Section 4

Human health

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Outline

The uses of genome editing in biomedical research are described, whereby the technique is used to investigate gene function in laboratory models, and to create models of genetic disease to study, and to screen potential medicines. Genome editing offers greater control than previous techniques over introduced genetic changes so that their effects can be isolated in laboratory experiments. The cost and efficiency advantages of genome editing are also making research using animal models, such as mice, more efficient, creating new opportunities and challenges. Genome editing is also improving basic biology research into early human embryo development and the treatment of rare genetic disease. Research is also leading to refinements of the genome editing techniques themselves. Moral and societal issues related to laboratory research include consequences for the rate of animal and human embryo experimentation, and shifts in the kind of animals used and in the way they are used (e.g. 'personalised' animals). Other issues include the co-ordination of research and management of research data, and the need to allow for mutual adaptation between research systems and the normative systems that govern them. The accessibility of genome editing may also raise the risk of researchers operating outside the norms of responsible scientific research. Genome editing also potentially disrupts the relationship between research and treatment, which raises further conceptual questions, and questions for the ability of governance systems to adapt, about how research should respond to public interest and about how it should engage with the public.

Research on the potential of genome editing techniques to control viruses and to modify white blood cells to make them effective at combatting HIV and types of blood cancer is described. The potential for genome editing to overcome some of the limitations of existing gene therapy techniques is noted and the potential of epigenome editing described. However, the use of genome editing remains limited by delivery challenges that are familiar to gene therapy. The potential of genome editing to revive the prospects of xenotransplantation is noted, in particular pig-to-human transplants. The effects of economic conditions on the development of commercial therapeutic products are noted. Genome editing therapies raise familiar questions of safety and efficacy that are considered by existing regulatory systems. These may be circumvented or distorted, however, for a number of reasons that are enumerated. Further considerations relating to the relative pace of development and potential reversibility are noted.

The case in which genome editing can produce a normal phenotype in single-gene disorders, through modification of embryo or gamete genomes prior to implantation is noted. This potential future procedure is placed in the context of the current standard of reproductive care for those who wish to avoid passing on genetic disease to their offspring. While indications may be currently very limited, ways in which these might expand can be anticipated. It is noted that such edits would be transmissible through subsequent generations. The existence of various legal and regulatory prohibitions is noted, including the possible need for interpretation or revision in the light of technical advance. The transformative implications of genome editing are considered and a plausible route to genome editing supplanting existing treatment strategies is sketched out; attention is then given to the way in which such developments may be affected by how intermediate social and personal decisions are framed (in particular, the contingency of seeking 'genetic' solutions to 'genetic' problems). The way in which the situation to be addressed and the available means of addressing it are framed may, in fact, strongly condition both the choices open to individuals and how technology and technology governance co-evolve. However, the interrogation of the social meaning of those decisions both brings into question collective values and aims, revealing dissonances and divisions, and also highlights consonances and sympathies.

The continuum of interventions between avoiding serious disease and introducing enhancements, which includes disease prevention, is described. The possibility of selecting beneficial variants and, more generally, of humans taking control of their own evolution in response to potentially catastrophic environmental threats is suggested. Concerns are identified, however, about how non-therapeutic use of genome editing might be constrained and about the social consequences of 'consumerised' biology, although why genomic choices should be of *exceptional* concern invites further investigation.

Introduction

4.1 In this section we identify moral and societal questions that arise in relation to genome editing and human health. There is clearly a coincidence between the questions that are being raised now in relation to genome editing and those that have been discussed in the past in relation to all of those contexts in which genome editing might be used: research involving animal models, human embryos and experimental subjects; cell and gene therapies, 'germ line' interventions, and human enhancement. The aim, in this section and in those that follow, is to explore whether genome editing raises any distinctively new questions, or whether the arrival of genome editing techniques changes the answers to questions that have already been given.

Improving understanding of health and disease

4.2 Genome modification is a standard approach to the investigation of basic biological processes. This takes place using laboratory-grown cell lines or model organisms (for example, fruit flies or mice). A conventional method is to investigate the role of a gene of interest through loss-of-function ('knock out') experiments, in which changes are introduced to prevent the gene from functioning normally in order to study phenotypic consequences that are observable in a laboratory setting.[116] Such consequences may vary according to a host of variables, including the nature of the mutation introduced, the genetic background of an organism, its conditions of housing and the robustness of the tests performed. Thus, the functions ascribed to a gene are usually, to some extent, context-dependent. Genome editing techniques, especially the CRISPR-Cas9 system, have increased the pace and lowered the cost of research, thereby widening the possibilities and allowing the genetic manipulation of cells and organisms that have historically been difficult to modify.[117] A major direction of travel with genome editing is towards making specific changes to a DNA sequence to see how these alter gene function, rather than to delete the gene function completely.[118] This approach also allows the 'repair' of non-functioning genes or the creation of new variants.[119]

4.3 Genome editing techniques can be used to generate cell lines with specific characteristics to provide disease models and investigate underlying pathology, as well as to screen potential medicines by evaluating their toxicity before they are considered for trials in animals and use in human subjects. Many animal models are highly inbred, offering near defined genetic backgrounds for analysis of the consequences of specific mutation. A longstanding limitation with certain human cells (e.g. induced pluripotent stem cells – iPS cells) or outbred animals that are used 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.[120] In combination with other technologies (e.g. iPS cell production), genome editing can be used to develop cells whose genetic background is identical (isogenic) to that of the disease model. Editing isogenic genomes introduces a change so that the cell line differs only in respect of that specific change. This gives greater certainty about the effect of the precise, known difference between the disease variant and the control.

Box 4.1: Example of CRISPR-Cas9 use in basic research

A research group led by Dr Adrian Saurin from the University of Dundee, is funded by Cancer Research UK to use CRISPR-Cas9 to target and edit genes in cell lines in order to understand how the proteins produced by these genes work. They have a particular interest in studying proteins involved in cell division. Before CRISPR-Cas9 was available, Dr Saurin's research relied on making the cells that artificially produce excess amounts of the protein they were interested in, which is not representative of the normal biology of the cells. Moreover, if they wanted to switch off the gene, they would have had to rely on technology that was not very efficient or precise.

Source: Response to *Call for Evidence* by the AMRC.

4.4 Much basic research takes place using animal models to study biological functioning and the causes of disease. Mice are a common animal model because they are relatively easy to manipulate and breed (compared to larger animals), their development, genetics and husbandry are well-understood, they are cost effective, and they share significant similarities with human

[116] Response to *Call for Evidence* by the Royal Society.
[117] See, generally, section 2 (above) and, in this connection, Sander JD and Joung JK (2014) CRISPR-Cas systems for editing, regulating and targeting genomes *Nature Biotechnology* **32**(4): 347-55.
[118] Researchers have used gRNAs separated by several kb to clip out gene segments and applications are developing. See, for example: Boroviak K, Doe B, Banerjee R, *et al*. (2016) Chromosome engineering in zygotes with CRISPR/Cas9 *Genesis* **54**(2): 78-85.
[119] Response to *Call for Evidence* by the Royal Society; Dow LE (2015) Modeling disease in vivo with CRISPR/Cas9 *Trends in Molecular Medicine* **21**(10): 609-21.
[120] Musunuru K. (2013) Genome editing of human pluripotent stem cells to generate human cellular disease models *Disease Models and Mechanisms* **6**(4): 896-904.

biology. There are nevertheless a number of limitations in using mouse models: despite their advantages compared to other animals, substantial time, cost and skill are still required to generate and analyse new variants. Genome editing is helping to overcome the technical and financial obstacles to mouse research and to bring them within the cost and time constraints of, for example, a 3 to 4-year PhD or post-doctoral research project.[121] At the same time, however, new genome editing methods are bringing new challenges, including the curation of many different genetically altered lines and managing genetic complexity made possible through editing of multiple loci.[122] Meanwhile the use of genome editing strategies is expected to increase dramatically, with the focus slowly shifting to larger animal models such as dogs, pigs, sheep and primates as biological limitations in other models are discovered.[123] There is also an expectation that increased use of CRISPR-Cas9 will make it more likely that research will diversify into modelling a greater variety of diseases, including individually 'rare' diseases.[124] These are a growing focus as more disease-causing mutations are discovered, which are potentially more tractable to the available technology than complex polygenic diseases.[125] An intriguing prospect is the development of 'personalised' mutant animals that model a disease variant affecting a particular human family or individual.[126]

4.5 Genome editing is also a promising technique for increasing understanding of basic human biology and investigating early development in human embryos. Where such research is permitted, the embryos are either donated by couples who are undergoing assisted conception treatment and who no longer need the embryos to complete their families, or they may be created in the laboratory with donated sperm and eggs specifically for the purposes of research. Although not all jurisdictions permit research on human embryos, in the UK such research may be carried out only under licence from the regulator, the Human Fertilisation and Embryology Authority. The first such licence was granted to the Francis Crick Institute in London for research to understand embryonic development and developmental problems that might contribute to implantation failure and miscarriage.[127] Elsewhere, two Chinese research groups have modified embryos in order to edit genes involved in human disease, although in each case tripronuclear embryos were used, as these are thought to be unable to develop into a baby.[128]

4.6 Greater use of genome editing in biological research can also be expected to lead to greater understanding and refinement of the techniques themselves. In the context of genome editing, a new generation of Cas9 protein has been engineered that appears to be so efficient that no off-target cutting is detectable across the whole genome when this is sequenced.[129] The technique has also been extended, for example to overcome limitations to the visualisation of multiple genomic loci by using 'nuclease-dead' Cas9 to bind to cells with up to seven distinct fluorescent markers. This allows researchers to track the location of genes in a chromosome in living cells, which is important in understanding what happens (and what can go wrong) in cellular

