (in response to the question about the distinction of genome editing from other technologies; paragraph 6) there are certain ethical similarities with gene therapy as well as reproductive technologies including in vitro fertilisation (IVF), pre-implantation genetic diagnosis (PGD), and the more recently legalised mitochondrial replacement therapies - all of which have been subject to intense ethical scrutiny and have been explored by other activities performed by the Nuffield Council on Bioethics.
25. Accordingly, although there has been significant and rapid progress in the field in recent years, the Academy is reassured that there have been numerous previous opportunities to explore many of these ethical questions (for example the Clothier committee report on the ethics of gene therapy[8] and previously published Nuffield Council on Bioethics reports), meaning there is now an extensive history of such discussions from which lessons can be learnt. In turn, the existing moral and legal frameworks are a helpful resource that can be used to inform the

[7] Kaur K, *et al* (2015). *CrisprGE: a central hub of CRISPR/Cas-based genome editing*. Database doi: 10.1093/database/bav055. http://database.oxfordjournals.org/content/2015/bav055.abstract
[8] Committee on the Ethics of Gene Therapy (1992). *Report of the Committee on the Ethics of Gene Therapy*. https://repository.library.georgetown.edu/handle/10822/544675

moral and ethical questions now raised by genome editing technologies for research and clinical use.

Biomedical research and human applications

What is the current state of the art in the field? What are the current technical limitations and constraints/bottleneck?

26. Due to its ease of use and cost-effectiveness, there is now a particular focus on the use of CRISPR/Cas9 as a genome editing tool. Accordingly, since its advent there have been numerous incremental, yet rapid, improvements in almost all components of the CRISPSR/Cas9 technology. These components (or 'reagents') include the 'Cas9' enzyme which cuts the DNA, and an 'RNA guide' which guides Cas9 to the specific sequence of DNA to be cut. In cases where a precise genetic modification is to be made, a DNA template which contains the desired modification is also required. This template is used by one of the cell's repair mechanisms to insert the desired genetic material into the region cut by Cas9, thereby editing the genome (this is known as homology-directed repair (HDR)). Improvements to these reagents can be expected to advance the use of genome editing within a research capacity, and for potential clinical applications.
27. More specifically, the ability to deliver sufficient amounts of the CRISPR genome editing reagents (i.e. Cas9, the guide RNA, and DNA template) into mammalian cells to have an effect but with minimal toxicity has posed a technical limitation which remains a focus of ongoing research. Recently however, it has been demonstrated that a high level of targeted gene modification can be achieved using glass-needle microinjection to deliver the reagents into human cells.[9] Such an approach allows more control over the amount of reagents added to the cells, and avoids some of the safety concerns associated with using viruses to deliver them. On the other hand, for somatic gene therapies, where large numbers of cells need to be targeted, viral vectors are still generally the delivery methods of choice, although electroporation and hydrodynamic transfection can be used in some circumstances.
28. In addition to improving delivery into cells, there have also been improvements directly to the CRISPR reagents in order to improve their editing abilities. For example, altering the Cas9 enzyme in the part that contacts the DNA target has been shown to improve editing accuracy compared to the unaltered form of Cas9 - that is it causes fewer off-target edits.[10] Work has now also shown that using a shorter strand of guide RNA to direct Cas9 to its DNA target could reduce errors.[11]
29. The identification of Cpf1 (which can be used in place of Cas9 to cut the DNA) is also expected to improve the CRISPR system by virtue of its different cutting abilities compared to Cas9. Further still, Cpf1 is smaller than Cas9 and uses a shorter (therefore also cheaper) RNA molecule to target DNA meaning Cpf1 may be easier to deliver to cells, which is important for the reasons outlined in the previous paragraph.[12]
30. The majority of predicted clinical applications of genome editing are yet to be fully realised, and are therefore discussed below in response to questions about predicted directions of travel

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[9] Cottle RN, *et al*. (2015). *Controlled Delivery of B-Globin-Targeting TALENs and CRISPR/Cas9 into Mammalian Cells for Genome Editing Using Microinjection*. Scientific Reports **5**, 16031. http://www.nature.com/articles/srep16031

[10] Kleinstiver BP, *et al.* (2016). *High-fidelity CRISPr-Cas9 nucleases with no detectable genome-wide off-target effects*. Nature. **529**, 490-495. http://www.nature.com/nature/journal/v529/n7587/full/nature16526.html

[11] Fu Y, *et al*. (2014). *Improving CRISPR-Cas nuclease specificity using truncated guide RNAs*. Nature Biotechnol **32**, 279–284. http://www.ncbi.nlm.nih.gov/pubmed/24463574