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[121] Response to *Call for Evidence* by MRC Harwell.
[122] Ibid.
[123] Whitelaw CBA, Sheets TP, Lillico SG and Telugu BP (2015) Engineering large animal models of human disease *The Journal of Pathology* **238**(2): 247-56.
[124] Though individually rare, there are thought to be between 6,000 and 8,000 rare diseases, affecting an estimated 3.5 million people in the UK and 350 million worldwide. See: http://www.raredisease.org.uk/about-rare-diseases.htm; https://globalgenes.org/rare-diseases-facts-statistics/.
[125] See Department of Health (2013) The UK strategy for rare diseases, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf.
[126] Response to *Call for Evidence* by MRC Harwell. That this is an area of active interest was confirmed in interview with a biotech services and product company (research interview with Ruby Yanru Chen-Tsai, Applied Stem Cell, Inc.).
[127] Licence granted on 1 February 2016; see: http://www.hfea.gov.uk/10187.html.
[128] Liang P, Xu Y, Zhang X, *et al*. (2015) CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes *Protein and Cell* **6**(5): 363-72; Kang X, He W, Huang Y, *et al*. (2016) Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing *Journal of Assisted Reproduction and Genetics* **33**(5): 581-8. Tripronuclear embryos have traditionally been considered to be non-viable, but it has recently been shown that some can develop for several days and form embryos with the normal number of chromosomes (see: Yao G, Xu J, Xin Z, *et al*. (2016) Developmental potential of clinically discarded human embryos and associated chromosomal analysis *Scientific Reports* **6**: 23995).
[129] Slaymaker IM, Gao L, Zetsche B, *et al*. (2016) Rationally engineered Cas9 nucleases with improved specificity *Science* **351**(6268): 84-88; Kleinstiver BP, Pattanayak V, Prew MS, *et al*. (2016) High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects *Nature* **529**(7587): 490-95.

development.[130] As well as developing greater power to effect precise and reliable changes, development of genome editing tools may help to give greater confidence in their use in clinical conditions to treat disease by addressing safety concerns.

Moral and societal questions identified

4.7 There is some dispute concerning whether the cost, efficiency and versatility advantages of genome editing will lead to the use of more or fewer animals in research. By refining targeted genome modification (for example, through CRISPR-Cas9-mediated multiplex editing in zygotes, the method promises to reduce the number of animals required for a given experiment, consistent with the principles of reduction and refinement in the '3Rs' (refine, reduce, replace)).[131] However, the relative efficacy and ease-of-use of CRISPR-Cas9 mean that more researchers are likely to use it to address questions in whole animals that were previously technically beyond their reach, potentially increasing the overall number of animal experiments performed. This may mean a lower animal use *relative to the rate of knowledge production* but it is also possible that it will lead to an increased rate of experimentation, and to the risk of poorly planned or coordinated research.

4.8 Whether or not the concern about the rate of use of animals is misplaced, there are possibly other reasons to worry about the rate of experimentation (although generation of mutant animals may not be the rate-limiting step).[132] These other reasons may include contingent limits on the rate of adaption to new knowledge within the scientific community (and the relative capacity of ancillary functions such as scientific publishing and peer-to-peer communication), leading to a lack of coordination among research groups and unnecessary duplication of work. On the other hand, increased competition might, in principle, streamline experimental output and enhance data quality.[133] Interpreting genome editing data may depend on the effectiveness of associated knowledge forms (e.g. technical, scientific, social science and moral knowledge) necessary to understand its likely impacts and implications. It may also require the adaptation of normative structures – such as laws, codes of conduct and regulatory protocols – to govern it effectively and to ensure public confidence.

4.9 As well as its potential impact on small animal research, concerns have arisen about the use of genome editing in larger animal models (e.g. use of primates for modelling neurological disorders). There are indications that, for example, the Chinese Government is making prodigious amounts of money available for large animal research.[134] Demand for more larger animal research may increase as genome editing fulfils the promise to overcome hitherto intractable research problems, such as the elimination of porcine endogenous retroviruses (PERVs) in pigs modified for xenotransplantation (see below).

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[130] Ma H, Tu L-C, Naseri A, *et al*. (2016) Multiplexed labeling of genomic loci with dCas9 and engineered sgRNAs using CRISPRainbow *Nature Biotechnology* **34**(5): 528-31.

[131] For '3 Rs' see: https://www.nc3rs.org.uk/the-3rs; Association of Medical Research Charities (AMRC); Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC), responding to our *Call for Evidence*. See also: Nuffield Council on Bioethics (2005) *The ethics of research involving animals*, available at: http://nuffieldbioethics.org/wp-content/uploads/The-ethics-of-research-involving-animals-full-report.pdf.

[132] In most cases, the majority of the time and cost is accounted for by phenotypic and molecular analyses and the identification of a 'mechanism', which is often required for publication.

[133] Resources to collate, share and understand data generated through genome editing are being developed. By the end of 2014, CRISPR had been mentioned in more than 600 research publications and by June, 2016 this figure had more than doubled; a PubMed search for 'CRISPR' hits around 3900 papers. CRISPR research dominates the genome editing literature (Ledford H (2015) CRISPR, the disruptor *Nature* **522**(7554): 20-4). "[…] in terms of shaping research and development, resources for cataloguing the vast quantities of data CRIPSR generates are sorely needed to encourage and facilitate collaboration and knowledge sharing. One such rare resource is CrisprGE: a dedicated repository-containing total of 4680 genes edited by CRISPR/Cas approach (Kaur et al., 2015). Allocations of realistic funding in all areas across this field are essential to achieve this", response to *Call for Evidence* by Dr. Helen O'Neill; Kaur K, Tandon H, Gupta AK and Kumar M (2015) CrisprGE: a central hub of CRISPR/Cas-based genome editing *Database: The Journal of Biological Databases and Curation* **2015**: bav055, doi: 10.1093/database/bav055.

[134] Cyranoski D (2016) Monkey kingdom *Nature* **532**(7599): 300-2.

4.10 The possibility of 'personalised mutant animals' may raise new issues for the relationship between medicine and research as a direct connection is made between specific patients and animal models in the laboratory.[135] Some patients may find this personal correspondence significantly different from the more conventional case in which animal models are used for research into the condition by which they are affected generally, rather than their 'own' condition. As well as being a novel prospect for psychology, it may also raise questions of privacy and of equity (e.g. who should have, and who not have, a personalised animal model, and under what conditions?).

4.11 Concerns also arise about the instrumental use of human embryos in biomedical research using genome editing. Many people, and a number of faith groups, have a principled opposition to destructive embryo research. Such opposition is enshrined in national legislation in many countries and many more countries permit the use of supernumerary embryos from fertility treatment yet forbid the creation of embryos for the purposes of research rather than reproduction (although the relationship between these two positions is not ethically straightforward). Questions about the acceptability of using human embryos in research are, of course, not peculiar to genome editing and are likely to continue to be divisive. As with animals, there is a question about potentially increasing demand, although this prospect, too, arose in relation to the demand for embryos for human embryonic stem cell (hESC) research in the first decade of the present century.[136]

4.12 A distinctive consideration relating to genome editing is that it potentially brings 'basic' biological research and translation to clinical treatment into closer conjunction. This is so because, in some cases, alteration of a genome sequence could, in principle, serve both to discover the function of the gene and to enable treatment. For example, where genome editing is used to modify mutations known to lead to disease (see below), the edit that is made to study the disease in a laboratory cell population may, *mutatis mutandis*, be the same edit that is required to treat the disease in a human subject; the proof of concept of the research technique may equally constitute a proof of concept for a prospective treatment. This argument was used in support of the first two published cases of genome editing in human embryos.[137] One reason this research excited international controversy was that, although non-viable tripronuclear embryos were used, the outcome brought the prospect of preimplantation embryo modification significantly closer.[138] The controversy has prompted those who wish to protect genome editing research involving human embryos to re-emphasise the conceptual distinction between research and innovation.[139] This situation has parallels with the development of somatic cell nuclear transfer ('cloning') techniques in the late 1990s, when a distinction was drawn between 'therapeutic cloning' and 'reproductive cloning' on the basis of whether the cloned embryos were intended to be transferred to a woman.[140]

4.13 Those who publicly opposed the application made by the Francis Crick Institute in the UK to perform genome editing for research on human embryos may have taken comfort from the fact that (although the use of embryos in the research project was licensed under multiple purposes

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[135] See the Genome Editing Mice for Medicine (GEMM) initiative launched in 2016 by the Mary Lyon Centre at MRC Harwell, to include the generation of bespoke genetically altered mice harbouring specific point mutations equivalent to those associated with disease in humans. See: https://www.har.mrc.ac.uk/gemm-call-guidence-applicants.

[136] Araki M and Ishii T (2014) International regulatory landscape and integration of corrective genome editing into in vitro fertilization *Reproductive Biology and Endocrinology* **12**: 108; Baumann M (2016) CRISPR/Cas9 genome editing – new and old ethical issues arising from a revolutionary technology *NanoEthics* **10**(2): 139-59.

[137] Liang P, Xu Y, Zhang X, *et al*. (2015) CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes *Protein and Cell* **6**(5): 363–372; Kang X, He W, Huang Y, *et al*. (2016) Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing *Journal of Assisted Reproduction and Genetics* **33**(5): 581-8.

[138] As it was, the research demonstrated a high failure rate and (it has been argued) provided little scientific insight (see, for example, Scott C (2015) Treading the line between sensational and groundbreaking science *The American Journal of Bioethics* **15**(12): 1-2). Much of the frustration among scientists may have been to do with the fact that it represented the prospects for embryo modification poorly by offering a compromised example, whilst demonstrating a failure of self-regulation in the global scientific community and calling down public disapproval. It did, however, have the effect of provoking important debates, both scientific and ethical (see: Kaiser and Normile (2015) Embryo engineering study splits scientific community *Science* **348**(6234):486-7).

[139] The Wellcome Trust argue, for example, that "[…] Research need not necessarily lead to clinical applications, and regulators and society will need to consider the two issues independently", response to *Call for Evidence* by the Wellcome Trust.

[140] Gurdon JB and Colman A (1999) The future of cloning *Nature* **402**(6763): 743-6.

that included 'developing treatments for serious diseases or other serious medical conditions', 'increasing knowledge about the development of embryos' and 'promoting advances in the treatment of infertility') reassurance was given that the procedure used in the research could not be adapted as a treatment.[141] (Transferring modified embryos to a woman would, in any case, be unlawful in many jurisdictions, including the UK.) It is, nevertheless, a possible peculiarity of the genome editing technique that demonstrating success with the technique in certain research contexts could constitute a proof of concept that would support – that may, arguably, be *sufficient* to support – a hypothetical treatment application using the same (proven) technique on a different but well-characterised target. If this were the case, the conjectured proof-of-principle would remove any comfort derived from a situation in which the research could not be turned into treatment, or in which success in research does not make genome editing treatments more likely. This might be articulated as a concern about 'technological momentum' whereby the speed and impact of advancing technology pressurise normative structures, which may be unable to adapt at the same pace and may be ridden over by innovation without regard for any external considerations.[142] (This is potentially different from the case of cloning (referred to above) in that there were few reasons put forward in support of human 'reproductive' cloning in the face of overwhelming international opposition.)

4.14 Another dimension of the concern about the elision of basic and applied research is the potential for basic research to be applied in uncontrolled ways and by scientists who may not be socialised into the notional global community of responsible researchers. Some of these concerns have surfaced in relation to the amenability of CRISPR-Cas9 tools for use by DIY biologists, raising biosafety concerns.[143] Others have been expressed in relation to the potential of CRISPR-Cas9 for harmful gain-of-function research and 'dual use'.[144] Inasmuch as some may regard the researchers who reported human embryo genome editing experiments as 'mavericks' in relation to the responsible mainstream 'international scientific community', this may reinforce scepticism that such a community exists or is able to regulate itself effectively. This scepticism has been a constant presence in discussions about the conduct and inclusiveness of various high level meetings organised by leading members of the scientific community, and about the need that some claim for an international moratorium to reinforce the weakened distinction between research and application, to provide a circumvallated space for free scientific inquiry.[145] Among certain leading researchers, favourable parallels have been drawn to the Asilomar conference of 1975, which has become emblematic in the debate about regulation.[146] The calls for a 'second Asilomar', however, have drawn criticism, firstly, in relation to the lack of similarity between

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[141] This is notwithstanding the fact that the licence authorises the use of embryos for the purpose of 'developing treatments for serious diseases or other serious medical conditions'. In complex research projects, the HFEA accepts applications that involve a number of different activities under multiple purposes in Sched.2, para.3A (1) and (2) although the correspondence between the activities and purposes is not always clear. This is potentially another area where a margin of trust lies between regulation and research. See HFEA Licence Committee Minutes at: http://guide.hfea.gov.uk/guide/ShowPDF.aspx?ID=5966.

[142] See Hughes TP (1994) Technological momentum, in *Does technology drive history? The dilemma of technological determinism*, Smith MR and Marx L (Editors) (Cambridge, MA and London: MIT Press), pp 101-113. The impact of genetic testing and particularly of genome sequencing and associated data science, for example, has required reconsideration of information governance norms that assume simple models of correspondence between data and people and the sufficiency of simple methods of anonymisation.

[143] See section 7 (below).

[144] Lentzos F (2015). *Dual use in biology and biomedicine*, background paper commissioned by the Nuffield Council on Bioethics, available at: http://nuffieldbioethics.org/wp-content/uploads/Background-paper-2016-Dual-use.pdf. See also: The Guardian (26 April 2015) *Can we trust scientists' self-control?*, available at: https://www.theguardian.com/science/political-science/2015/apr/26/can-we-trust-scientists-self-control; Lentzos F (2015) Engage public in gene-editing policy *Nature* **521**(7552): 289.

[145] Sharma and Scott (2015) contend that there is "a gathering consensus to ban germline research that would make babies, but the dividing line has become whether *in vitro* research such as the *Protein & Cell* paper should be permitted" and that in vitro human germline research should not be prohibited given that risks can only be assessed once better understood and that early human development "differs substantially from the development of other animals" (Sharma A and Scott CT (2015) The ethics of publishing human germline research *Nature Biotechnology* **33**(6): 590-2, at page 591); an editorial in *Nature* summarised there is "a strong basic-science incentive for such experiments, which can help us to understand human development and perhaps be used to produce useful cell lines" (Nature editorial (2015) Splice of life *Nature* **521**(7550): 5).

[146] See section 3 above. See also: Miller HI (2015) Recasting Asilomar's lessons for human germline editing *Nature Biotechnology* **33**(11): 1132-4. (On the 1975 Asilomar Conference on recombinant DNA, see Box 3.1 above.)

genome editing and early recombinant DNA research in terms of the size of the community of practitioners and the scope of the issues, and, secondly, with regard to the narrowness of the debate process and the dominance of scientific interests within it, which a 'second Asilomar' would repeat.[147] Many have conceded that – unlike the case at Asilomar – a moratorium, even if it were desirable, would be unfeasible.[148]

4.15 To the extent that the distinction between basic and translational research, and between research and clinical treatment, is weak in the case of genome editing, a corresponding question arises about how far public interest reaches through into 'basic' research. This touches on the extent to which the aims of research, research funding and research policy should be subject to public scrutiny and influence. The public interest in embryology research is already recognised in the UK in the existence of the HFEA and the publicly engaged way in which HFEA has developed some of the more controversial aspects of its licensing policy. Research in other areas, however, is largely influenced by funding that has tended to follow expert advice based on criteria of research excellence, inflected by political *dirigisme* to a historically varying extent (a stronger orientation towards societal challenges, 'impact' and economic value have emerged in recent years). The development of responsible research and innovation (RRI) approaches has drawn attention to the failures of political and economic control of research to respond to public interest and social values, and the moral imperative of greater public engagement with science at all levels.[149] In its statement on genome editing technologies, the Council of Europe Bioethics Committee, while asserting the principles contained in the Oviedo Convention as a reference point, has called for enhanced public debate.[150] The engagement of public interest potentially brings in a wider set of questions, some of which go to the social value and moral good of science itself or challenge the contingent (or arbitrary) allocation of resources to particular areas of research on grounds of global equity.[151]

Treating disease

4.16 A potential use of genome editing is preventing the transmission of communicable diseases, for example as a component of gene drive technologies that can be used to manage disease vectors, such as mosquitoes. As the direct focus of such interventions is on insect ecologies rather than patients we will consider these in a subsequent section (section 6) that addresses the impact of genome editing technologies in the environment. Engineering disease resistance into humans, a more speculative strategy, is considered below. Here, however, we focus on the use of genome editing in gene, cell and tissue transplantation-based therapies. Just as genome editing promises to help scientists overcome some of the road blocks that have held up 'basic' research, it also offers promising approaches to overcoming some of the difficulties that have impeded the development of medical treatment. The potential to overcome such road blocks is most apparent in the areas of gene therapy and xenotransplantation.

4.17 There is evidence that CRISPR-Cas9 can be used to target and disrupt the genomes of viruses directly, in order to inactivate the pathogen. Research with the Hepatitis B virus suggests that

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147 Jasanoff S, Hurlbut JB and Saha K (2015) CRISPR democracy: gene editing and the need for inclusive deliberation *Issues in Science and Technology* **32**(1), available at: http://issues.org/32-1/crispr-democracy-gene-editing-and-the-need-for-inclusive-deliberation/.

148 Adashi EY and Cohen IG (2015) Editing the genome of the human germline: may cool heads prevail, *The American Journal of Bioethics* **15**(12): 40-2; Hawkes N (2015) UK scientists reject call for moratorium on gene editing *BMJ* **350**: h2601, doi: 10.1136/bmj.h2601.

149 This has been developed, in particular, through initiatives by the Science and Technology Studies (STS) disciplines; see, for example, Stilgoe J, Owen R, and Macnaghten P (2013) Developing a framework for responsible innovation *Research Policy* **42**(9): 1568-80. See also: RRI in Horizon 2020, the EU framework programme for research and innovation, https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation.

150 See https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=090000168049034a.

151 For example: "It is outrageous to discuss genetic enhancements for the privileged in developed countries, when the poor of these same nations and of others around the world lack even rudimentary access to the health-care services needed to ensure basic survival. [...] If the gap between the privileged and the underprivileged continues to grow, wealth-based access to health care and future genetic enhancements will threaten the basic structures of society." Mwase IM (2005) Genetic enhancement and the fate of the worse off *Kennedy Institute of Ethics Journal* **15**(1): 83-9.

genome editing approaches could control the virus and possibly cure patients.[152] HIV has been another target, although using CRISPR-Cas9 to attack HIV directly has recently been questioned: researchers have demonstrated that many 'indels' (see section 1) introduced to HIV-1 by CRISPR-Cas9 are lethal for the virus, as expected, but others can lead to increased virulence.[153]

4.18 One promising area of research has been the use of genome editing to modify T cells to attack HIV infection.[154] (T-cells are a kind of lymphocyte – a white blood cell – involved in the elimination of pathogen-infected cells). Similar strategies are being researched for the treatment of leukaemia, lymphoma and other types of blood cancer.[155] Cell-based therapies have potentially significant advantages over conventional treatment options in terms of both effectiveness and legacy, since the modified immune cells selectively and continuously attack the cancer cells without damaging unaffected tissues. Using TALENS to edit the T-cells, this strategy was used successfully to treat a child with acute lymphoblastic leukaemia in 2015, the first reported therapy involving genome edited cells (in this case from donors rather than the child herself).[156]

Box 4.2: TALENS used successfully to treat acute lymphoblastic leukaemia

The team at Great Ormond Street Hospital (GOSH) used modified T-cells from donors, known as UCART19 cells, to treat a one-year-old child with an aggressive form of acute lymphoblastic leukaemia (ALL) who had already had unsuccessful chemotherapy and for whom palliative care was the only other remaining option.