[12] Zetsche B, *et al*. (2015). *Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*. Cell **163**, 759 – 771. http://www.cell.com/abstract/S0092-8674%2815%2901200-3

(paragraph 33). However, ZFNs have already been investigated in a phase I clinical trial to assess the safety of CCR5 modified T-cells for the management of HIV infection.[13] There is also the recent report that TALENs have been used to edit T-cells to successfully treat a case of leukaemia at Great Ormond Street.[14]

31. Safety remains a concern for the clinical application of genome editing techniques; defining and reaching an acceptable standard of safety is therefore one of the more prominent constraints in terms of the translation of genome editing. Such concerns must be explored by ongoing research.

What are the main directions of travel? What are the envisioned endpoints/applications? What is the rate of travel? What are the expected timescales for realising the envisioned endpoints? What are the main 'drivers' and 'obstacles' in relation to envisaged endpoints?

32. As already discussed in response to the question on the value of genome editing as a research tool (paragraph 15), the Academy believes that the ongoing use of genome editing techniques within research has the potential to continue to progress our fundamental understanding of biology while also leading to refinements in the techniques.
33. In terms of clinical applications, the use of genome editing technologies to correct or prevent disease arising from known genetic defects is a key aim for many researchers and patients. TALENs and ZFN technology for use in individual disease gene therapy is being further explored in pre-clinical research using animal models and human cells *in vitro*.[15] Recent proof-of-principle papers for the treatment of Duchenne muscular dystrophy through the use of gene therapy using genome editing (in a mouse model) provides additional, and considerable, hope that genome editing might be a safe and effective treatment option for individuals affected by an otherwise untreatable disease.[16,17,18]
34. These above examples refer to somatic cell therapy applications, and consequently to the use of genome editing to treat an established disease, rather than prevent it. Genome editing could however also conceivably be used to correct a genetic defect in human gametes or pre-implantation embryos. Such an application could be used to prevent the inheritance of a genetically defined disease, and therefore may offer an alternative option to pre-implantation genetic diagnosis (PGD) and pre-natal gene therapy especially in the (admittedly rare) cases where such techniques have limited utility. For example, in cases where both parents are homozygous for a recessive disorder (such as Sickle-cell disease or cystic fibrosis sufferers), or where one parent is homozygous for a dominant disease (such as Huntington's disease), all resulting embryos will be affected and therefore there is no opportunity to select an unaffected

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[13] Tebas P, *et al.* (2014). *Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV*. N Engl J Med **370**, 901-910. http://www.ncbi.nlm.nih.gov/pubmed/24597865?dopt=Abstract&holding=npghttp://www.ncbi.nlm.nih.gov/pubmed/24597865?dopt=Abstract&holding=npg%20

[14] Great Ormond Street Hospital. (2015). *World first use of gene-edited immune cells to treat 'incurable' leukemia.* http://www.gosh.nhs.uk/news/press-releases/2015-press-release-archive/world-first-use-gene-edited-immune-cells-treat-incurable-leukaemia

[15] Urnov FD *et al.* (2015). *Clinical-Scale Genome Editing of the Human BCL11A Erythroid Enhancer for Treatment of the Hemoglobinopathies*. Blood **126.23**: 204-204. https://ash.confex.com/ash/2015/webprogram/Paper83534.html

[16] Long C, *et al*. (2015). *Postnatal genome editing partially restores dystrophin expression in a mouse model of muscular dystrophy*. Science. **aad5725**. http://science.sciencemag.org/content/early/2015/12/29/science.aad5725

[17] Nelson C, *et al.* (2016). *In vivo genome editing improves muscle function in a mouse model of Duchenne muscular dystrophy.* Science. **351**, 403-407. http://science.sciencemag.org/content/351/6271/403

[18] Tabebordbar M, *et al*. (2016). *In vivo gene editing in dystrophic mouse muscle and muscle stem cells*. Science **351**, 407-411. http://www.ncbi.nlm.nih.gov/pubmed/26721686

(or carrier) embryo through PGD.[19] Conversely, it may be possible to correct the genome of such embryos allowing parents to have a biologically related and unaffected child. It should however be remembered that other options (such as gene therapy or PGD) will likely remain valid alternatives in many cases for reasons including suitability, cost, efficiency, and ease of use.