The treatment worked by editing healthy donor T-cells, using molecular tools (TALENs) to cut specific genes in order to make them behave in two ways. Firstly, they become invisible to a powerful leukaemia drug, Alemtuzumab, that would usually kill them and, secondly, they are reprogrammed specifically to target and fight against leukaemia cells.

The team at GOSH and the Institute of Child Health, with investigators at University College London and the biotech company Cellectis, had been developing 'off-the-shelf' banks of these donor T-cells, the first of which was due to be used for final stage testing ahead of clinical trials. However, the team received a request for therapy on a compassionate basis for an 11-month old girl with refractory relapsed B-acute lymphoblastic leukaemia, and were able to provided treatment under UK special therapy regulations. At an early stage of follow up, the team reports induced molecular remission in this patient where all other treatments had proved ineffective.

Source: See: http://www.gosh.nhs.uk/news/press-releases/2015-press-release-archive/world-first-use-gene-edited-immune-cells-treat-incurable-leukaemia; Qasim W, Amrolia PJ, Samarasinghe S, *et al*. (2015) First clinical application of Talen-engineered universal CAR19 T cells in B-ALL *Blood* **126**(23): 2046.

4.19 Cell based therapies involve transfusion or transplantation of cell populations that are edited expanded and prepared in the laboratory. For diseases where the affected cell type is hard to graft back, for solid tumours, and to target affected tissue directly, it may be possible to use a vector (e.g. a virus) as a kind of Trojan Horse to introduce the genome editing tools to make the necessary repairs within the patient's body. Genome editing offers a promising strategy to overcome difficulties associated with lack of precision when inserting new genetic material and the potential effects of viral vectors that have limited the success of *in vivo* gene therapy to date. Research is being carried out, for example, using the CRISPR-Cas9 system to edit the *CFTR*

[152] Ramanan V, Shlomai A, Cox DBT, *et al*. (2015) CRISPR/Cas9 cleavage of viral DNA efficiently suppresses hepatitis B virus *Scientific Reports* **5**: 10833.

[153] Some indels "lead to the emergence of replication competent viruses that are resistant to Cas9/sgRNA. This unexpected contribution of Cas9 to the development of viral resistance is facilitated by some indels that are not deleterious for viral replication, but that are refractory to recognition by the same sgRNA as a result of changing the target DNA sequences. This observation illustrates two opposite outcomes of Cas9/sgRNA action, i.e., inactivation of HIV-1 and acceleration of viral escape, thereby potentially limiting the use of Cas9/sgRNA in HIV-1 therapy." Wang Z, Pan Q, Gendron P, *et al*. (2016) CRISPR/Cas9-derived mutations both inhibit HIV-1 replication and accelerate viral escape *Cell Reports* **15**(3): 481-9.

[154] Tebas P, Stein D, Tang WW, et al. (2014) Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV *New England Journal of Medicine* **370**(10): 901-10.

[155] See, for example, research on editing specificity and function to enhance T cell therapy of haematological malignancies funded by Bloodwise by Professors Hans Stauss and Emma Morris at UCL Medical School cited by the AMRC, responding to our *Call for Evidence*.

[156] See: http://www.gosh.nhs.uk/news/press-releases/2015-press-release-archive/world-first-use-gene-edited-immune-cells-treat-incurable-leukaemia; Reardon S (2015) Gene-editing wave hits clinic *Nature* **527**(7577): 146-7.

gene in order to repair mutations that lead to cystic fibrosis and in the dystrophin gene, in which mutations lead to Duchenne and Becker muscular dystrophy (see Box 4.3).[157]

Box 4.3: Muscular dystrophy research

There are some genetic diseases that 'conventional' gene therapy will struggle to address for technical reasons; for example, Duchenne muscular dystrophy (DMD), in which the size of the dystrophin gene makes it difficult to express using the currently available gene therapy vector systems.[158] DMD, with a life expectancy of mid-20s, and Becker muscular dystrophy (BMD), which is progresses more slowly, are X-linked muscle wasting conditions affecting 2,500 and 2,400 children and adults in the UK respectively.

In one project example, Muscular Dystrophy UK is co-funding research in Professor George Dickson's laboratory at Royal Holloway, University of London. The team have developed an innovative gene editing technique with the potential to repair the genetic mutations that cause DMD. The technique could be the first therapy that offers permanent correction of these genetic mutations. The technique is applied to adult muscle cells.

Muscular Dystrophy UK is also co-funding a three-year project in Professor Francesco Muntoni and Dr Francesco Conti's laboratories at the UCL Institute of Child Health. The aim of the study is to develop the use of gene editing to treat children with DMD in cases where the condition is caused by a duplication in exon 2 of the dystrophin gene (the cause of 10-15% of DMD cases). Genome editing will be used to excise the duplicated exon 2 and restore an intact dystrophin gene so that it is fully functional. It would, in effect, be a permanent treatment for Duchenne muscular dystrophy caused by a duplication.

Like other research bodies, Muscular Dystrophy UK are keen to distinguish somatic and germ line research: "It is vital to gain public understanding of the different ways in which gene editing is being used, so that this technique is not only associated with embryonic research."

Source: Response to *Call for Evidence* by Muscular Dystrophy UK.

4.20 Another potential therapeutic strategy for diseases of epigenetic dysregulation, such as cancers, is to use epigenomic editing. This could be achieved using a Cas9 protein that has been modified to deliver an epigenetic modification to a target site rather than to cut the genome.[159] Cas9 might also be altered, or related enzymes may be employed, to cleave different forms of RNA, with potential application to the removal of infectious RNA viruses (e.g. rotavirus, Ebola and Zika) or in the recognition of eukaryotic RNA carrying modifications such as methylation.[160]

4.21 While genome editing is a promising development in the field of gene therapy, it faces many of the delivery challenges faced by gene transfer. In particular, ways must be found to target and deliver the genome editing machinery to sufficient numbers of specified cells within the patient to ameliorate or reverse the disease symptoms.[161]

4.22 While bottlenecks to many gene therapy applications remain to be overcome, genome editing has, however, revived the prospects of another therapeutic strategy: xenotransplantation. (Xenotransplantation is transplanting tissues or organs from one species to another, for example, pig hearts into human patients.) A longstanding challenge for pig-to-human xenotransplantation is the presence of the porcine endogenous retrovirus (PERV) in pig tissues. This is a significant safety concern in pig-to-human transplants, because some PERVs are able to skip from pig to human cells, raising the possibility of trans-species infection (zoonosis) after the xenotransplantation procedure. In a reported experiment, CRISPR-Cas9 was used to excise all

[157] For CF, see research led by Dr Patrick Harrison at University College Cork and funded by The Cystic Fibrosis Trust, to develop the next generation of genetic therapy for cystic fibrosis. (See: https://www.cysticfibrosis.org.uk/the-work-we-do/research/research-areas/gene-therapy/second-generation-cftr-gene-repair.)

[158] Response to *Call for Evidence* by the Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC).

[159] Yao S, He, Z and Chen, C (2015) CRISPR/Cas9-mediated genome editing of epigenetic factors for cancer therapy *Human Gene Therapy* **26**(7):463-71; Sayin VI and Papagiannakopoulos T (2016) Application of CRISPR-mediated genome engineering in cancer research *Cancer Letters*, doi: http://dx.doi.org/10.1016/j.canlet.2016.03.029 (published online 18 March 2016).

[160] Abudayyeh OO, Gootenberg JS, Konermann S, *et al*., (2016) C2c2 is a single-component programmable RNA-guided RNA-targeting CRISPR effector *Science*, doi: 10.1126/science.aaf5573; Price AA, Sampson TR, Ratner HK, Grakoui A and Weiss DS (2015) Cas9-mediated targeting of viral RNA in eukaryotic cells *Proceedings of the National Academy of Sciences* **112**(19): 6164-9.

[161] Maeder ML and Gersbach CA (2016) Genome-editing technologies for gene and cell therapy *Molecular Therapy* **24**(3): 430-46.

62 copies of the PERV in porcine cells cultured *in vitro*.[162] Xenotransplantation researchers view genome editing as having 'game changing' potential to accelerate research in this area.[163]

> "In the last five years, with the advent of programmable nucleases more recombinant pigs have been generated than in the previous 25 years combined by conventional genetic engineering. It is reasonable to assume that, in the next 5 years, due to genome editing further considerable advancements will be made. This is expected to rapidly impact on clinical applications that entail the use of cells, tissues or scaffolds and, within 10 years, on the clinical application of solid organ xenotransplantation (heart, kidney, liver)."[164]

4.23 Genome sequences are now available for several different pig breeds, reducing the time needed to design specific editing tools. A significant obstacle will be achieving results in primate models that are required before moving into humans.[165] Because it requires a relatively large capital outlay, the development of xenotransplantation is particularly subject to business conditions, as the research is concentrated in academic spin-outs that are reliant on their edited pigs for their intellectual property, which they need in order to attract pharmaceutical industry backing before they can move into trials.

4.24 Most of the therapeutics currently in development are being developed by small and medium-sized enterprises (SMEs), often spin-outs from academic research institutes, some of which have been acquired by traditional pharmaceutical companies, replaying the pattern established for biotechnology in the 1980s. Many spin-outs have assembled significant finance and are aligned with the principal patent claimants on the underlying technology. Thus, *Editas Medicine* (established in 2013 and backed by Bill Gates and *GV*, the venture capital arm of *Alphabet*, *Google*'s parent company) are aligned with the patent claim filed by Feng Zhang and the Broad Institute at Harvard.[166] They have a wide range of therapeutic targets but intend to begin clinical trials in 2017 with a treatment for eye disease.[167] Jennifer Doudna, the rival claimant in the dispute over ownership of IPR in CRISPR-Cas9, co-founded *Caribou Biosciences* to develop the technique for therapeutic, agricultural and industrial uses. *Intellia Therapeutics* (the therapeutic part) has licensed its technology to the pharmaceutical company, *Novartis*, to develop new CRISPR-Cas9-based therapies using chimeric antigen receptor T cells (CAR T cells) and hematopoietic stem cells,[168] and to *Regeneron* pharmaceuticals to edit liver cells to treat disease.[169] Other research is well advanced using different genome editing techniques: *Sangamo Biosciences* are pursuing ZFN strategies in which they have strong intellectual property interests, to develop therapeutics for lysosomal storage disorders and other monogenic diseases, hemoglobinopathies, HIV/AIDS, cancer immunotherapy, as well as using genome editing and gene and cell therapeutics for clinical applications in the liver.[170] This landscape is changing continuously and is avidly reported in the business press.

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[162] Yang L, Güell M, Niu D, *et al*. (2015) Genome-wide inactivation of porcine endogenous retroviruses (PERVs) *Science* **350**(6264): 1101-4.

[163] Response to *Call for Evidence* from researchers involved in two large EU-funded xenotransplantation projects: Xenoislet (http://xenoislet.eu/) and TransLink (http://www.translinkproject.com).

[164] Response to *Call for Evidence* by Galli C, Takeuchi Y, Gianello P, Scobie L, and Cozzi E, Xenoislet and TransLink projects.

[165] It is possible that work on this front will progress more rapidly in China than elsewhere. See: Cyranoski D (2016) Monkey kingdom *Nature* **532**(7599): 300-2.

[166] Wired (4 February 2016) *CRISPR gene-editing upstart Editas goes public as patent battle rages*, available at: http://www.wired.com/2016/02/crispr-gene-editing-upstart-editas-goes-public-as-patent-battle-rages/.

[167] Research interview with Editas. See also: New Scientist (27 July 2016) *CRISPR genome editing could save sight by tweaking DNA*, available at: https://www.newscientist.com/article/mg23130843-900-crispr-genome-editing-could-save-sight-by-tweaking-dna.

[168] Mullard A (2015) Novartis secures first CRISPR pharma collaborations *Nature Reviews Drug Discovery* **14**(2): 82.

[169] Tech Times (12 April 2016) *CRISPR/Cas firm Intellia files IPO, announces $125 million deal with Regeneron*, available at: http://www.techtimes.com/articles/149334/20160412/crispr-cas-firm-intellia-files-ipo-announces-125-million-deal-with-regeneron.htm.

[170] http://investor.sangamo.com/releasedetail.cfm?ReleaseID=941603; http://www.streetinsider.com/Corporate+News/Sangamo+Biosciences+%28SGMO%29+to+Present+Data+From+Several+ZFP+Therapeutic+Programs+at+ASGCT+Meeting/11514295.html.

Moral and societal questions identified

4.25 There is always some risk attached to the introduction of a new therapeutic product. This ever-present possibility raises issues that are familiar in medical ethics. In the case of genome editing, these issues can be posed in terms of whether, having regard to what is known about the safety of the technique and its likelihood of working, it should be preferred as a treatment strategy over the best available alternative. The main safety concerns about genome editing are the possibility of off-target effects, with unknown consequences that may range from none to immediate or delayed catastrophic harm. The difficulty of each of these challenges will vary with a large number of factors, including the characteristics of the technique used, the method and timing of delivery, and the characteristics of the target cells. Complicated regulatory pathways are established in most jurisdictions covering research involving human subjects and clinical trials, and for obtaining marketing approval for new medicinal products.[171] Approval for research in humans will involve review of scientific evidence of safety and efficacy from the most relevant model systems and consideration by a research ethics committee (an 'institutional review board' in the US). Research ethics review is intended to ensure that the interests of research participants are sufficiently protected and includes reviewing the justification for the research, the adequacy and suitability of the information provided, their opportunity freely to consent or refuse to participate, and measures for protecting their dignity and rights.[172] Risk cannot be eliminated, however: a notable early adverse outcome leading to the death of a research subject cast a long shadow over the field of gene therapy from which it has taken a long time to emerge.[173] As a result, the field has highly refined protocols for translational medicine.[174] It is unlikely that, for the most part, therapies based on genome editing will raise distinctive issues for the handling of safety and efficacy considerations.

4.26 These governance measures notwithstanding, the first genome editing therapy was authorised under 'compassionate use', short-circuiting the usual approval process (in the absence of any alternative treatment other than palliative care for what was expected to be a fatal condition).[175] Although the reported treatment was not preceded by a publicity campaign, it suggests the potential for publicity and public expectation around genome editing to distort funding whilst simultaneously placing pressure on approvals and licensing decisions, or, conceivably (although there is as yet no full-blooded competition between health systems in the UK) to attract patients. Individual fundraising, charitable initiatives supporting innovative treatments for the benefit of seriously ill children (or established *in memoriam*) stoked by the media, and the Cancer Drugs Fund (CDF), which circumvents the rational funding of drug treatments determined by NICE, are further potential sources of distortion.[176] They mirror distortions wrought by advertising or publicity and are not dissimilar to the effect sought by marketing departments of pharmaceutical companies, which reputedly account for around half of the overall 'cost' of a new drug.

4.27 The pace of genome editing advances may result in special considerations for clinical translation, just as in basic research: there may be arguments in favour of delaying clinical implementation until the rate of progress has slowed given that any application of genome editing today may turn out to have been better if done tomorrow.[177] A difficulty may lie, therefore, in deciding what is the proper context in which to consider the question of implementation: whether the alternative is no treatment, the best currently available treatment or a treatment that may be available in the near

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[171] See: Medicines and Healthcare products Regulatory Agency MHRA medicines – Clinical Trial Authorisation (CTIMPs): http://www.hra.nhs.uk/research-community/applying-for-approvals/medicines-and-healthcare-products-regulatory-agency-mhra-medicines-clinical-trial-authorisation-ctimps/; European Medicines Agency (EMA): Clinical trials in human medicines: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp.

[172] See: World Medical Association, *Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: http://www.wma.net/en/30publications/10policies/b3/.

[173] Jenks S (2000) Gene therapy death — "everyone has to share in the guilt" *Journal of the National Cancer Institute* **92**(2): 98-100.

[174] Nevertheless, only two products have received market approval in Europe. See: A (2016) EMA greenlights second gene therapy *Nature Reviews Drug Discovery* **15**(5): 299.

[175] See Box 4.2 (above).

[176] A new operating model for the CDF came into effect on 29 July 2016, which, though to be managed by NICE, will still allow exceptions to standard method of drugs appraisal (see https://www.england.nhs.uk/ourwork/cancer/cdf/).

[177] Response to *Call for Evidence* by Dr. Helen O'Neill.

future. A further consideration that is relevant, in possibly unique ways, to genome editing treatments is the potential for reversibility: to what extent are alterations to the genome of cells in patients reversible? While this issue is being addressed by research, it is likely that the first interventions will be carefully chosen to work in limited and well characterised tissue systems, with time-limited effects.

Avoiding genetic disease

4.28 One challenge for genome editing techniques in the treatment of genetic disease is the need to correct a sufficient number of affected cells to produce a 'normal' or sufficiently improved phenotype. Where a mutation is well characterised within a family and has a determinate inheritance pattern – as with some inherited genetic conditions – there is one way potentially to ensure that the genome edit is present in all cells of the affected person. This is to deliver the editing machinery into a single-cell embryo (zygote), shortly after fertilisation or to edit the gametes (sperm or egg) prior to or during fertilisation.[178]

4.29 Manipulation of human embryos outside the body (*in vitro*) is possible as an adjunct to *in vitro* fertilisation (IVF), which is now a relatively routine treatment for infertility; more than two in every hundred children born in the UK are now conceived using IVF procedures.[179] IVF has been practised in humans since 1978, although micromanipulation techniques and the genetic testing of cells removed from early embryos were developed during the 1990s.[180] To date, however, no genetic modification of human embryos has been reported as part of reproductive treatment: this is illegal or otherwise forbidden in many jurisdictions.[181] Nevertheless, the techniques that would make this possible have been developed and used in many organisms, including mice and monkeys, and explored in research on human embryos in two cases.[182]

4.30 For genome editing to be a reasonable strategy to avoid a genetic disease, a significant risk of occurrence would have to be established prior to conception, through family history or preconception screening, and the specific underlying mutation(s) known. There are an estimated 10,000 inherited single-gene conditions with a wide variety of phenotypes, ranging broadly in penetrance and severity. These are individually rare in the general population, although some are much more prevalent in certain communities. The most common (familial hypocholesterolaemia) has a prevalence of about 1:500 in the general population in the UK, although most, especially the more severe and life-limiting conditions, are much less common, having a prevalence of one in several thousand or several tens of thousands. The WHO estimates that the prevalence of all

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[178] For a survey of methods, see: Sato M, Ohtsuka M, Watanabe S and Gurumurthy CB (2016) Nucleic acids delivery methods for genome editing in zygotes and embryos: the old, the new, and the old-new *Biology Direct* **11**: 16. See also Suzuki T, Asami M and Perry ACF (2014) Asymmetric parental genome engineering by Cas9 during mouse meiotic exit *Scientific Reports* **4**: 7621.

[179] See: HFEA (2016) *Fertility treatment 2014 – trends and figures*, available at: http://www.hfea.gov.uk/docs/HFEA_Fertility_treatment_Trends_and_figures_2014.pdf.

[180] Steptoe PC and Edwards RG (1978) Birth after the reimplantation of a human embryo *The Lancet* **312**(8085): 366; Palermo G, Joris H, Devroey P and Van Steirteghem AC (1992) Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte *The Lancet* **340**(8810): 17-8; Handyside AH, Kontogianni EH, Hardy K and Winston RML (1990) Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification *Nature* **344**(6268): 768-70.

[181] There have been cases in which sub-cellular structures containing functional genes have been transferred (see Cohen J, Scott R, Alikani M, *et al*. (1998) Ooplasmic transfer in mature human oocytes *Molecular Human Reproduction* **4**(3): 269-80). Mitochondrial donation has been approved in principle in the UK (but not licensed at the time of writing), although in the passage of the enabling regulations the government minister explicitly asserted that the government did not regard the procedures in question as producing 'genetic modification') see *Hansard* HL Deb, 5 February 2015, cW (Earl Howe in reply to Lord Alton).