35. Lastly, although most discussion surrounding the use of genome editing focuses on its use on the nuclear genome, genome editing using TALENs has been attempted in mouse eggs with the overall aim of preventing the germline transmission of mitochondrial diseases through the selective elimination of mutated mitochondrial DNA (mtDNA). Although technically feasible, this approach eliminates mutated mitochondria and therefore can cause a detrimental reduction in the total mitochondria copy number, and is not applicable to those women who only harbour mutated mtDNA. Genome editing using CRISPR/Cas9 would be an attractive alternative if it were possible to correct the defect, yet there remains a major technical limitation with respect to getting the CRISPR reagents into the mitochondria. Should this significant technical hurdle be overcome, CRISPR/Cas9 mediated genome editing could become another complementary option alongside the current mitochondrial donation techniques which essentially use the mitochondria from another women unaffected by disease.
36. However, before heritable genetic changes in germline or pre-implantation embryos are considered for therapeutic editing, there is a need to further explore the safety questions raised by such a technique as well as the ethical issues. For example, there is a need to be able to demonstrate approaches that measure the risk, level, and consequences of off-target editing, even if these appear to be low in human cell lines and animal models.

What bearing do international ethical debates and agreements (e.g. high level statements or calls for moratoria) have on the pace or organisation of research?

37. The Academy welcomes and supports the statement published following the International Summit on Human Gene Editing.[20] Although the Academy is supportive of the development of therapeutic approaches based on genome editing, should there be sufficient evidence to do so, we are aware that others have called for a moratorium on germline editing. We believe however that there is a clear and valid distinction between the use of genome editing within research and its potential use for clinical purposes. We are therefore concerned that a moratorium based largely on clinical concerns would directly or indirectly prohibit the use of genome editing techniques within research. While a moratorium would prevent any premature clinical application of this technology, it should not also inhibit the research that is necessary to better understand and mitigate any associated risks. Ongoing research is needed to address the current uncertainties and concerns regarding the efficiency and safety of this technique.

Who should lead and who should be involved in setting policy for research and human applications of genome editing? Is this significantly different from other kinds of experimental or reproductive medicine?

38. The Academy believes the UK is particularly well placed to address the issue of genome editing by virtue of its highly developed bioscience capacity and well-considered regulatory environment. The existing regulatory frameworks (governing research, and both somatic and germline therapies) have robust mechanisms in place that embody the guiding principles of

[19] Lander, ES. (2015). *Brave new genome.* N Engl J Med **373**, 5–8. http://www.nejm.org/doi/full/10.1056/NEJMp1506446?af=R&rss=currentIssue&http://www.nejm.org/doi/full/10.1056/NEJMp1506446?af=R&rss=currentIssue&%20

[20] International Summit on Human Gene Editing. (2015). *On Human Gene Editing: International Summit Statement*. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a

safety and efficacy. In doing so, they provide sufficient grounding for cautiously proceeding with research to explore the possibilities and boundaries of genome editing, and its potential clinical applications, without subjecting humans to undue risk.

39. The editing of somatic cells for research or within a clinical setting would be overseen by the Human Tissue Authority (HTA). The clinical application of somatic cell therapies, including those based on genome editing technologies, would be regulated by the HTA and licensed by the Medicines and Healthcare products Regulatory Agency (MHRA). The Gene Therapy Advisory Committee (GTAC), under the auspices of the Health Research Authority (HRA) is also well placed and has the relevant experience to consider developments coming from this science. In this regard, the policies governing the use of genome editing are not significantly different from other kinds of experimental or reproductive medicine.
40. The use of genome editing in human embryos is a particularly sensitive topic. However, as above, there is already a well-established and rigorous regulatory framework in place in the form of the Human Fertilisation and Embryology Authority (HFEA). The HFEA provides a robust and sufficiently flexible architecture to govern the ethically sound use of human embryos within research up to 14 days post-fertilisation, and under license. In doing so, the HFEA also has the oversight authority to monitor and control research advances well before they reach human intervention.
41. The Academy recognises that there is future potential for genome editing to be used clinically on human germ cells or embryos, although any such application will require a change in law. The HFEA have however shown a strong tradition of being able to satisfactorily govern clinical procedures involving human gametes and embryos (for example, pre-implantation genetic diagnosis (PGD)), and could continue to do so. The recent adoption of mitochondrial replacement therapies - following extensive public and stakeholder engagement - is another good parallel to consider in this context.
42. Broad dialogue will also be important in this case, and a variety of stakeholders should be involved in setting policy for research and clinical applications. Such deliberations should include academic scientists (including those not directly involved in genome editing who may nonetheless be able to provide complementary expertise and insight), ethicists, clinical and wider healthcare professionals, funders, regulators (such as those mentioned above), and patients. Wider public input and consultation is also vitally important, and should continue to be sought throughout.