[182] At the time of writing two published Chinese research papers, both using tripronuclear embryos, have attempted to evaluate the possibility of introducing genetic edits using the CRISPR-Cas9 system into early human embryos. The first, published in April 2015, attempted to edit the human β-globin (HBB) gene, which encodes a subunit of the adult haemoglobin and is mutated in the disease β-thalassaemia. See: Liang P, Xu Y, Zhang X, *et al*. (2015) CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes *Protein and Cell* **6**(5): 363–372. For the second paper, see note 204 below. In both cases, the authors reported low efficiency and significant off-target effects.

single-gene diseases at birth is approximately 1 per cent worldwide.[183] It is likely that all conditions have a genetic component and that many arise as a result of the interactions of several – perhaps hundreds – of gene variations. These synergise with environmental factors that, in many cases, cause epigenomic changes; synergistic interactions between genomes, epigenomes and the environment that cause disease are today difficult or impossible to predict. Genetic conditions that arise *de novo* may, in principle, be identified by embryo screening when the embryo has developed to a stage where one or two cells may safely be removed for analysis.[184]

4.31 Simply knowing that there is a significant risk of a serious, well-characterised genetic condition, however, would not make genome editing an obvious reproductive option. Where there is a known risk of genetic disease with a well-characterised genetic basis, it is often possible to exclude affected embryos after preimplantation genetic diagnosis (PGD). In practice, this requires the creation of a number of embryos using IVF procedures and the testing of cells removed from those embryos, either at cleavage stage (2-3 days) or, increasingly, at the blastocyst stage (5-6 days, when cells from the trophectoderm – the structure that will form the placenta in pregnancy – can be used). While PGD is available for a large number of single-gene and chromosomal disorders, there are a few cases in which selection of unaffected embryos using PGD would not be possible and effective, that is, where no embryos from a given couple are unaffected.[185] In these exceptional cases, genome editing might offer an alternative approach. They include:

- where there are Y chromosome defects
- eliminating or perhaps correcting mutated mitochondrial DNA
- dominant genetic disease (e.g. late onset, such as Huntington's or Alzheimer's disease, or breast cancer) where one parent is homozygous (100% risk to the offspring) or both parents are heterozygous (75% risk)
- recessive genetic disease where both parents are homozygous (100% risk) or one parent homozygous, one heterozygous (50% risk)
- inversions and deletions of chromosome segments
- where there are no suitable, unaffected embryos available for transfer, for example where multiple, independently assorting, traits are sought (as in the case where one wants to select an embryo with both a particular disease-related genotype and a specific HLA tissue type).[186]

4.32 While these exceptions may be very limited, it is possible to imagine that advances in the allied technology of whole genome DNA sequencing will increase the detection of gene variants or combinations of variants that may be associated with heightened disease risk. If developments in personalised genomic medicine drive the identification of such disease-predisposing variants, it is likely there will be pressure to apply this knowledge to embryos. Indeed, if less severe or penetrant conditions are brought into consideration, it will be highly unlikely that any embryo will be free of every risk-associated variant.[187]

4.33 In a possible, plausible future genome editing could, in principle, allow embryos created *in vitro* to be 'treated' rather than either being discarded or being transferred with the result that an affected child is born. Established micromanipulation techniques, such as intracytoplasmic sperm injection (ICSI) could, in principle, be used to introduce the genome editing machinery to oocytes during or before sperm injection, or into zygotes (early embryos), overcoming the need for viral vectors and maximising the likelihood that the edits would be replicated in all cells of the developing embryo. The efficacy of the procedure and the risk of off-target effects could be assessed by sequencing

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[183] See: http://www.who.int/genomics/public/geneticdiseases/en/index2.html.

[184] For more context, data on the prevalence of birth defects (in the US) can be found at www.cdc.gov/ncbddd/birthdefects/data.html. These affect approximately 3% of all babies, accounting for 20% of all infant deaths. However, this does not include the large number of deaths that occur in utero.

[185] A list of conditions for which the HFEA has issued PGD licences is available at: http://guide.hfea.gov.uk/pgd/.

[186] Adapted from presentation to Nuffield Council Workshop by Robin Lovell-Badge (April 2015) – last bullet added by authors. George Church has argued that for an increasing number of known cases in which several genes are involved in a disease, most embryos need to be discarded in which case editing would greatly increase the odds of getting a healthy embryo (Church in Cyranoski D (2015) Embryo editing divides scientists *Nature* **519**(7543): 272.

[187] Hens K, Dondorp W, Handyside AH, *et al*. (2013) Dynamics and ethics of comprehensive preimplantation genetic testing: a review of the challenges *Human Reproduction Update* **19**(4): 366-75.

cells from the embryo before transfer to the woman, although single cell sequencing, which is a necessary enabling technology, currently has contingent limitations.[188] If the edit were successful, however, it would represent a complete and enduring way of removing an underlying cause of genetic disease. Moreover, if efficient as a process, it would have the advantage of ensuring that the highest clinical grade embryos were available for transfer, which is not always the case with PGD. From one point of view, this is the most optimistic vision. Even before considering the ethical and social challenges that would have to be confronted, however, there may be confounding, possibly insuperable, challenges, involved in making multiple edits, including unanticipated pleiotropic effects, possibly resulting in new pathologies, which might take a long time to surface.

4.34 Edits made in early embryos are conserved as the cells divide and differentiate and are not only persistent through the lifetime of the person that may result from that embryo but are also likely to be conserved in subsequent generations, being inherited by their descendants through sexual reproduction. Alongside concerns about the safety of the technique it is this prospect, in particular, that has given rise to ethical opposition to reproductive genome editing especially where scope for unforeseen consequences is considered to be great or editing is regarded as irreversible.[189]

4.35 These concerns have been sufficient to warrant inclusion in a number of relevant prohibitive conventions and legal instruments, including laws covering biomedical practice and assisted conception specifically, as well as more general anti-eugenics laws in some jurisdictions. They vary according to the legal system and range from international-level declarations (e.g. the UNESCO Declaration on the Human Genome and Human Rights) and legally binding conventions (such as the Council of Europe Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, also known as the 'Oviedo Convention') to community and national law (such as the UK's Human Fertilisation and Embryology Act, 2008).[190] The regulatory systems (such as that of the HFEA in the UK and FDA in the US), are backed by public and professional guidelines from a number of national and international organisations (such as those of the International Society for Stem Cell Research) as well as by national, institutional and professional community policies, including funding policies (such as that of the US National Institutes of Health).[191]

4.36 Policies vary greatly in terms both of approach and content, which may be attributable to different legal traditions and social outlooks. Over 40 jurisdictions have written law and policy on heritable genome modification, ranging from the highly restrictive (e.g. Germany) to reasonably permissive (Mexico).[192] In particular the relevant normative distinctions are cast in different ways, referring variously to the type of activity involved, the aims they are intended to secure, and the type of cells involved (e.g. reproductive cells, gametes and embryos) and different combinations of these things. Some refer explicitly to modifications of the human 'germ line' (integrity of inheritance), others to the protection of 'the human genome' (integrity of the reservoir of human genetic variants); the Oviedo Convention (which is binding law in the 28 member states that have ratified the Convention) does not make reference to either, but only to procedures that aim to introduce 'modifications in the genome of any descendants'. It seems clear that, in trying to frame a measure

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[188] Wen L and Tang F (2016) Single-cell sequencing in stem cell biology *Genome Biology* **17**: 71.

[189] Center for Genetics and Society, *About human germline gene editing*, available at: http://www.geneticsandsociety.org/article.php?id=8711; Lanphier E, Urnov F, Ehlen Haecker S, Werner M and Smolenski J (2015) Don't edit the human germ line *Nature* **519**(7544): 410-11.

[190] For the UNESCO Declaration, see: http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html; for the Oviedo Convention, see: http://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164; for the Human Fertilisation and Embryology Act, see: http://www.legislation.gov.uk/ukpga/2008/22/contents.

[191] For the HFEA, see: http://www.hfea.gov.uk/; for the ISSCR Guidelines for Stem Cell Science and Clinical Translation, see: http://www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-science-and-clinical-translation.pdf?sfvrsn=2; for NIH funding policy, see www.nih.gov/about/director/04292015_statement_gene_editing_technologies.htm.

[192] Isasi R and Knoppers BM (2015) Oversight of human inheritable genome modification *Nature Biotechnology* **33**(5): 454-5; Isasi R, Kleiderman E and Knoppers BM (2016) Editing policy to fit the genome? *Science* **351**(6271): 337-9.

to secure the normative intention, the correspondence between the legal mechanism and the technical procedures it covers requires interpretation in most cases, and particularly in the light of technical advances.

Moral and societal questions identified

4.37 One set of objections to the use of genome editing in reproductive treatments is that it is unnecessary since, in all but a small subset of cases, proven alternatives already exist. In this context, the introduction of an untried treatment considered by some to be unsafe, especially one of questionable moral acceptability, is unwarranted. For reproductive uses of genome editing to provide a substantial benefit compared to the current standard of care, it would have to be superior to PGD in terms of clinical outcomes, cost-effectiveness and ethical concerns.[193] Furthermore, even if genome editing were to be used, PGD would probably continue to be needed in order to verify the success of the edit, at least at early stages in its implementation, so 'nothing would be gained'.[194]

4.38 The proposition that there are alternatives to genome editing, however, potentially misunderstands not only the features of the technology but the context in which it is implemented. This context has two important sets of conditions: the conditions of innovation (see also section 2, above) and the conditions of (personal and social) choice. With regard to the first, as we have said above, genome editing is a potentially transformative technology; its development in other fields (research, animals, gene therapy) may lead to greater understanding of its capabilities and limitations, and provide a ground for addressing some of the safety concerns that are currently raised. This is a recognised pattern with 'disruptive technologies', which, though initially less effective than incumbent technologies, are adopted by a subset of potential users owing to some feature which is particularly desirable to those users and, through use, develop to overcome the initial limitations and eventually to supplant the incumbent technology.[195] For example, it might be argued that technological improvements to genome editing could be expected, at some point, to obviate the need for confirmatory procedures such as PGD or whole genome sequencing when applied to human embryos.[196] One might see it developing, for example, as a 'research' method to 'treat' compromised embryos in Roman Catholic countries.[197] In any case, the technologies in use in any society are often the result of both moral and technical co-evolutions that function to embed the characteristics of a given technology in a set of normative conditions in a way that might make genome editing the 'technology of choice' for a variety of applications.