Have advances in genome editing affected what research is funded, what research strategies are used, or the comparative development of therapeutic strategies?

43. The speed and ease with which genome editing, and in particular CRISPR/Cas9, can facilitate research has opened up a number of experimental avenues. It is therefore likely that such strategies will become more popular in research. In turn, as they become more widespread and refined, the costs and experimental risk associated with these techniques may fall, making them a particularly desirable technique for inclusion in grant applications.
44. Care should however be taken to ensure that a greater emphasis on using and developing genome editing techniques as a preventative mechanism should not detract the research impetus to continue to develop treatments for genetic diseases.

What are the significant decisions that need to be taken before therapeutic use of genome editing may be contemplated (for non-heritable and heritable genetic changes) and who should have the responsibility for those decisions?

45. Ongoing research to better assess and, where appropriate, improve both the safety and efficacy of genome editing is needed before the therapeutic use of genome editing may be contemplated. For example, scientists should be able to demonstrate approaches that measure the risk, level, and effect of off-target editing.
46. For somatic therapies, even very low levels of off-target effects could prove problematic as millions of cells need to be edited, thereby increasing the chance of an off-target effect occurring. However, the most likely off-target sites are those which have a very similar sequence to the desired target sequence and so can be identified by sequencing. Due to the increasing knowledge of the human genome it may also become increasingly possible to predict whether an off-target event will have an effect. Further, ongoing research and refinements to genome editing techniques have led to reductions in the likelihood of off-target modifications (see paragraph 28), and they are becoming progressively rare. Consequently, in situations where a single cell is edited (e.g. fertilised eggs) off-target effects may actually be uncommon, although it is important to note that the science is still largely in its infancy and it is imperative to confirm this through ongoing research.
47. The accuracy and efficiency of on-target (i.e. desired) events should also be considered. Low efficiency editing may be problematic for certain somatic therapies, but is likely to be a particular problem if modifications are being made to early embryos for clinical purposes. For many diseases, low efficiency editing - such that there are both un-modified and successfully modified cells in the embryo (mosaicism) - might not be expected to be sufficient to fully prevent the onset of genetic disease in the resulting offspring.[21]
48. While the risk-benefit considerations are likely to be more complex should genome editing be used for heritable purposes in human gametes or embryos, it may be helpful to be mindful that all somatic therapeutics are associated with a level of risk. It is therefore important to determine what constitutes an acceptable standard of safety, and whether it is appropriately in line with already approved therapies. The protection of patient safety is paramount, but unnecessary regulation of genome editing has the potential to delay beneficial therapies.
49. The Academy believes that the potential of non-heritable and heritable therapeutics based on genome editing should be explored, but we reiterate that their introduction must be based on a strong evidence base, be in line with societal values, and be supported by active engagement with patients and the public to effectively communicate the conditions in which genome editing can, and cannot, be helpful.

Are the benefits and costs of treatments that involve genome editing likely to be distributed equitably (or any more or less equitably than existing or alternative treatments)? In what way might genome editing differentially affect the interests of people in vulnerable or marginalised groups?

50. It is difficult to predict whether treatments based on genome editing will be distributed equitably, as it will be dictated in part by its safety and possible side effects. However, and while continuous monitoring is important, there are no immediately apparent reasons to suggest that they will be differently distributed from existing treatments (such as gene therapy and pre-implantation genetic diagnosis (PGD)). With respect to cost, the considerations will be complex. For example, germline editing might in fact be the least expensive treatment option,

[21] Ishii T. (2015). *Germ line genome editing in clinics: the approaches, objectives and global society*. Briefings in Functional Genomics doi: 10.1093/bfgp/elv053. http://bfg.oxfordjournals.org/content/early/2015/11/27/bfgp.elv053.full

and less so per person than somatic therapies based on genome editing. Both may also be less expensive than conventional life-time treatments.

51. It is important to be aware that there may be some diseases where there are currently no treatments, and alternative options such as PGD are less helpful - for example where one parent is homozygous for a dominant disease (such as Huntington's disease) meaning all embryos will inherit one mutated allele and be affected by disease. In such cases genome editing may be the only efficacious means by which to treat or prevent a disease, and so the perceived need for this technique is likely to be high. Although such cases may be rare, the distress to patients and their families (which may have been present for generations) is an important consideration when decisions are made about investment in finding treatments. However, care should be taken to ensure that the desires of such patients and families to rapidly introduce genome editing do not compromise the appropriate pre-clinical safety and efficacy testing.

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