4.39 With regard to the second set of conditions (the conditions of personal and social choice), the 'alternatives' may only appear to be alternatives because of a particular framing of the challenge to which they respond. That frame is, equally, the result of a number of constraints, many of which are themselves chosen and reflect a situation that may change. If the objective is to produce a healthy child for a couple at risk of passing on a serious genetic condition to any child they conceive naturally, the alternative of adoption, surrogacy and egg donation, as well as PGD may be available. This frame is narrowed if the object is to have a child that is genetically related to both parents; it is broadened if possible alternatives include not only to avoid the condition but also to treat the condition at a later stage, or to adapt to the presence of the condition (as some

[193] Mertes H and Pennings G (2015) Modification of the embryo's genome: more useful in research than in the clinic *The American Journal of Bioethics* **15**(12): 52-3. The space for moral debate opens up partly because other reproductive options (including PGD, but also gamete donation, using prenatal diagnosis and possible termination of affected pregnancies, or not having children) have very different sets of implications – they are not simply alternative paths to the same outcome.

[194] Peter Braude quoted in Hawkes N (2015) UK scientists reject call for moratorium on gene editing *British Medical Journal* **350**: h2601.

[195] Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.

[196] A speculative route might be where the edits are performed in stem cells (iPS cells) that may have their genomes sequenced prior to conversion into functional gametes for use in assisted conception.

[197] Some countries (such as Italy) that clearly prohibit instrumental use of human embryos for research, nevertheless permit research where it is of direct benefit to the embryo. (See Boggio A (2005) Italy enacts new law on medically assisted reproduction *Human Reproduction* **20**(5): 1153-7.) This point was also made from a logically consistent Roman Catholic perspective in response to our *Call for Evidence*: if all human life has equivalent moral status from the point of conception, genome editing is potentially an acceptable form of early gene therapy to save the embryo.

people living with disabilities may prefer). It is reasonable, in most cases, to question whether the focus is on genetic solutions just because the problem is conceived as a 'genetic' one and genetic technology is what is in view.

4.40 It clearly matters whether this potential application of genome editing is seen as a technique for treating an embryo (as a morally considerable being that, *a priori*, deserves treatment to address a medical condition) or as increasing the reproductive options available to those who know themselves to be at risk of passing on a genetic condition. Genome editing is not straightforwardly therapeutic in the way that gene therapy is therapeutic, treating an existing patient who is affected by an unwelcome condition; nor is it preventative in the way that some public health measures are preventative by addressing an imminent risk, since the risk itself can be avoided by not conceiving children. On the other hand, it *is* therapeutic, in the sense that it potentially overcomes infertility (albeit that the infertility is voluntary, a hard choice among an undesirable set of options) and it *is* preventative in that, taking the decision to reproduce as given (or, at least, one that a couple is entitled to make and should not be prevented from making), it may prevent any child they have being born with a serious or life-limiting disability. How these things are governed depends greatly on how reproductive choice is valued and the legitimate extent of society's interest in its members' choices and welfare.[198] Whether PGD or egg donation, or any of the other paths that may be available, count as alternatives to genome editing, depends on these matters of value as much as on matters of fact.

4.41 As with PGD, the fact that genome editing consolidates, at a genomic level, the choices of some in the possibilities open to others, brings it into conjunction with the particularly toxic concept of eugenics (the control of reproduction to increase the occurrence of desired heritable characteristics in a population) as well as with concerns about social justice (including how it might contribute to or detract from a just society, one that, for example, fosters respect and fair treatment for women and people with disabilities).[199] Some of these concerns lie implicitly (and, in some cases, explicitly) behind the existing prohibitions that cover reproductive genome editing.[200] As with the framing of distinctions to which moral significance attaches (such as that between 'somatic' and 'germ line' interventions), there may be reasons to examine more closely and dispassionately how effective the existing measures are at achieving their implied aims. Such a re-evaluation might be justified in the light of technical developments (they may accommodate more or less than is necessary) and in order to question whether genome editing needs to, or is likely to, express 'eugenic' views or exacerbate what has been described as a 'selection society'.[201]

4.42 A re-evaluation of how existing measures relate to their aims in the light of recent technical developments is, in turn, bound to focus attention on how collective values and aims can be articulated, and, at the same time, on differences and the forces of division in society. An ethical inquiry of this kind therefore inescapably involves both risk and renewal. One question such an enquiry must therefore confront is a consideration of the nature of the 'public' that is implied in the term 'public interest'. (Is genome editing the business of nation states, scientific communities, groups or individuals who are themselves affected?[202] Can the content of this interest, for example, be determined independently for a given political community or is it coextensive with the scope of universal human rights?) These questions invite a reflection on the grounding of moral and legal norms and their intersection with political realities, from which to return to practical

[198] Note that, in the case of assisted conception, society's interest includes the welfare of the child that may be born as a result of treatment. Up until the 7th edition, the HFEA Code of Practice set out guiding principles that included "a concern for the welfare of any child who may be born as a result of treatment services […] which cannot always be adequately protected by concern for the interests of the adults involved." See: http://www.hfea.gov.uk/docs/CodeOfPracticeold.pdf.

[199] Research interview with Jackie Leach Scully.

[200] See above – the discussion about structural v. heritable senses of 'genetic'.

[201] Ishii T (2015) Germ line genome editing in clinics: the approaches, objectives and global society *Briefings in Functional Genomics*, doi: 10.1093/bfgp/elv053 (published online: 27 November 2015); Pollack R (2015) Eugenics lurk in the shadow of CRISPR *Science* **348**(6237): 871.

[202] For a study of national governance instruments and measures, see: Ishii T (2015) Germline genome-editing research and its socioethical implications *Trends in Molecular Medicine* **21**(8): 473-81.

questions of morality, policy and governance. Returning thus, it is possible that the answers may not be capable of being read off from those that were given for other reproductive technologies, in other circumstances, at other times.

Enhancing biological function and performance

4.43 The relationship between genes and disease is complex and is rarely deterministic although our current state of knowledge may contribute to some of this uncertainty. Even single-gene conditions are often not fully penetrant (that is, the phenotype does not occur in all individuals who have the genetic mutation). Furthermore, it might be argued that mutations (or combinations of mutations) do not cause, but rather predispose to disease, even if they are highly penetrant. Interactions between a given gene variant associated with disease, other genes and gene products, and environmental conditions therefore can only be said to produce a probabilistic outcome in terms of phenotype. For example, a genetic variant may cause susceptibility to disease in certain conditions (e.g. pregnancy) or in the presence of certain environmental factors (e.g. low oxygen levels) without presenting a higher than average risk in normal circumstances. Some may have deleterious consequences in some cases but beneficial ones in others (e.g. confer protection against disease).[203] Between modifying single mutations that are likely to cause serious and life-limiting disorders, and changing individual variants that are associated with marginally increased absolute risk, there is a large grey area before one arrives at the threshold of enhancement. This grey area includes the morally important objective of preventing disease as well as its treatment.[204]

4.44 In the same way that it is possible to conceive of genome editing technologies delivering treatments for conditions that have an underlying genetic component, it is similarly possible to conceive of them being used to reduce the risk of conditions for which genetic variations are known risk factors, or to prevent disease, for example, by enhancing immunity. A paper published by a Chinese research group in April 2016 – only the second paper to report genome modification of human preimplantation embryos – reported the introduction of the naturally occurring *CCR5Δ32* variant, which is protective against HIV.[205] In principle, it might be possible to confer any well-characterised phenotypic trait for which there is an (epi)genetic basis by genome or epigenome editing (although it is uncertain how many traits may have a sufficiently robust basis). The prominent genome scientist, George Church, has listed ten naturally occurring gene variants with significant impact, including variants that are protective against Alzheimer's disease, diabetes and coronary disease as well as conferring stronger bones, lean muscles and 'low odour production'.[206]

4.45 Evolution is a process by which randomly occurring genetic variants are selected by environmental conditions, producing adaptation. In this way the genetic variant responsible for sickle cell trait, which causes severe disease in homozygous patients, may persist with significant prevalence in areas in which Malaria is endemic because when there is only one variant copy (and the corresponding copy is normal) it is protective against the disease.[207] Genetic traits might be equally useful in any environment that presents a higher than normal health risk. Low gravity is unfavourable for the human body but if humans were to embark on long distance space travel, engineered resistance to radiation and osteoporosis among other things would be potentially desirable.[208] Although Darwinian adaptation responds to environmental factors, it might be easier in future to anticipate what new environments will be encountered and engineer traits accordingly. For particular tasks, such as space travel, that might be easier than trying to recruit someone with

[203] See note nr. 207 below.
[204] Cf. Baumann M (2016) CRISPR/Cas9 genome editing – new and old ethical issues arising from a revolutionary technology *NanoEthics* **10**: 139-59.
[205] Kang X, He W, Huang Y, *et al*. (2016) Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing *Journal of Assisted Reproduction and Genetics* **33**(5): 581-8.
[206] See: https://www.ipscell.com/2015/03/georgechurchinterview/.
[207] Wadman M (2011) Sickle-cell mystery solved *Nature News*, doi:10.1038/nature.2011.9342.
[208] The Economist (6 September 2014) *Welcome to my genome*, available at: http://www.economist.com/news/technology-quarterly/21615029-george-church-genetics-pioneer-whose-research-spans-treating-diseases-altering.

those traits from the general population. Indeed, there might be no one who had all of the desirable traits in combination, and even if they could be found, they might have no interest in becoming an astronaut. As a species facing a number of potential environmental catastrophes, Darwinian evolution may just be too slow.[209]

4.46 Some have suggested that the rate of environmental change caused by human activity may be too rapid for humans to adapt comfortably, or at all, posing an existential risk. Transhumanism is, in part, a set of arguments and conclusions that relate to the imperative for humans to take rational control of their own evolution at the biological level and to construct a matching morality adequate to this.[210] Some argue that human enhancement is desirable for *supra-human* ends: rather than for the benefit of humans, human enhancement is necessary to preserve the conditions of existence of the biosphere more generally.[211] Whereas many of the genes discussed in these contexts are variants found in existing populations, synthetic biologists have suggested that humans might be engineered to include genes found in other organisms – such as those enhancing night vision or olfactory sensation – or even wholly synthetic genes.[212]

Moral and societal questions identified

4.47 Enhancement could take place either through gene therapy or through interventions around reproduction. Many of the questions that arise in respect of the use of genome editing beyond treatment and (arguably also) prevention of disease are not new and have been raised in relation to gene therapy and embryo selection following PGD. Others have been discussed in the context of gene doping (e.g. improvements in skeletal muscle) where they may be time limited (for example, for the duration of a sporting tournament.)[213] Whether the genetic component is an exceptional consideration has also been discussed at length in relation to comparators such as cosmetic surgery.[214]

4.48 Some see human enhancement as an inevitable evolution in the use of technology, although this is often presented in somewhat paradoxical terms as a consequence of extreme respect for individual free choice and a liberal willingness to accept cultural relativism, all despite allegedly sound philosophical objections.[215] It is necessary to distinguish here between the concept of 'technological momentum' that was discussed in Section 2 (whereby the technological conditions supervene on human agency) and the concept of a 'slippery slope' whereby objections to further uses of genome editing fail to gain purchase in the absence of a secure rational distinction between therapy (and prevention) and enhancement. One way of drawing such a distinction is to define these terms in relation to some specifiable concept of normal functioning so that treatment (and prevention) concern restoring (or preserving) what is considered normal function and enhancement involves moving beyond normal. A way in which attempts have been made to make the distinction at the genomic level is in terms of protecting the integrity of the existing range of

[209] Rees M (2003) *Our final century: will the human race survive the twenty-first century?* (London: Heinemann).
[210] See, for example, Savulescu J and Bostrom (Editors) (2011) *Human enhancement* (Oxford: Oxford University Press); Persson I and Savulescu J (2014) *Unfit for the future: the need for moral enhancement* (Oxford: Oxford University Press).
[211] Persson and Savulescu (2014), op. cit.
[212] See, for example, Motherboard (10 February 2015) *Eating the sun: can humans be hacked to do photosynthesis?*, available at: http://motherboard.vice.com/read/human-photosynthesis-will-people-ever-be-able-to-eat-sunlight.
[213] Brzeziańska E, Domańska D and Jegier A (2014) Gene doping in sport – perspectives and risks *Biology of Sport* **31**(4): 251-9.
[214] See, for example, Bostrom N and Roache R (2008) Ethical issues in human enhancement, in *New waves in applied ethics*, Ryberg J, Petersen T and Wolf C (Editors) (Basingstoke: Pelgrave Macmillan), pp120-52.
[215] Baylis and Robert (2004), for example, suggest that sound philosophical objections "are insufficient to stop the development and use of genetic enhancement technologies [...] the inevitability of the technologies results from a particular guiding worldview of humans as masters of the human evolutionary future," Baylis F and Robert JS (2004) The inevitability of genetic enhancement technologies *Bioethics* **18**(1): 1-26. This is echoed in Craig Venter's view that "Our species will stop at nothing to try to improve positive perceived traits and to eliminate disease risk or to remove perceived negative traits from the future offspring, particularly by those with the means or access to editing and reproductive technology". The question is when, not if" (Venter in Bosley KS, Botchan M, Bredenoord AL, *et al*. (2015) CRISPR germline engineering – the community speaks *Nature Biotechnology* **33**(5): 478-86, at page 479); for a contrastive perspective see Morange M (2015) Genetic modification of the human germ line: the reasons why this project has no future *Comptes Rendus Biologies* **338**(8/9): 554-8.

human genetic variation. Examples include the UNESCO International Declaration on the Human Genome and Human Rights. Given this view, any modification might be legitimate if it alters any allele to a 'wild type' variant.[216] This is, however, also probably too strong to admit 'natural' evolution, which is the process of incorporating new variations (through random mutation), as well as shuffling the differences that already exist in a population. Furthermore, and unlike protecting the integrity of descent, this distinction does not address questions of frequency and distribution within a population, which are surely relevant to the justice concerns underlying it.[217]

4.49 A particular concern that has been raised is that genome editing combined with social liberalism may facilitate the 'consumerisation' of human biology, and the spread of 'consumer' or 'liberal' eugenics, driven by the choices of parents rather than by state policy, but with possibly similar, socially divisive results.[218] Objections here concern the practice as well as the consequences: that the biological conditions of human existence should not be the subject of choice since they allegedly interfere with identity of the person in morally significant ways.[219] Once again, the argument turns, in part, around what is exceptional about genetic choices, and particularly those that are made through 'precision' technologies, rather than through deliberate choices of reproductive partner. For the time being the arguments about what is morally acceptable are obscured by a working consensus about the balance of potential benefits and harms in the current state of knowledge, using current techniques.[220] As this balance shifts, however, arguments that have subsisted in academic literature and debate are likely to be called up again and engaged in the space of public policy.

Conclusion

4.50 Many of the issues raised in this section are familiar from the ethical literature that has grown around human genetics. There are, nevertheless, important conceptual questions that genome editing and related scientific developments raise.

4.51 In relation to research, consequences may follow from the extent to which genome editing, because of its unique features, effaces the distinction between basic and applied research, or contributes to the orientation of biological research towards medical impact. A related question is the extent to which, because of these same features, public interest reaches through into underpinning research and qualifies the trust and freedoms traditionally granted to scientists by the public, placing new responsibilities on them, and to what extent there is a constituted research community that can respond to this.[221] Related questions concern the means and modes by which a 'public' may become engaged with research.[222]

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[216] See response to *Call for Evidence* by Julian Hitchcock.

[217] The contrast is between the UNESCO Declaration (integrity of the gene pool) and the Oviedo Convention (integrity of descent) both of which are mechanisms that have in their sights the proscription of 'eugenic' practices.

[218] Agar N (2004) *Liberal eugenics: In defence of human enhancement* (Oxford: Wiley-Blackwell). For 'consumerisation' see Nuffield Council on Bioethics (2010) Medical profiling and online medicine: the ethics of 'personalised healthcare' in a consumer age, available at: http://nuffieldbioethics.org/project/personalised-healthcare-0/.

[219] Habermas J (2003) *The future of human nature* (Cambridge: Polity Press).

[220] "In the pursuit of more controversial benefits for individuals, enhancements can even invite serious new harms for their recipients, including new disease states. And without therapy's or prevention's unobjectionable goal of keeping those suffering harms—or likely to do so—at a level of health normalcy, they can introduce social evils in the form of disturbing new problems of inequality and competition. This does not mean that enhancements are always morally wrong, unjust, or even outside the scope of medicine. In the nongenetic area, society permits plastic surgeons to offer purely cosmetic enhancements. What it does mean, however, is that enhancements are always more controversial than therapies or preventions, less likely to be funded by society, and more likely to be morally and legally prohibited if the risks for individuals or society are seen to outweigh their benefits", Green RM (2005) Last word: imagining the future *Kennedy Institute of Ethics Journal* **15(1)**: 101-6, at page 104.

[221] Sankar PL and Cho MK (2015) Engineering values into genetic engineering: a proposed analytic framework for scientific social responsibility *The American Journal of Bioethics* **15**(12): 18-24; Mathews D, Lovell-Badge R, Chan S, *et al*. (2015) A path through the thicket *Nature* **527**(7577): 159-61; Sugarman J (2015) Ethics and germline gene editing *EMBO reports* **16**(8): 879-80.

[222] This was discussed in: Sciencewise and Nuffield Council on Bioethics (2016) *Public dialogue on genome editing: why? when? who?*, available at: http://nuffieldbioethics.org/wp-content/uploads/Public-Dialogue-on-Genome-Editing-workshop-report.pdf.

4.52 A second set of questions concerns the ground of public interest in the application of genome editing and how this relates to the jurisdictional scope of governance: whether this should be local, national or regional or global; whether it can be determined in relation to geopolitical categories at all, or should be construed in terms of differently constituted communities of interest. And what is the relationship between governance and leadership?[223]

4.53 A third set of questions concerns the identification of morally significant distinctions consistent with the current state of scientific knowledge, so that they can provide a sufficient level of legal and moral certainty. Such distinctions include that between 'germ line' and 'somatic' cells, which is required to do so much normative work, and between genomic and epigenomic changes, in view of the potential of each for reversibility and their relation to personal identity.

4.54 There are further conceptual questions concerning how to distinguish need and preference, treatment, prevention and enhancement, fair access and just distribution. In shoring up or remaking these judgements it may be necessary to begin by exploring anew exactly what it is we wish to avoid and what we hope to achieve, and then how these conclusions can be articulated in terms of purposes, types of activities, the cell types involved, and the institutional arrangements for managing and regulating in the light of the resulting consensus.

[223] "The UK is well positioned to lead research into somatic and germline editing, having both the scientific expertise and the societal, parliamentary, and regulatory frameworks within which to debate, consult, legislate, and monitor use of new techniques." Lancet editorial (2015) Editing the genome – will society catch up science? *The Lancet* **386**(10012): 2446.